Table I. Activation and Thermodynamic Parameters for Reaction of Ca^{2+} Ion with Cryptands in Water at 25°, $I = 0.1\ M$

Cryptand	k_f, M^{-1} sec^{-1}	$\Delta H_f^{\ddagger}$, kcal mol^{-1}	$\Delta S_f^{\ddagger}$, cal mol^{-1} deg^{-1}	k_d, sec^{-1}	$\Delta H_d^{\ddagger}$, kcal mol^{-1}	$\Delta S_d^{\ddagger}$, cal mol^{-1} deg^{-1}
1	6.6×10^{3a}	7.5	−15	0.26^a	8.2	−33
2	1.2×10^4	10.6	−4	1.9×10^{-3}	17.8	−11
3	1.6×10^2	7.8	−22	0.10	2.7	−54

Cryptand	K,^{b} M^{-1}	ΔH,^{b} kcal mol^{-1}	ΔS,^{b} cal mol^{-1} deg^{-1}	K,^{c} M^{-1}	ΔH,^{c} kcal mol^{-1}	ΔS,^{c} cal mol^{-1} deg^{-1}
1	2.5×10^4	−0.7	+18	2.5×10^4 $(3.7 \times 10^4)^d$	−0.2 $(-0.2)^d$	+20 $(+20)^d$
2	6.2×10^6	−7.1	+7	9.0×10^6	−2.7	+23
3	1.6×10^3	+5.1	+32	6.3×10^2	0	+13

[a] Reference 1 cites values for $k_f \geqslant 10^3$ and $k_r \approx 0.1$ at 25° by a potentiometric method. [b] From kinetic data, $K = k_f/k_d$; $\Delta H = \Delta H_f^{\ddagger} - \Delta H_d^{\ddagger}$; $\Delta S = \Delta S_f^{\ddagger} - \Delta S_d^{\ddagger}$. [c] From potentiometric and calorimetric studies in 0.04–0.08 M NMe_4Br solutions ref 3 and 18. [d] Reference 19.

the predominant form in solution, and the equilibrium is established rapidly,[12] the rate of reaction could be substantially reduced, e.g.

$$\text{exo-exo} \overset{K_c}{\rightleftharpoons} \text{endo-endo} \xrightarrow[\text{Ca}^{2+}]{k_{\text{Ca}^{2+}}} \text{Ca}\cdot(\text{endo-endo})^{2+} \tag{3}$$

from which $k_f \sim K_c k_{Ca^{2+}}$. If $k_{Ca^{2+}}$ is a "normal" rate constant[5,13] $\sim 10^9\ M^{-1}\ \text{sec}^{-1}$, K_c would need to be $\sim 10^{-5}$ to produce the observed formation rate constants. The values of K_c might be expected to vary for the three cryptands leading to some variation in k_f. For a particular cryptand, and a series of reactions with different metal ions M^{n+}, k_f might parallel the substitution lability of M^{n+}.[5,13] Preliminary data[1,4] support this for the reaction of **1**, $Ca^{2+} \sim Sr^{2+} < Ba^{2+}$; $Na^+ < K^+ < Rb^+$. This reactivity pattern does not support the idea of a rate-limiting conformational change associated with complexation (as proposed in the Ca^{2+}, antamanide case).[14]

It has been suggested[1,8] that the transition state involves little loss of water bound to metal ion. The activation entropies support this idea. While ΔS is positive in all three cases, reflecting the fact that most,[15] if not all,[16] of the water coordinated to the metal is lost on complex formation,[17] $\Delta S_f^{\ddagger}$ is negative and $\Delta S_d^{\ddagger}$ is more negative. While some water may be lost on going to the transition state, this could be balanced by a considerable decrease in ligand internal entropy resulting in $\Delta S_f^{\ddagger}$ being negative. The remaining water molecules are then stripped off as rapid insertion into the bicyclics occurs. In the reverse direction, the water molecules are again coordinated to Ca^{2+}, giving a large negative $\Delta S_d^{\ddagger}$.

Acknowledgment. This research was supported in part by a research grant from the National Science Foundation Grant No. GP 36783 and MPS75-00679.

References and Notes

(1) J. M. Lehn, *Struct. Bonding* (*Berlin*), **16**, 1 (1973).

(2) Y. M. Cahen, J. L. Dye, and A. I. Popov, *J. Phys. Chem.*, **79**, 1289 (1975), see footnote 3.

(3) J. J. Cristensen, D. J. Eatough, and R. M. Izatt, *Chem. Rev.*, **74**, 351 (1974).

(4) J. M. Lehn, J. P. Sauvage, and B. Dietrich, *J. Am. Chem. Soc.*, **92**, 2916 (1970).

(5) H. Diebler, M. Eigen, G. Ilgenfritz, G. Maass, and R. Winkler, *Pure Appl. Chem.*, **20**, 93 (1969).

(6) G. Schwarzenbach and H. Gysling, *Helv. Chim. Acta*, **32**, 1314 (1949).

(7) G. Geier, *Helv. Chim. Acta*, **51**, 94 (1968).

(8) J. M. Ceraso and J. L. Dye, *J. Am. Chem. Soc.*, **95**, 4432 (1973).

(9) J. M. Lehn and M. E. Stubbs, *J. Am. Chem. Soc.*, **96**, 4011 (1974).

(10) J. P. Kintzinger and J. M. Lehn, *J. Am. Chem. Soc.*, **96**, 3313 (1974).

(11) Y. M. Cahen, J. L. Dye, and A. I. Popov, *J. Phys. Chem.*, **79**, 1292 (1975).

(12) H. E. Simmons and C. H. Park, *J. Am. Chem. Soc.*, **90**, 2428 (1968), interpret ^1H NMR spectrum of a macrobicyclic diamine with bridgehead nitrogens, 1,10-diazabicyclo[8.8.8]hexacosane, in $CFCl_3$ in terms of a rapid conformational change (possibly nitrogen inversion) with $k = 1.4 \times 10^7\ \text{sec}^{-1}$ at 25°C.

(13) R. G. Wilkins, The Kinetics of Complex Formation, Dahlem Conference on Nature of Seawater, E. D. Goldberg, Ed., Berlin, March 1975, p 397.

(14) W. Burgermeister, T. Wieland, and R. Winkler, *Eur. J. Biochem.*, **44**, 305 (1974).

(15) B. Metz, D. Moras, and R. Weiss, *J. Am. Chem. Soc.*, **93**, 1806 (1971).

(16) B. Metz, D. Moras, and R. Weiss, *Chem. Commun.*, 217 (1970).

(17) Although loss of water tends to make ΔS positive, some cryptates show negative ΔS (several alkali metals with these cryptands) and $\Delta S \sim 0$ for the reaction of Ba^{2+} with **1**.[3,18,19] This reflects the importance of such factors as ordering of the ligand on complexation, solvation of the complex, and solvation of the ligand. The importance of ligand solvation has been emphasized recently (F. P. Hinz and D. W. Margerum, *Inorg. Chem.*, **13**, 2941 (1974)).

(18) J. M. Lehn and J. P. Sauvage, *Chem. Commun.*, 440 (1971).

(19) G. Anderegg, *Helv. Chim. Acta*, **58**, 1218 (1975).

V. M. Loyola, R. G. Wilkins*
Department of Chemistry
New Mexico State University
Las Cruces, New Mexico 88003

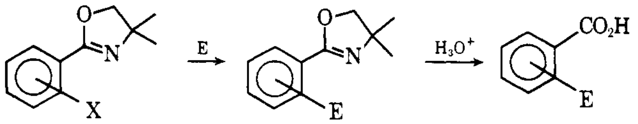
R. Pizer
Department of Chemistry
Brooklyn College of the City University of New York
Brooklyn, New York 11210

Received July 28, 1975

Oxazolines. XXII. Nucleophilic Aromatic Substitution on Aryl Oxazolines. An Efficient Approach to Unsymmetrically Substituted Biphenyls and *o*-Alkyl Benzoic Acids

Sir:

In previous reports, we[1a,b] and others[1c] have demonstrated that aryl oxazolines **1a**, **1b** may be transformed into their metalated derivatives **1c**, **1d** which are capable of elaboration with a variety of electrophiles, E, to substituted aryl oxazolines **2**. Hydrolysis in aqueous acid provides a route to ortho-, meta-, and para-substituted benzoic acids. We now report that aryl and alkyl substitution may be readily accomplished via a nucleophilic mode by displacement of an *o*-methoxy group with organometallics in 2-(*o*-methoxyphenyl)oxazolines **4**. Treatment of **4a**[2] or **4b** with either Grignard reagents (Et_2O-THF, 25°) or organolithium reagents (THF, −45°) gave good-to-excellent yields of the 2-substituted phenyl oxazolines **5** which were hydrolyzed to the corresponding biphenic acids **6** (R = aryl) or alkyl benzoic acids **6** (R = alkyl). The results of various organometallic reactions with **4a** and **4b** are tabulated in Table I. It is interesting to note that in those instances where the aryl lithium reagents gave poor yields of **5**, the corresponding Grignard reagent proved to be much more effective (compare entries 6 and 7, 8 and 9). For alkyl metallics, there appears to be little difference in the yield of aromatic substitution (entries 10 and 11) although the alkyl

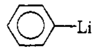
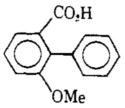
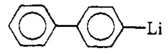
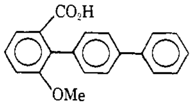
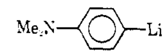
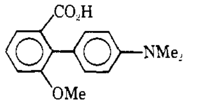
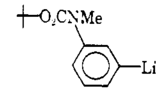
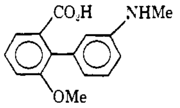
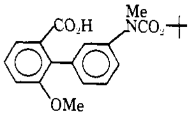
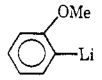
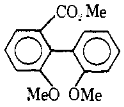
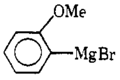
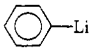
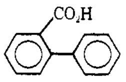
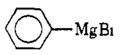
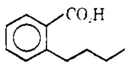
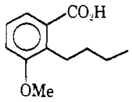
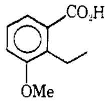
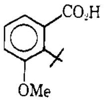


1a, X = *o*-, *m*-, *p*-Br
1b, X = H
1c, X = MgBr
1d, X = Li

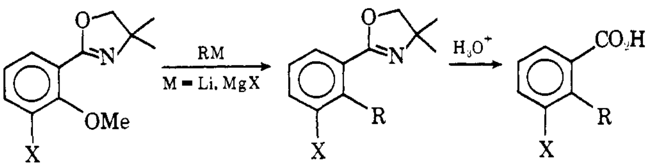
2
(E = alkyl, allyl, D, acyl, thioalkyl)

3

Table I. Nucleophilic Substitution of 2-(*o*-Methoxyphenyl)oxazolines 4 Leading to Biphenic and Benzoic Acids 6

Entry	Aryl oxazoline	RM[a]	Reaction temp (°C)	% 5[b]	Products 6	Yield (%)[b,c]
1	4a		−45	~100		70
2	4a		−45	73		48
3	4a		−45	66		69[f]
4	4a		−45	51		36
5						65[d]
6	4a		−45	13[e]		78
7	4a		25	95		
8	4b		0	45		75
9	4b		25	95		
10	4b	*n*-BuMgCl	25	85		74
11	4a	*n*-BuLi	−45	98		85
12	4a	EtLi	−45	88		73
13	4a	*t*-BuLi	−45	~100		43[d]

[a] Commercially available organolithium reagents (1.05–1.30 equiv) were used in entries 1, 8, 11–13 whereas the other reagents were prepared in situ from the corresponding bromides and *n*-BuLi (−78°, 15 min) prior to addition of 4a or 4b. Grignard reagents (2.0–3.0 equiv) were added as ether or THF solutions to a THF solution of 4a or 4b. [b] Yields are for distilled, recrystallized, or chromatographed products and have not been optimized. All products were amply characterized by the usual analytical techniques. [c] Hydrolysis of 5 was performed in refluxing 4.5 *N* hydrochloric acid (12 hr) excepted as noted. [d] Hydrolysis performed on the methiodide salt of 5 in methanolic NaOH. [e] 30% unreacted 4a was also recovered. [f] Isolated as the hydrochloride salt.

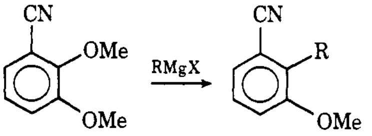


4a, X = MeO
4b, X = H

5

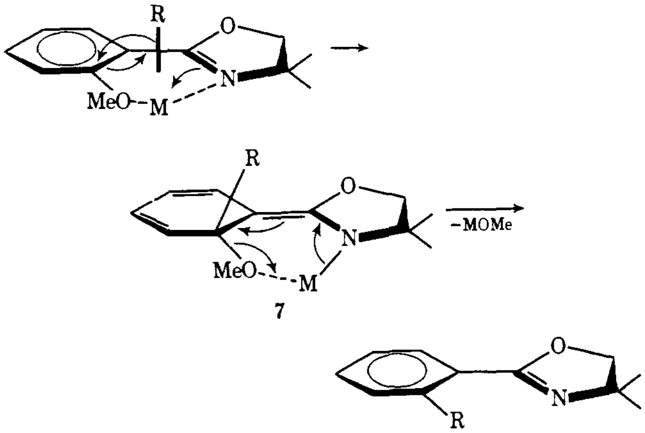
6, R = alkyl, aryl
X = MeO, H

lithiums react at considerably lower temperatures. Nucleophilic aromatic substitutions have been explored extensively with a variety of "activating" groups present on the aromatic substrate,[3] but none allows alkylation or arylation to proceed with the generality witnessed in this report. The studies of Richtzenhain[4] in the 1940's which described the addition of Grignard reagents to 2,3-dimethoxybenzonitrile is worthy of note (eq 1). The reaction proceeded in 50-80%



(1)

yields with primary and secondary alkyl Grignard reagents, but was poor (~30%) for aryl Grignard and failed with *tert*-butyl. In all cases, addition to the nitrile function was a troublesome side reaction. Furthermore, the reaction proceeded only when the vicinal methoxy groups were present. Fuson[5] has extensively studied nucleophilic substitution on highly hindered *o*-methoxybenzophenones utilizing Grignard and organolithium reagents and the yields rarely exceeded 50%, whereas Risaliti[6] reported nucleophilic displacement of aryl methoxyl groups in azobenzenes using aryl Grignard reagents. In all previous observations involving methoxyl group displacement by organometallics, a mechanism has been invoked which involved complexation of the metal to both the methoxyl group and the "activating" group followed by 1,4-addition. The oxazoline moiety provides an excellent activating group and it is undoubtedly a more effective ligand than the cyano or the azo function (the latter requires a specific conformation in order to be effective) due to the ready chelation which leads to the enamine-like intermediate **7**.



7

The present method was also shown to provide excellent latitude with respect to the synthesis of biphenyls and benzoic acids possessing labile substituents. The oxazoline moiety may be removed under alkaline conditions when substituents are acid-sensitive (entries 5 and 13). In both of these examples acid cleavage of **5** resulted in loss of the *t*-Boc group and *tert*-butyl group, respectively. However, if **5** is converted to its methiodide salt (MeI, 5-7 equiv. 25°, 15 hr) and then treated with 1:1 methanol-20% NaOH (reflux, 15 hr), the *t*-Boc-substituted biphenyl and *o*-(*tert*-butyl)benzoic acid are isolated without event.

Studies are continuing to determine the scope of this novel nucleophilic substitution which promises to provide a versatile approach to various biphenyl and monoaryl derivatives.[7,8]

Acknowledgment. The authors wish to thank the National Science Foundation and the National Institutes of Health for financial support, and Mr. David Muffly for technical assistance.

References and Notes

(1) (a) A. I. Meyers, D. L. Temple, D. Haidukewych, and E. D. Mihelich, *J. Org. Chem.*, **39**, 2787 (1974); (b) A. I. Meyers and E. D. Mihelich, *ibid.*, in press; (c) H. W. Gschwend and A. Hamdan, **40**, 2008 (1975).

(2) The oxazolines **4a** and **4b** were readily prepared in 75–85% yield from the corresponding *o*-methoxy- or 2,3-dimethoxybenzoic acids and 2-amino-2-methyl-1-propanol according to the procedure given in ref 1a (above) for 2-(*o*-bromophenyl)-4,4-dimethyl-2-oxazoline.

(3) (a) J. F. Bunnett, *Q. Rev., Chem. Soc.*, **12**, 1 (1958); (b) S. D. Ross, *Prog. Phys. Org. Chem.*, **1**, 31 (1963); (c) J. Sauer and R. Huisgen, *Angew. Chem.*, **72**, 294 (1960).

(4) H. Richtzenhain and P. Nippus, *Chem. Ber.*, **82**, 408 (1949), and earlier references cited therein.

(5) R. C. Fuson, *Adv. Organomet. Chem.*, **1**, 221 (1964).

(6) S. Bozzini, A. Risaliti, and A. Stener, *Tetrahedron*, **26**, 3927 (1970), and earlier references cited.

(7) The known decarboxylation of aromatic acids should provide further unsymmetrically substituted biphenyls; cf. H. Rappoport, A. R. Williams, and M. E. Cisney, *J. Am. Chem. Soc.*, **73**, 1414 (1951).

(8) Since oxazoline-methiodide salts are readily converted to aldehydes, this method may also lead to aryl aldehydes (cf. I. C. Nordin, *J. Heterocycl. Chem.*, **3**, 531 (1966)) and these in turn may be decarbonylated efficiently; K. Ohno and J. Tsugi, *J. Am. Chem. Soc.*, **90**, 99 (1968).

(9) Eastman Kodak Fellow, 1974–1975.

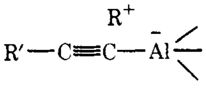
A. I. Meyers,* Edward D. Mihelich[9]
Department of Chemistry, Colorado State University
Fort Collins, Colorado 80523
Received August 11, 1975

A Convenient Method for the Tertiary Alkyl-Alkynyl Coupling via Organoalanes

Sir:

We wish to provide a solution to a long-pending problem of developing a direct and satisfactory procedure for the tertiary alkyl-alkynyl coupling. In our study directed toward the synthesis of terpenoids and related compounds, it became desirable to be able to introduce a quaternary carbon in a position adjacent to an alkyne group. No general and satisfactory method permitting direct tertiary alkyl-alkynyl coupling appeared available,[1] the reaction of alkynylmetals containing lithium, magnesium, or certain transition metals with tertiary alkyl halides being dominated by elimination and other side reactions.

The following facts and reasoning led us to investigate the feasibility of using alkynylalanes as intermediates. (1) Tertiary carbocations are reasonably stable with respect to elimination under nonbasic or weakly basic conditions.[2] (2) Certain trisubstituted aluminum compounds not only promote the formation of carbocations from the corresponding halides and sulfonates but transform the anion residues into much weaker bases. (3) Alkynylaluminum derivatives might be particularly suited for effecting the tertiary alkyl-alkynyl coupling via an electrostatically directed substitution at the α alkynyl carbon involving the ion pair **1**.



$$\overset{R^+}{}\; R'{-}C{\equiv}C{-}\overset{-}{Al}\!\lessgtr$$

1

We have indeed found that trialkynylalanes, readily obtainable from the corresponding alkynyllithiums and anhydrous aluminum chloride, undergo a remarkably clean reaction with tertiary alkyl halides to produce cross-coupled products in high yields (eq 1, X = Cl, Br, or sulfonate).

$$RX + (R'C{\equiv}C)_3Al \xrightarrow[0°]{(CH_2Cl)_2} RC{\equiv}CR' \qquad (1)$$

As indicated by the following examples, the reaction appears general with respect to the structural types of tertiary alkyl halides. The yields reported here are based on alkyl halides or sulfonates. Two of the three acetylene molecules that are not utilized can be recovered nearly quantitatively, if the reaction mixture is worked up soon after the completion of the desired coupling. These results sharply contrast with those observed in the reactions of tertiary alkyl halides with alkynes and certain alkyne derivatives in the presence of Friedel-Crafts catalysts,[1c] where the yields of the coupling products are, in general, disappointingly low. It is worth pointing out that the reaction permits a novel geminal alkyl-alkynylation of ketones which should find a number of applications in the natural product synthesis.

The development of the successful procedure is critically dependent on proper selection of alkynylalanes and solvents. Alkynyldialkylalanes, such as those derived from diethyl-