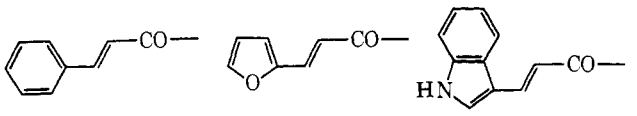
Table I. λ_{max} Values of β-Arylacryloyl Derivatives



A B C

	λ_{max}, nm ($\epsilon_{max} \times 10^4$) for acyl groups[c]		
	A	B	C
O-Acylchymotrypsins[a]			
Native (pH 4.2)	288[b] (1.78[d])	321	359 (1.78[d])
Denatured	280 (1.78[d])	309	334 (1.90[d])
O-Acyl-*N*-acetylserinamides[a]			
H_2O	281 (2.43[d])	309	335 (2.70[d])
10 *M* LiCl in H_2O	285	314	
Methyl esters			
H_2O	279	306	330
10 *M* LiCl in H_2O	280	310	335
Lactones (II, III, IV)			
H_2O	285 (2.28)	314 (2.48)	341 (2.07)
10 *M* LiCl in H_2O	288 (1.85)	320 (2.11)	349 (1.46)
EtOH	280 (2.51)	309 (2.59)	339 (2.14)

[a] See ref 4. [b] Corrected for tyrosine and tryptophan. See M. L. Bender, 143rd National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 9–14, 1962; J. F. Wooten and G. P. Hess, *Nature (London)*, **188**, 726 (1960). [c] A, B, and C are shown above. [d] See ref 12.

chymotrypsins cannot be explained solely on the basis of medium changes.

Binding of dyes and various reporter experiments have been interpreted to show that the active site of chymotrypsin possesses very polar[12] and nonpolar[13] regions. From observations of the ^{19}F chemical shift of chymotrypsin-bound *N*-trifluoroacetylphenylalanine, Zeffren and Reavill[13b] have concluded that either the environment is of polarity approached by *ca.* 10 *M* NaCl or that the fluorine nuclei are situated adjacent to an aromatic ring and subject to its anisotropic effect. Recent nmr experiments[14a,b] provide strong evidence that cinnamate and several *N*-acyltryptophanate ions bind to native α-chymotrypsin in an identical manner, presumably at the "tosyl hole."[15] It seems reasonable to assume that the acyl groups of the chymotrypsin derivatives discussed above occupy this same location in the acylated enzymes. Examination of a model of chymotrypsin shows that this binding site encompasses regions of both polar and nonpolar character, but it is not clear which areas will be dominant in determining the ultraviolet behavior of these chromophores.

We conclude that the "cis hypothesis," if combined with the assumption of a polar binding site, might explain both the reactivity of acylchymotrypsin intermediates and the red shift noted for the β-arylacryloyl reporter groups when esterified to the hydroxyl group of serine-195. However, the cis hypothesis cannot be considered a unique explanation since the chromophore is undoubtedly held in a heterogeneous milieu and chemical or theoretical models for electronic perturbation by a heterogeneous milieu are not available.[16]

(12) (a) R. J. Foster, *Fed. Proc.*, **27**, 784 (1968); (b) J. Kallos and K. Avatis, *Biochemistry*, **5**, 1979 (1966).

(13) (a) M. B. Hille and D. E. Koshland, Jr., *J. Amer. Chem. Soc.*, **89**, 5945 (1967); (b) E. Zeffren and R. E. Reavill, *Biochem. Biophys. Res. Commun.*, **32**, 73 (1968).

(14) (a) J. T. Gerig and J. D. Reinheimer, *J. Amer. Chem. Soc.*, **92**, 3146 (1970); (b) J. T. Gerig and R. A. Rimerman, work in progress.

(15) T. A. Seitz, R. Henderson, and D. M. Blow, *J. Mol. Biol.*, **46**, 337 (1969).

(16) It should be noted that a trans-to-cis conformational change of substrate bound to chymotrypsin cannot reasonably be employed to explain the facility of the acylation step. Thus, the normal substrates for chymotrypsin are amides, and it is known that amides and lactams exhibit similar rates of alkaline hydrolysis.[17] Lactones II, III, and IV exhibit no appreciable reaction with chymotrypsin. Therefore, a cis configuration of substrate does not impart great lability of substrate to attack by chymotrypsin.

(17) M. Gordon, Ph.D. Thesis, Manchester, 1950.

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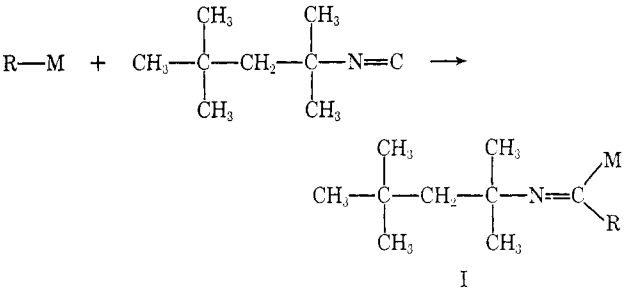
Metallo Aldimines. II. A Versatile Synthetic Intermediate[1]

Sir:

We have previously reported on the preparation of lithium aldimines and their use as intermediates for the preparation of aldehydes, C-1-deuterated aldehydes, and α-keto acids.[2] We now wish to report that aliphatic Grignard reagents[3a] also add to 1,1,3,3-tetramethylbutyl isocyanide (TMBI)[3b] to yield the corresponding metallo aldimine (I).



I

M = Li, MgBr

The aldimine I (M = MgX) is prepared by the addition of 1 equiv of TMBI to the desired alkylmagnesium halide in tetrahydrofuran.[4] Hydrolysis of I with D_2O or H_2O followed by steam distillation from a solution of oxalic acid yields the desired aldehyde in yields of 48–67%. Carbonation provides the corresponding α-keto acid. The results are summarized in Table I.

Although the yields of aldehydes and α-keto acids prepared from I (M = MgX) are lower than those prepared using the lithium aldimine reagent[2] (I, M = Li), the use of a Grignard reagent may be more expedient whenever the alkyllithium reagent is not readily available. However, we have observed that when C-1 deu-

(1) The support of this work by grants from the National Science Foundation and Public Health Service Grant No. 04064 from the National Cancer Institute is gratefully acknowledged.

(2) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969).

(3) (a) For other attempts to add Grignard reagents to isonitriles see I. Ugi and U. Fetzer, *Chem. Ber.*, **94**, 2239 (1961), and references cited therein. (b) Available from Columbia Organic Chemicals, Columbia, S. C.

(4) The Grignard reagent is standardized using the method of Gilman prior to the addition of the isocyanide (H. Gilman, E. H. Zoellner, and J. B. Dickey, *J. Amer. Chem. Soc.*, **51**, 1576 (1929).

Table I. Aldehydes and Keto Acids from Alkyl Grignard Reagents and TMBI

RMgBr[b]	T, °C	Time, hr	Aldehyde, %	α-Keto acid, %
sec-Butyl	25	3	67 (96)[a]	47
tert-Butyl	66	24	48	
n-Hexyl	66	1.5	62	26
2-Phenylethyl	66	1.5	63 (80)[a]	
Cyclopentyl	66	1.5	66 (89)[a]	
n-Butyl	66	1.5		34

[a] Per cent deuterium at C-1 as determined by nmr. [b] Concentrations of Grignard reagents were *ca.* 0.1 *M*.

terioaldehydes are prepared using the Grignard route, one does not obtain 100% deuterium incorporation at C-1.[5] In this respect the lithium aldimine reagent would be the method of choice for the preparation of pure C-1 deuterioaldehydes as well as aromatic aldehydes since aromatic Grignard reagents do not add well to TMBI.

In addition we would like to report on the versatility of the lithium aldimine reagent. As shown in Chart I, besides providing a convenient synthesis of aldehydes and α-keto acids, the lithium aldimine I (R = *n*-butyl) can be alkylated with ethyl bromide to yield after hydrolysis an 87% yield of 3-heptanone. An 86% yield of 3-methyl-2-pentanone was also realized by alkylating, with methyl iodide, the aldimine prepared by the addition of *sec*-butyllithium to TMBI (see Table II). Attempts to alkylate I with isopropyl halides were abortive due to the preference for an elimination pathway. The elegant Meyers[6] synthesis of ketones suffers from a similar difficulty in the introduction of bulky groups.

Chart I. Reactions of Lithium Aldimine

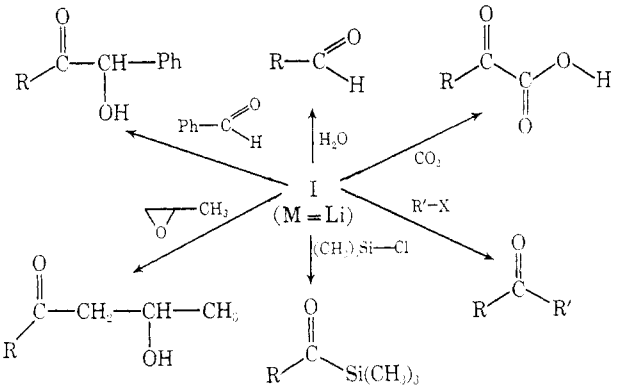


Table II. Reactions of Various Lithium Aldimines

R–Li	R''–NC	R–X	Product	Yield, %
sec-Butyl	TMBI	CH_3I[a]	3-Methyl-2-pentanone	86
n-Butyl	TMBI	C_2H_5Br[a]	3-Heptanone	87
n-Butyl	TMBI	Propylene oxide	2-Hydroxy-4-octanone	90
Ethyl	TMBI	Benzaldehyde	1-Phenyl-1-hydroxy-2-butanone	81
Ethyl	TMBI	$(CH_3)_3$-Si–Cl	Trimethylsilyl ethyl ketone	40[d]
Ethyl	DMPI[b]		1-(*N*-Propylideneamino)-2,6-dimethylbenzene	50
n-Butyl	TBI[c]		2-(*N*-Pentylideneamino)-2-methylpropane	92

[a] Reaction run at −78° in THF. [b] 2,6-Dimethylphenyl isocyanide. [c] *tert*-Butyl isocyanide. [d] Better conditions for the hydrolysis of the imine precursor are being investigated.

Alkylation using propylene oxide yields a β-hydroxy ketone in very good yield. Under the reaction conditions used very little, if any, dehydration occurs. This reaction shows promise in providing a convenient means for preparing mixed aldols. As should be noted, α-hydroxy ketones can also be prepared by the condensation of I with benzaldehyde.[7]

It should also be noted that silyl ketones[8] can be very conveniently prepared by the use of lithium aldimines. The yield of trimethylsilyl ethyl ketone prepared by this method was 40% (nmr analysis). The intermediate imine can also be isolated (in 80–94% yield) if desired.[9]

Further exploration of these intermediates is being continued.[10]

(5) The reason for this is currently under investigation and will be reported in our full paper.

(6) A. I. Meyers, I. R. Politzer, B. K. Bandlish, and G. R. Malone, *J. Amer. Chem. Soc.*, **91**, 5887 (1969).

(7) The scope and limitations of these reactions are currently under investigation and will be discussed in our full paper.

(8) A. G. Brook, J. M. Duff, P. F. Jones, and N. R. Davis, *J. Amer. Chem. Soc.*, **89**, 431 (1967); E. J. Corey, D. Seebach, and R. Freedman, *ibid.*, **84**, 434 (1967).

(9) The preparation of other metallic ketones is under investigation.

(10) Solvent effects have been noted in the addition reaction. Moreover, the structure of the isocyanide is important. We have prepared and evaluated a large number of isocyanides which do not have α hydrogens. For reactions of α-hydrogen containing isocyanide swith organometallics, see U. Schöllkopf and G. Fritz, *Angew. Chem., Int. Ed. Engl.*, 7, 805 (1968).

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Syntheses *via*-2-Oxazolines. I. The Formylation of Grignard Reagents in the Presence of Hexamethylphosphoramide

Sir:

In the course of a study to evaluate the synthetic utility of 2-oxazolines which have been found to be useful precursors to a variety of aliphatic and aromatic carboxylic esters and acids,[1] we examined the readily obtainable 4,4-dimethyl-2-oxazoline (**1**)[2] as a potential formylating reagent for organometallics. In a previous report[3] we described the addition of organolithium reagents to the dihydro-1,3-oxazine system producing the homologated aldehyde precursor **4**. Although this process proceeded in satisfactory yield the difficulty in obtaining the requisite dihydro-1,3-oxazine detracted from the utility of this method. The ease and quantity with which the 2-oxazoline could be prepared suggested that the five-membered ring system would be a more attractive route to aldehydes from

(1) A. I. Meyers and D. L. Temple, Jr., *J. Amer. Chem Soc.*, **92**, 6644 (1970).

(2) This hitherto unknown compound was prepared in 70% yield by heating an equimolar mixture of 90% formic acid and 2-methyl-2-aminopropanol to 130–140° for 45 min, followed by distillation into cold ether. The aqueous distillate layer was removed, saturated with salt, and extracted with ether, and the combined ethereal solution dried and concentrated. Distillation gave pure **1** [bp 99–100°; ir (neat) 1630 cm^{-1}; nmr (CCl_4) δ 6.55 (s, 1 H), 3.77 (s, 2 H), 1.19 (s, 6 H)]. P. Allen and J. Ginos [*J. Org. Chem.*, **28**, 2759 (1963)] have reported a synthesis of 2-oxazolines upon which this experiment was based.

(3) A. I. Meyers and H. W. Adickes, *Tetrahedron Lett.*, 5151 (1969).

organolithium reagents. We were surprised to learn that under a variety of conditions, little or no addition of organolithium to the C=N link occurred; only proton abstraction. Thus, **1** was completely deuterated (**2**, 99%) when treated with 1 equiv of butyllithium in THF followed by addition of heavy water.[4] Furthermore, attempts to formylate Grignard reagents led only to recovered starting material. This result is consistent with our previous observation[1] that the 2-oxazolines were inert to Grignard reagents.

The 2-oxazoline (**1** or **2**) was converted to the methiodide derivative (**5** or **6**) in 89% yield (**5**, mp 215° dec, 1650 cm^{-1}, δ (CH_3CN) 9.15 (s, 1 H), 4.87 (s, 2 H), 3.37 (s, 3 H), 1.55 (s, 6 H), which proved to be a useful and convenient reagent for the formylation or deuterioformylation of a variety of Grignard reagents.[5]

The addition of a Grignard reagent containing 2.0 equiv of hexamethylphosphoramide (HMPA) to a THF suspension of **5** resulted in good yields of the oxazolidine **7** after overnight stirring at room temperature (Table I). Hydrolysis of the crude oxazolidine

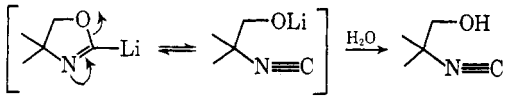
Table I. Reaction of RMgX·2HMPA with **5** to Form RCHO

RMgX	% 7	Aldehyde	% overall	2,4-DNP
$C_6H_5CH_2MgCl$	89	$C_6H_5CH_2CHO$	87	120–121[a]
$C_6H_5CH{=}CHMgBr$	80	$C_6H_5CH{=}CHCHO$	64	250 dec[a]
$C_6H_5C{\equiv}CMgBr$	65	$C_6H_5C{\equiv}C{-}CHO$	51	
o-$CH_3OC_6H_4MgBr$	96	*o*-$CH_3OC_6H_4CHO$	90	253[b]
o-$CH_3OC_6H_4MgBr$	81	*o*-$CH_3OC_6H_4CDO$	70[c]	253

[a] A. I. Vogel, "Elementary Practical Organic Chemistry," Part 2, Longmans, Green and Co., New York, N. Y., 1962. [b] M. Stiles and A. Sisti, *J. Org. Chem.*, **25**, 1691 (1960). [c] Reaction was carried out in the identical manner using **6**.

in aqueous oxalic acid led to the aldehyde **8** or its C-1 deuterated derivative **9** in 51–90% overall yield for the two-step process. The use of HMPA is of critical importance since, in its absence, the Grignard reagents appear to complex with the heterocyclic oxygen **10** resulting in ring cleavage by virtue of addition of a second equivalent of the Grignard, producing the dialkylated amino alcohol **11** in excellent yields. The complexing ability of magnesium in **10** is minimized by the addition of the strongly solvating HMPA, thus allowing the uninterrupted formation of the oxazolidine **7**.[6] Examination of Table I reveals that *aliphatic* Grignard reagents were not successfully formylated using the oxazolinium iodide. In every case using aliphatic Grignard reagents complexed with HMPA, only proton abstraction from **5** took place.

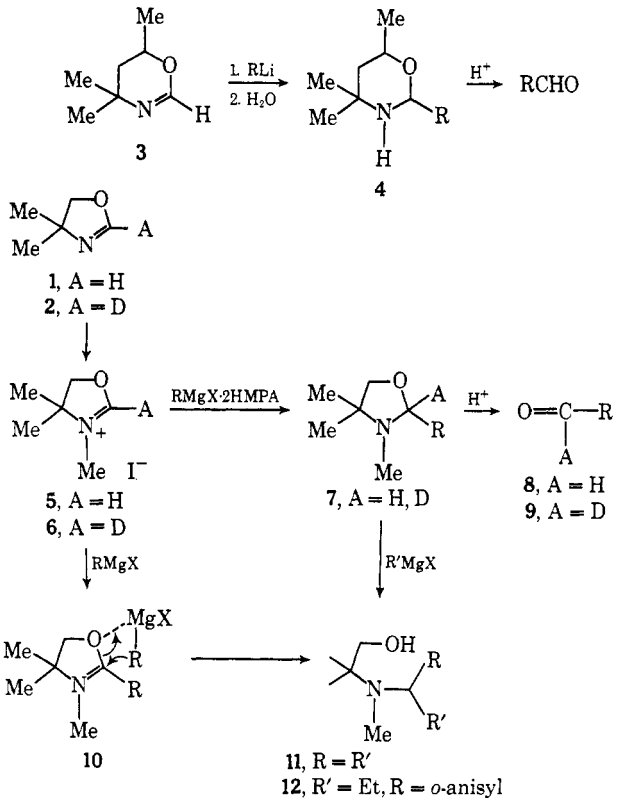
(4) The lithio salt of **1** was found to be in equilibrium with the open-chain isonitrile. Upon careful hydrolysis the isonitrile could be isolated



(ir 2145 cm^{-1}) along with the 2-oxazoline [see also F. Gerhart and U. Schollkopf, *Tetrahedron Lett.*, 6231, (1968); *Angew. Chem., Int. Ed. Engl.*, **9**, 301 (1970)].

(5) The formylation of Grignard and organolithium reagents has been reviewed (J. Carnduff, *Quart. Rev., Chem. Soc.*, **20**, 169 (1966)).

(6) Oxazolidines of the type **7** prepared from 2-amino-2-methylpropanol and aldehydes have been shown to react with Grignard reagents producing the amino alcohols **11** [M. Senkus, *J. Amer. Chem. Soc.*, **67** 1515 (1945)].

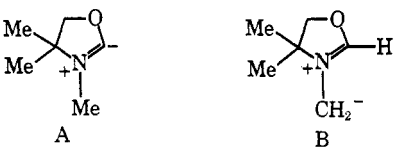


This was amply demonstrated when 3-phenylpropylmagnesium bromide–2HMPA was treated with the 2-deuterio derivative, **6**. The only isolable product was 3-phenylpropane (30% *d*, comparison made with an authentic sample). In the absence of HMPA, the phenylpropylmagnesium bromide added in the usual manner to give **11** (R = $PhCH_2CH_2CH_2$) *via* **10**. It is clear that the HMPA complex[7] with Grignard reagents caused a significant enhancement in the base strength of RMgX when R is aliphatic (sp^3 carbanion) but does not exert any noticeable effect when R represents an sp or sp^2 carbanion.[8]

The dramatic effect of the HMPA in this process was exemplified when the oxazolinium salt **5** was treated with excess *o*-anisylmagnesium bromide producing the adduct **7** (R = *o*-anisyl) in 96% yield. After isolation, **7** was then added to ethylmagnesium bromide in the absence of HMPA, and gave the amino alcohol **12** in 92% yield. This result suggests two new and useful synthetic techniques: (a) the oxazolidines may be useful carbonyl protecting groups against the Grignard reagent if the latter is previously complexed with HMPA, and (b) unsymmetrical amino alcohols of the type **12** may now be prepared by utilizing two different Grignard reagents as described above, instead of the earlier method described by Senkus.[6]

(7) The term "complex" is used somewhat loosely since the only evidence to support this interaction is the fact that when 2.0 equiv of HMPA is added to a THF solution of the Grignard reagent, an exothermic reaction ensues.

(8) It has now been determined that proton abstraction from the methiodide **6** occurs both at the 2 (30%) and *N*-methyl (70%) positions producing ylides A and B. The fate and utility of these ylides are currently under investigation.



The reaction of **6** with RMgX·2HMPA coupled with the recently reported[9] addition of organolithiums to *tert*-alkyl isocyanides now provides a facile technique for the deuterioformylation of the two most common classes of organometallics. Furthermore since formic acid-^{14}C is routinely available, this method allows an easy entry into C-14 labeled aldehydes.

A typical procedure for formylating a Grignard reagent follows. ***N*,4,4-Trimethyl-2-oxazolinium iodide (5)** was prepared by stirring **1** (20 g) in 25 ml of methyl iodide for 20 hr and removing unreacted components *in vacuo*. The solid was washed with ether, dried, and purified by precipitation of an acetonitrile solution with ether, producing **2** in 89% yield. The salt, although slightly hygroscopic, could be stored in an inert atmosphere without deterioration.

***o*-Methoxybenzaldehyde.** The Grignard reagent of *o*-bromoanisole (11 mmol) was prepared in THF (15 ml) and treated with dry HMPA (22 mmol). The resulting solution was added dropwise to a stirred suspension of **2** (10 mmol) in THF (30 ml) at room temperature and allowed to stir for 15–16 hr. The reaction mixture was decomposed with ice–water and acidified with 3 *N* hydrochloric acid. The acid solution was extracted with hexane (discarded) and then carefully made alkaline with sodium hydroxide solution (30–40%). The crude oxazolidine **6** was removed by ether extraction[10] and, after concentration, was heated to reflux for 15 min in an aqueous oxalic acid (45 mmol/25 ml) solution. The cooled acid solution was extracted with ether and the extracts were concentrated yielding the aldehyde as a crystalline residue (mp 36–38°).

Acknowledgments. Financial assistance from the National Science Foundation (GP-2254), Petroleum Research Fund, administered by the American Chemical Society, National Institutes of Health (GM-06248011), CIBA, and Hoffmann-La Roche is gratefully acknowledged. We are also indebted to the Lithium Corporation for generous supplies of organolithium reagents used in this study.

(9) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969); H. M. Walborsky, W. H. Morrison, III, and G. E. Niznik, *ibid.*, **92**, 6675 (1970). In the latter study, the magnesium aldimines do not appear to react with Grignard reagents other than aliphatic (sp^3 carbon bonded to magnesium). Thus, this method is limited to formylation of alkyl residues whereas the present technique complements nicely by allowing formylation of aryl, benzyl, alkynyl, allyl, and vinyl Grignard reagents.

(10) If pure oxazolidine is required, final traces of HMPA can be removed by elution of the ethereal solution through silica gel (8–20 mesh).

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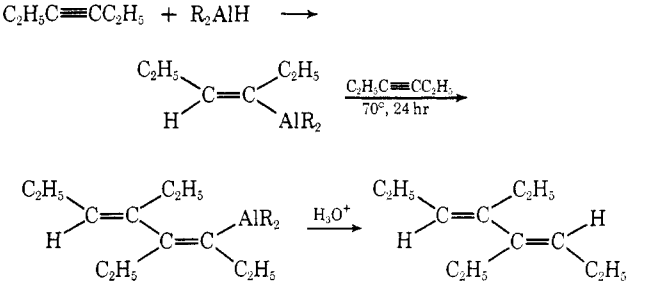
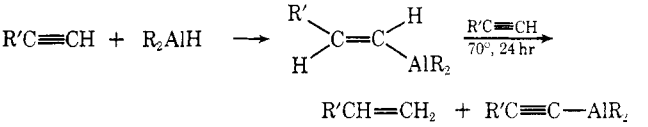
A Novel Stereoselective Synthesis of 1,3-Dienes from Alkynes *via* the Addition of Cuprous Chloride to Vinylalanes[1]

Sir:

An interesting reaction specific to the vinylalanes derived from disubstituted alkynes is their addition to the triple bonds of disubstituted acetylenes to form dienylalanes.[2] These derivatives yield, after hydrolysis, tetrasubstituted trans,trans 1,3-dienes. Thus, hydroalumination of 3-hexyne with diisobutylaluminum hydride in a 2:1 ratio at 70° followed by hydrolysis of the intermediate dienylalane gives 4,5-diethyl-*trans*,-*trans*-3,5-octadiene in high yield.[3] Unfortunately, our

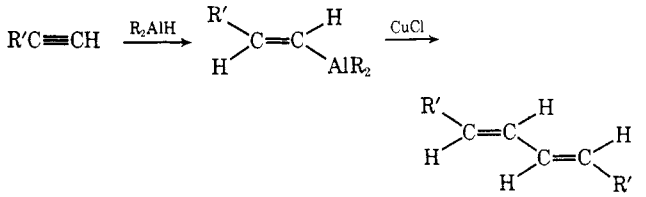


endeavours to utilize 1-alkynes for the above dimerization reaction were unsuccessful due to competing metalation of the acetylenes. Likewise, attempts to



add the vinylalane derived from 3-hexyne and diisobutylaluminum hydride to 1-hexyne afforded *cis*-3-hexene and diisobutyl(1-hexyn-1-yl)alane.

In exploring alternate routes for the synthesis of dienes from terminal acetylenes *via* the hydroalumination reaction we have now found that terminal vinylalanes, when treated with cuprous chloride in tetrahydrofuran solution, react to give isomerically pure trans,trans 1,3-dienes. Thus, addition at 25° of a 20%



molar excess of cuprous chloride to a tetrahydrofuran solution of the vinylalane derived from 1-hexyne and diisobutylaluminum hydride resulted in the precipitation of copper and a 73% isolated yield of *trans,trans*-5,7-dodecadiene.[4] Increasing the size of the alkyl group attached to the triple bond from *n*-butyl to *tert*-butyl had little effect on the yield and stereochemistry of the diene formed. For each of the reactions studied, glpc analysis of the crude reaction mixture revealed that formation of the diene occurred with nearly complete retention of configuration around the carbon–carbon double bond. The results are summarized in Table I.

The facile coupling reaction with cuprous chloride is also applicable to vinylalanes derived from disub-

(1) This research was supported by the National Science Foundation through Grant No. GP-9398.

(2) G. Wilke and H. Müller, *Justus Liebigs Ann. Chem.*, **629**, 222 (1960).

(3) G. Zweifel, N. L. Polston, and C. C. Whitney, *J. Amer. Chem. Soc.*, **90**, 6243 (1968).

(4) Glpc examination of the reaction mixtures revealed that coupling products derived from isobutyl–isobutyl or isobutyl–hexenyl dimerization were formed in small amounts.