and $-C_{\epsilon 3}$'s. Since all the relevant coupling constants are essentially equal, the variations in peak intensities may reflect differences in ^1H T_2's which in turn are sensitive to differences in modes of internal motion. Indeed our failure to observe the Trp(63)-C_γ-$H_{\delta 1}$ cross peak is not unexpected, for it is known that the Trp(63)-$H_{\delta 1}$ resonance is broadened by conformational exchange.[12]

In summary the natural abundance ^{13}C shifts of the nonprotonated aromatic carbons in proteins can be readily determined by ^1H detection of long-range heteronuclear correlations provided the ^1H T_2's are long enough to preserve multiplet structure in the ^1H spectra. By taking advantage of the coupling properties of aromatic spin systems and choosing delay times appropriately, one can also impose a pattern on the 2D spectra that permits partial assignments without a priori assumptions about chemical shifts. Moreover if the proton assignments are known, one can, as demonstrated here for lysozyme, assign the quarternary aromatic carbon spectra completely without additional experimentation.

Supplementary Material Available: Fully annotated versions of the 2D long-range and one-bond $^1H\{^{13}C\}$ correlation spectra of the aromatic region of lysozyme (Figures S1 and S2) and a table of ^{13}C chemical shifts (4 pages). Ordering information is given on any current masthead page.

A Regioselective Synthesis of 2,3-Disubstituted-1-naphthols. The Coupling of Alkynes with 1,2-Aryldialdehydes Promoted by $NbCl_3(DME)$

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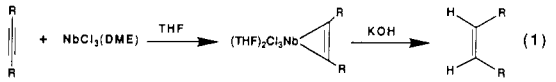
Recently we described a new synthesis of 2-amino alcohols via the reductive coupling of aldimines with aldehydes or ketones promoted by the niobium(III) reagent, $NbCl_3(DME)$.[1] Low-valent, early transition-metal halides, including some previously reported niobium(III) compounds are known to react with alkynes to give alkyne complexes.[2] $NbCl_3(DME)$ behaves in a similar fashion as shown in eq 1.[3] Hydrolysis of these complexes with

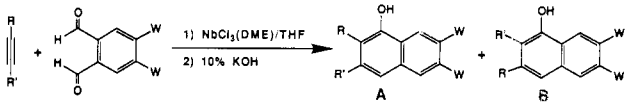


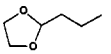
(1)

aqueous potassium hydroxide yields *cis*-olefins, indicating that such species may function as a source of 1,2-alkene dianions.[2c,4] Herein, we report a convenient and regioselective synthesis of 2,3-disubstituted-1-naphthols via the coupling of alkynes with 1,2-aryldialdehydes promoted by $NbCl_3(DME)$.

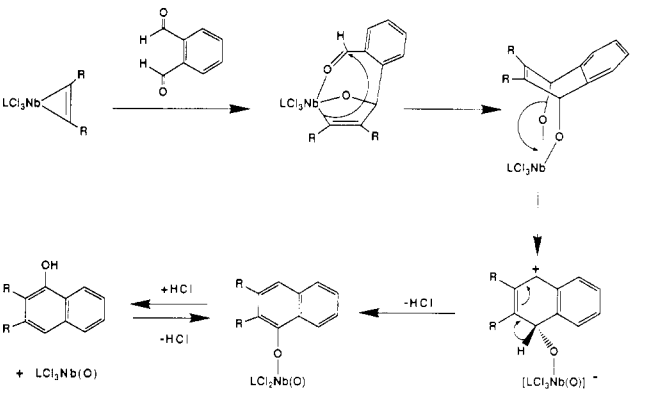
Niobium alkyne complexes are generated in situ by adding the alkyne to $NbCl_3(DME)$ in tetrahydrofuran and gently refluxing the solution for 10-14 h. These species may also be formed at room temperature employing longer reaction times. Addition of phthalic dicarboxaldehyde to complexes derived from symmetrical alkynes (R = R′, eq 1) leads to, after workup, the 1-naphthol products shown in Table I (entries 1-2). A mechanism that accounts for these products is proposed in Scheme I. Stepwise

Table I



entry	R	R′	W	A:B	yield (%)
1	Ph	Ph	H		87
2	*n*-Pr	*n*-Pr	H		81
3	4-MeOPh	Ph	H	3:1	61
4	Me	*i*-Pr	H	2:1	75
5	Me	*t*-Bu	H	>99:1	60
6	Me	Me_3Si	H	>99:1	70
7	Ph	(*t*-Bu)Me_2Si	H	>99:1	83
8	Ph	(*t*-Bu)Me_2Si	OMe	>99:1	66
9	TBDMSO$(CH_2)_2$	Me_3Si	H	>99:1	62
10		Me_3Si	H	>99:1	57
11	Ph	Me_3Si		>99:1	53

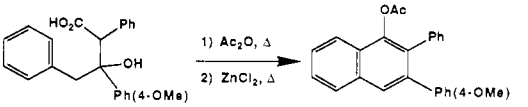
Scheme I



insertion of each formyl group into a metal-carbon bond would lead to the cyclic 1,4-dialkoxy-1,4-dihydronaphthalene intermediate. Ionization of one of the carbon-oxygen bonds followed by proton loss then leads to product.[5] When (4-methoxyphenyl)-phenylacetylene is used in this reaction a 3:1 mixture of isomeric naphthols is obtained (entry 3). The major isomer (established by independent synthesis of the minor isomer[6]) is that predicted from the mechanism proposed in Scheme I where the 4-methoxyphenyl group is better able to stabilize the developing positive charge than the unsubstituted phenyl ring. We have also confirmed by ^1H NMR experiments[7] that naphthol (or naphthoxide) is generated during the course of the reaction (i.e., before workup) as depicted in Scheme I. The driving forces behind this reaction are formation of an aromatic ring and a niobium-oxo group.

When trialkylsilyl-substituted alkynes are employed, good yields of a single regioisomer, namely the 3-(trialkylsilyl)-2-alkyl(or aryl)-1-naphthols, are obtained. The regiochemical assignments for entries 6 and 7 were established by preparing 2-methyl-[8] and 2-phenyl-1-naphthol,[9] respectively, by removal of the trialkylsilyl group (CF_3CO_2H[10]). The well-established synthetic utility of aryltrialkylsilanes[11] makes these products particularly attractive

(1) Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551.
(2) (a) Walborsky, E. C.; Wigley, D. E.; Roland, E.; Dewan, J. C.; Schrock, R. R. *Inorg. Chem.* **1987**, *26*, 1615. (b) Cotton, F. A.; Roth, W. J. *Inorg. Chim. Acta* **1984**, *85*, 17. (c) Theopold, K. H.; Holmes, S. J.; Schrock, R. R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22(12)*, 1010. (d) Cotton, F. A.; Hall, W. T. *Inorg. Chem.* **1981**, *20*, 1285. (e) Cotton, F. A.; Hall, W. T. *Inorg. Chem.* **1980**, *19*, 2352. (f) Greco, A.; Pirinoli, F.; Dall'Asta, G. *J. Organomet. Chem.* **1973**, *60*, 115.
(3) Details of these complexes will be described elsewhere.
(4) For examples of the relatively rare and unstable 1,2-dilithoalkenes, see: (a) Maercker, A.; Theis, M. *Top. Curr. Chem.* **1987**, *138*, 1. (b) Maercker, A.; Graule, T.; Girreser, U. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 167. (c) Levin, G.; Jagur-Grodzinski, J.; Szwarc, M. *J. Am. Chem. Soc.* **1970**, *92*, 2268.
(5) Analogous to acid-catalyzed dehydration of *cis*-1,4-dihydroxy-1,4-dihydronaphthalene: Jeffrey, A. M.; Yeh, H. J. C.; Jerina, D. M. *J. Org. Chem.* **1974**, *39*, 1405.
(6) Mondeshka, D. M.; Angelova, I. G. *Rev. Roumaine de Chemie* **1974**, *19*, 1759.



(7) Reactions were carried out in NMR tubes with purified alkyne complexes.
(8) An authentic sample was obtained from Aldrich Chemical Company.
(9) Barton, D. H. R.; et al. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2657.
(10) Diercks, R.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 3150.

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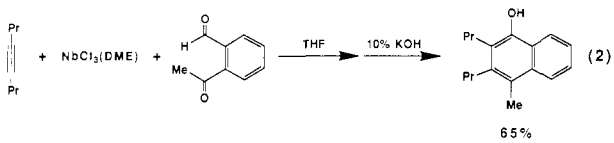
starting materials for the synthesis of more complicated polyaromatic compounds. The origin of the regioselection in these reactions appears to be due, in part, to steric effects (possibly dictated by the coordination environment of the metal) since 3,3-dimethyl-2-butyne gives rise to an analogous regioisomer (entry 5).[12]

Ketones (e.g., acetophenone) do not insert into the metal–carbon bonds of these niobium alkyne complexes. However, the stepwise mechanism in Scheme I suggested that the initial insertion of the formyl function in a 2-formylaryl ketone would lead to an intermediate that might facilitate coordination and insertion of the ketone into the second metal–carbon bond. As shown in eq 2,



the reaction between 4-octyne, $NbCl_3(DME)$, and 2-formylacetophenone in tetrahydrofuran leads to a good yield of 4-methyl-2,3-di-*n*-propyl-1-naphthol. Unfortunately, using (trimethylsilyl)phenylacetylene in a similar reaction only provided low yields of the desired naphthol along with a variety of other products. This can be rationalized by assuming that the formyl group selectively inserts into the least hindered metal–carbon bond,[13] forcing the keto group to react with the more hindered metal–carbon bond. The second insertion would therefore be slowed down allowing for secondary reactions to occur.

Sterically hindered alkynes such as bis(trimethylsilyl)acetylene fail to provide significant yields of the desired naphthols under the standard conditions, and terminal alkynes are consumed in cyclotrimerization reactions when reacted with $NbCl_3(DME)$.[14] We have also found that trialkylstannylalkynes do not appear to form stable alkyne complexes. Improved yields for all of the reactions discussed are usually obtained when 1.5 equiv of $NbCl_3(DME)$/alkyne are employed. A general experimental for the formation of 1-naphthols via the coupling of alkynes with 1,2-aryldialdehydes promoted by $NbCl_3(DME)$ is provided below. All reactions were carried out under a nitrogen atmosphere.

1-Naphthol Synthesis. A dry 250-mL flask was charged with $NbCl_3(DME)$[15] (2.0 g, 6.9 mmol) and tetrahydrofuran (ca. 100 mL). A tetrahydrofuran solution (ca. 5 mL) of alkyne (6.9 mmol) was then added (via syringe), and the stirred mixture was gently refluxed for 12 h. The reaction mixture was cooled to 0 °C, and a tetrahydrofuran solution (ca. 5 mL) of the dialdehyde (4.6 mmol) was added via syringe. The reaction was stirred for 1.5 h and then poured into a separatory funnel and treated with potassium hydroxide (10% w/v, 100 mL). The mixture was shaken until the aqueous layer was nearly colorless and then extracted with ether (3 × 100 mL). The combined ether layers were dried briefly over $MgSO_4$ and filtered. The ether was removed in vacuo yielding the crude product which was purified by flash chromatography[16] (silica gel, 230–400 mesh, hexane/ethyl acetate).

Acknowledgment. S.F.P. is grateful to the National Institutes of Health (GM38735-02), the National Science Foundation for a Presidential Young Investigator Award (Grant No. CHE-8552735), and Eli Lilly and Company for financial support.

Supplementary Material Available: NMR, IR, and mass spectral data and C, H, and N analysis information for all naphthols (5 pages). Ordering information is given on any current masthead page.

(11) (a) Sibi, M. P.; Shankaran, K.; Alo, B. I.; Hahn, W. R.; Snieckus, V. *Tetrahedron Lett.* **1987**, *28*, 2933. (b) Effenberger, F.; Spiegler, W. *Chem. Ber.* **1985**, *118*, 3900. (c) Trost, B. M.; Yoshida, J. *Tetrahedron Lett.* **1983**, *24*, 4895. (d) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983; Chapter 8. (e) Chan, T. H.; Fleming, I. *Synthesis* **1979**, 761.

(12) Confirmed by obtaining 2-methyl-1-naphthol after removing the *tert*-butyl group with $AlCl_3$/toluene (Tashiro, M. *Synthesis* **1979**, 921).

(13) We have observed such regioselective insertions when adding 1 equiv of a monoaldehyde to these niobium–alkyne complexes.

(14) Similar results have been obtained with other niobium(III) and tantalum(III) complexes: Cotton, F. A.; Hall, W. T.; Cann, K. J.; Karol, F. J. *Macromolecules* **1981**, *14*, 233.

(15) $NbCl_3(DME)$ was prepared as described in ref 1. Alternatively, it may be purchased from the Aldrich Chemical Company.

(16) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Solvent Effects in Intramolecular Diels–Alder Reactions of 2-Furfuryl Methyl Fumarates: Evidence for a Polar Transition State[1]

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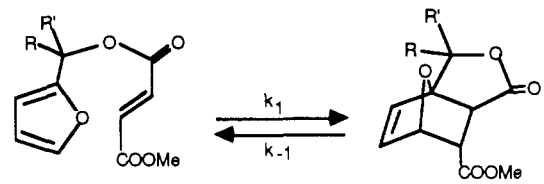
The Diels–Alder reaction proceeds via the concerted but nonsynchronous formation of the two new σ bonds.[2] For this reason, a large degree of charge separation is not developed in the transition state, and such cycloadditions are relatively insensitive to changes in solvent polarity.[2] In fact Berson and co-workers developed a parameter to measure solvent polarity, Ω, which was based on the difference in the endo/exo product ratio of the intermolecular Diels–Alder reaction of methyl acrylate with cyclopentadiene in various solvents.[3] However, the overall rates for the cycloadditions did not differ greatly with solvent polarity.[2,3] We now wish to report significant rate enhancement of the intramolecular Diels–Alder reaction of 2-furfuryl methyl fumarates **1** by the use of polar solvents.

Recently we described experiments which eliminated angle compression (the "Thorpe–Ingold effect") as the major reason for the *gem*-dialkyl effect in the cyclization of 2-furfuryl methyl fumarates.[4] Our results showed that in this reaction in which a three-atom tether leads to the formation of a five-membered ring, namely **2**, conformational changes with dialkyl substitution



1a	R = R' = H	**2a**
1b	R = H R' = Me	**2b**
1c	R , R' = $(CH_2)_2$	**2c**
1d	R , R' = $(CH_2)_3$	**2d**
1e	R = R' = Me	**2e**

("reactive rotamer effect") were more important in causing the large rate acceleration.[4] During these studies, we had occasion to examine the effect of solvent on the intramolecular cycloadditions of the furfuryl fumarates **1a–e**, which proceed at 25 °C to give cleanly the lactone cycloadducts **2a–e** as the sole reaction

(1) Presented at the 196th National Meeting of the American Chemical Society, Los Angeles, CA, September 1988; paper ORGN 191.

(2) (a) For an excellent review of the mechanistic aspects on the Diels–Alder reaction, including solvent effects, see: Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 779. (b) For earlier work, see: Wassermann, A. *Diels–Alder Reactions*; Elsevier: Amsterdam, 1965.

(3) Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.

(4) Jung, M. E.; Gervay, J. *Tetrahedron Lett.* **1988**, *29*, 2429.

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