

A NEW STEREOSPECIFIC SYNTHESIS OF 1,5-DIENES

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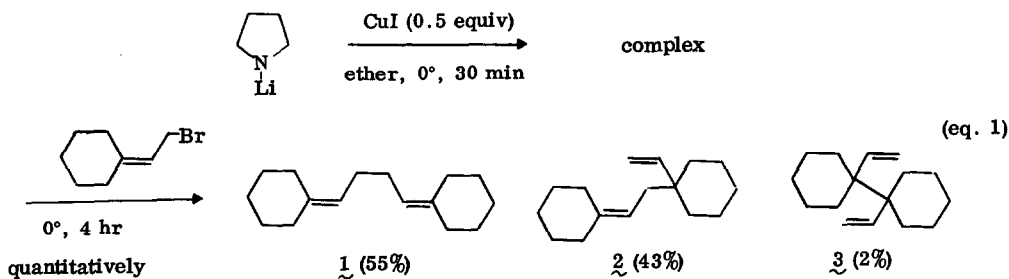
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Remarkable for its facile, and versatile 1,4-addition reaction to α,β -unsaturated carbonyl compounds,¹ the lithium dialkyl copper system also effects the cross coupling reaction with carbon halides and related electrophiles.² We now report the copper based, direct conversion of allylic halides to 1,5-dienes with preservation of stereochemistry.

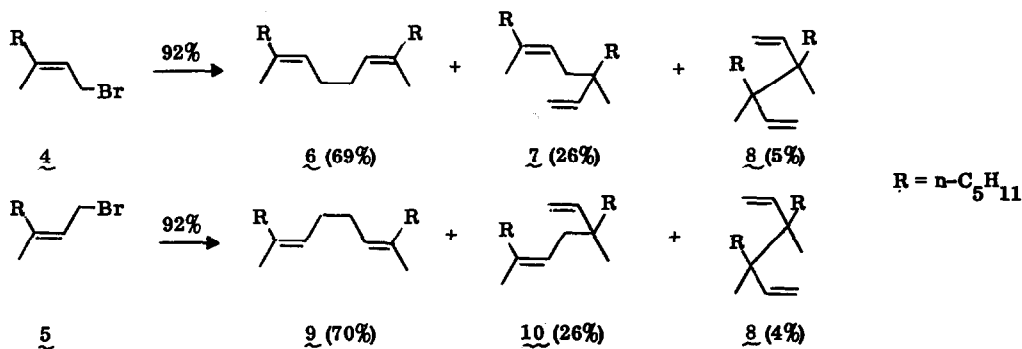
Addition of 0.5 equiv of cuprous iodide to a solution of lithium dialkylamide³ in ether or tetrahydrofuran at low temperature produces a grayish white precipitate which is stable at -78° but which decomposes slowly at 0° and rapidly at 25° .⁴ Of greatest interest to us with regard to the nature of the cuprous iodide dialkylamide complex was the finding that this suspension did serve as a reagent for the reductive coupling of allylic halides to 1,5-dienes. Best results were obtained in general by using two equiv of the copper complex over halide and conducting the coupling reaction in ether at 0° . Reaction of the complex (2 equiv), derived from lithium pyrrolidide in ether at 0° for 30 min, with cyclohexylideneethyl bromide for ca. 4 hr at 0° followed by addition of hexane, filtration through a pad of Celite 545, washing with dil. hydrochloric acid, and concentration in vacuo afforded the coupling product in essentially quantitative yield.⁵

The conditions and choice of lithium dialkylamide (eq. 1) were quite critical for efficient coupling. Some results are given in Table I. In general, lithium amide derived from pyrrolidine or *N,N'*-dimethylethylenediamine gave the most satisfactory results. There also appears to be a marked effect of

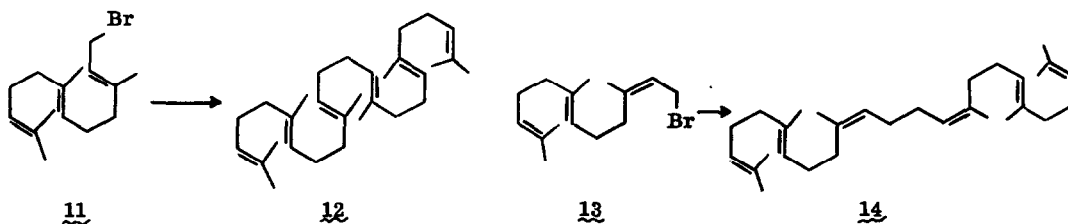


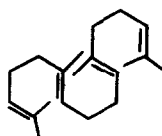
temperature on the reaction, and in many cases an optimum point can be located, above and below which yields of coupling product diminish.⁶ The fact that coupling is seen to be remarkably sensitive to solvent and temperature is not surprising in view of a similar dependence previously observed.^{1,2,7}

Although allylic coupling can be realized efficiently through nickel carbonyl in dimethylformamide or N-methylpyrrolidone with allylic halides,⁸ the 1,5-diene produced is mainly the *E,E*-compound, irrespective of the stereochemistry of the starting material. The isomerization is ascribed to allylic halogen-nickel exchange or allylic rearrangement within the organonickel complexes via α -allylnickel compounds.⁹ To investigate the stereospecificities of our new reaction, we studied the independent reaction of the *E*- and *Z*-bromide, 4 and 5, respectively,¹⁰ with the copper reagent derived from lithium pyrrolidide. In both cases, the isomeric ratios were determined by glpc analysis.¹¹ Furthermore, since each regioisomer was readily separated by chromatographic means ("pre-packed column" of E. Merck),¹² we were encouraged to continue study. Thus, the complete stereospecificity of this reaction was further confirmed by the pmr spectra at 100 MHz which were consistent with indicated structures: e. g., a six proton singlet at 1.56 (=C-CH₃) and only minor (<2%) absorption at 1.64 ppm in that of 6, and vice versa in that of 9.¹³

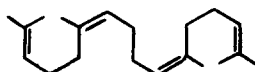


To illustrate one of the unique synthetic applications of our new reagent, (*E,E*)-farnesyl bromide (11)¹⁴ was converted to squalene (12) in 50% isolated yield, identical with an authentic sample by ir, mass, tlc, and pmr analyses.¹⁵ In contrast, (*Z,E*)-farnesyl bromide (13),¹⁴ on treatment with the copper reagent from lithium pyrrolidide, was transformed into (*E,Z,Z,E*)-squalene (14) in stereospecific manner.¹⁶ Analogously, geranyl bromide and neryl bromide were converted into the respective coupling products, 15 and 16, respectively.¹⁷



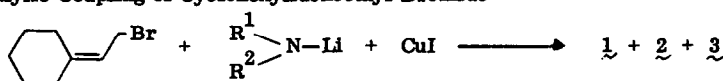


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There is at present no basis for mechanistic conclusions, especially with regard to the exact nature of the complex and to the question of whether the primary process involves nucleophilic replacement of halogen by metal or electron transfer from metal to halide. However, we have made some additional observations which support the generality of this reaction. Thus, other transition metals, e. g., iron(II) and nickel(II) also effect the similar coupling reaction with equal efficiency.^{18, 19}

Table I. Allylic Coupling of Cyclohexylideneethyl Bromide^a

Amine	Solvent	Ratio CuI:Amide: Substrate	Reaction time, hr. and temp., °C ^b	Dimer	
				% Yield ^c	Ratio, 1:2:3 ^d
Pyrrolidine	ether	2:4:1	4, 0	94	55:43:2
Pyrrolidine	ether	5:10:1	4, -78	61	57:42:1
Pyrrolidine	THF	2:4:1	4, 0	36	—
Pyrrolidine	ether	1:2:1	4, 0	82	55:43:2
Pyrrolidine	ether	5:10:1	4, -45	80	52:41:7
Pyrrolidine	ether	5:10:1	4, -26	78	57:40:3
<u>N, N'</u> -Dimethylethylenediamine	THF	2:2:1	4, 0	93	53:43:4
<u>N, N'</u> -Dimethylethylenediamine	ether	2:2:1	4, 0	81	56:42:2
<u>N, N'</u> -Dimethylethylenediamine	ether	5:5:1	4, -78	39	—
<u>N, N'</u> -Dimethylethylenediamine	THF	2:2:1	4, -26	73	56:43:1
<u>N, N'</u> -Diethyl-1, 3-propanediamine	ether	2:2:1	4, -26	53	54:43:3
Diethylamine	ether	1:2:1	5, 0	26	—
Diisopropylamine	ether	1:2:1	4, 0	51	54:43:3
Piperidine	ether	1:2:1	4, 0	59	—
2, 2, 6, 6-Tetramethylpiperidine	ether	1:2:1	5, 0	0	—
<u>N</u> -Methylethylenethiolamine	THF	2:2:1	3, 0	73	—

^a Most of these reactions were carried out on a 1 mmole scale. ^b The copper complex was prepared at the same temperature for 30 to 60 min. ^c Yields refer to purified product, isolated by simple column chromatography on silica gel (hexane). ^d Determined by gpc analysis. Each isomer was separated by pre-packed column chromatography and have been adequately characterized by analytical and spectral data.

Further work is in progress to explore the full range of reactivity of this useful copper complex with other electrophiles and to increase the regioselectivity of the above reactions.

REFERENCES

1. G. H. Posner, Org. Reactions, **19**, 1 (1972).
 2. J. F. Normant, Synthesis, **4**, 63 (1972) and references cited therein.
 3. The lithium amide was prepared in situ by treatment of the corresponding amide with n-butyllithium at 0° for 10 min.
 4. Although we have no evidence on the constitution of this complex, the formulation I seems not unreasonable, see copper monoamide and its reactions: F. D. King and D. R. M. Walton, J. Chem. Soc. Chem. Commun., 256 (1974). It should be noted that copper monoamide itself is a totally unsatisfactory reagent for such transformation (0% yield). Furthermore, we have found that lithium di-sec-butylcuprate effects such coupling reaction in ca. 10% yield: unpublished results of Y. K.
- $$\text{R}_2\text{N}-\overset{\ominus}{\text{C}}\text{u}-\text{NR}_2 \quad \text{Li}^+ \quad \text{I}$$
5. This crude material (colorless liquid) is almost free of by-products; so that for most further applications, purification is not necessary.
 6. In general, at low temperature, larger excess of the complex and longer reaction time is necessary for the efficient coupling reaction (see Table I).
 7. E. J. Corey and G. H. Posner, J. Amer. Chem. Soc., **90**, 5615 (1968).
 8. An excellent discussion of the synthetic values of these reactions: M. F. Semmelhack, Org. Reactions, **19**, 115 (1972). See also, R. Baker, Chem. Rev., **73**, 487 (1973) and W. Carruthers, Chem. Ind. (London), 931 (1973).
 9. E. J. Corey and E. K. W. Wat, J. Amer. Chem. Soc., **89**, 2757 (1967); see also ref. 8.
 10. The bromide 4 and 5 were synthesized from the corresponding α,β -unsaturated ester (H. Taguchi, K. Shimoji, H. Yamamoto, and H. Nozaki, Bull. Chem. Soc., Japan, **47**, 2529 (1974)) by reduction with aluminum hydride to the corresponding alcohol followed by reaction with phosphorus tribromide in ether.
 11. Using a 1.5-m, 5% Carbowax 20M column at 100°.
 12. Pre-packed column (silica gel 60) of E. Merck was found to be extremely useful for the complete separation of these regio-isomers using hexane as an eluant: the isomer 8 was eluted first, then 7 and 10, and finally the diene 6 and 9.
 13. W. S. Johnson, A. vander Gen, and J. J. Swoboda, J. Amer. Chem. Soc., **89**, 170 (1967); W. R. Bartlett, V. A. Fung, and W. S. Johnson, Bioorg. Chem., **1**, 243 (1971). The stereospecificity of the reaction was found to be ~98%.
 14. Prepared from (E,E)- or (Z,E)-farnesol by phosphorus tribromide in ether. The separation of (E,E)- and (Z,E)-farnesol was achieved by pre-packed column (20% ethyl acetate in benzene) chromatography on silica gel 60. This method was found to be much easier by the pre-existing procedure: see J. A. Katzenellenbogen, Ph. D. Thesis, Harvard University, 1969. Stereochemical purity: ~99%.
 15. Stereospecificity: ~98%.
 16. Consistent with all respects with the assigned structure. Surprisingly, (E,E,E,E)-squalene and (E,Z,Z,E)-squalene could be distinguishable by tlc analysis. R_f of 12: 0.32; R_f of 14: 0.41; silica gel, hexane, two developments.
 17. Regioselectivity of these reactions were 70% for geranyl bromide and 70% for neryl bromide.
 18. E. J. Corey and G. H. Posner, Tetrahedron Lett., 315 (1970).
 19. Detailed study of this point will be published in full paper.