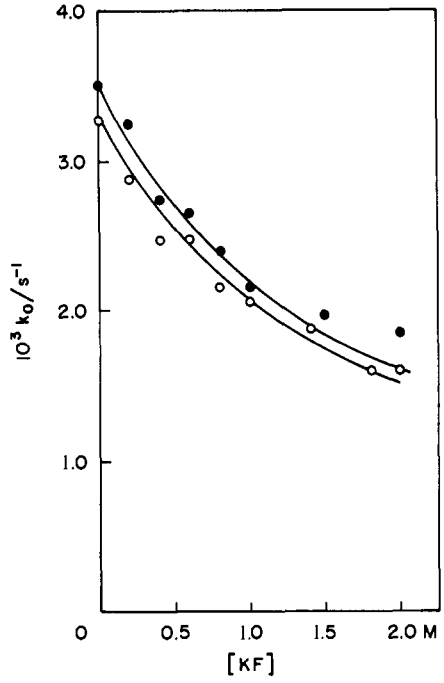

Figure 1. Dependence on potassium fluoride concentration of the hydrolysis of *p*-(dimethylamino)benzoyl fluoride in H_2O (●) and in D_2O (○) at 25 °C with ionic strength = 2.0 maintained with potassium chloride. The solid lines are calculated from eq 2.

Table I. Effects of Salts and Organic Solvents on the Hydrolysis of *p*-(Dimethylamino)benzoyl Fluoride[a]

salt/solvent	concn, M	ionic strength	10^3k_o, s^{-1}
no salt	0	0	3.5
$NaClO_4$	1.0	1.0	4.6[b]
NaCl	1.0	1.0	4.5[b]
KCl	1.0	1.0	3.9[b]
NaBr	1.0	1.0	4.6[b]
$NaNO_3$	1.0	1.0	4.0[b]
Na_2SO_4	0.33	1.0	3.8[b]
	0.6	1.8	3.8[b]
	1.0	3.0	3.9[b]
KH_2PO_4/K_2HPO_4(1:9)	0.36	1.0	3.9
	1.0	2.8	4.7
NaF	0.9	0.9	2.9
KF	1.0	1.0	2.5
HCOONa	1.0	1.0	4.2[c]
CF_3COONa	1.0	1.0	3.1[c]
CH_3COONa	1.0	1.0	3.0[c]
EtCOONa	1.0	1.0	2.5[c]
MeOH	1.0	0.02	2.8[b]
	1.0	1.0[e]	3.5[b]
CF_3CH_2OH	1.0	0.01	2.9[d]
	1.0	1.0[e]	3.0[d]
CH_3CH_2OH	1.0	0.02	2.5[b]
	1.0	1.0[e]	2.2[b]
CH_3CN	1.0	0.02	2.9[b]
	1.0	1.0[e]	2.3[b]
CH_3CONH_2	1.0	0.02	2.1[b]
	1.0	1.0[e]	2.3[b]

[a] At 25 °C. [b] In the presence of 0.01 M potassium phosphate, 50% dianion. [c] At ≈pH 6.5. [d] In the presence of 0.01 M sodium acetate, 90% base. [e] Ionic strength was maintained with NaCl.

Inhibition by fluoride ion is not a specific salt effect on the hydrolysis of **1**, on the basis of the following observations: Among the 13 salts examined (Table I), only NaF, KF, and some RCOONa inhibit, even though F^-, $RCOO^-$, HPO_4^{2-}, and SO_4^{2-} have similar properties,[8] including their basicity and their effect on the OH vibration frequency, ^1H chemical shift, reorientation time, and self-diffusion coefficient of water. The $HCOO^-$ ion does not inhibit; the inhibition by CF_3COO^-, CH_3COO^-, and $CH_3CH_2COO^-$ ions may be attributed to a medium effect of the nonpolar group because large rate decreases are caused by 1.0 M CH_3CN, CH_3CONH_2, CF_3CH_2OH, MeOH, and EtOH (Table I). Therefore, there is specific inhibition by fluoride ion.

The entropies of activation for hydrolysis in water are −12.3 eu for methyl chloride and −26.2 eu for methyl fluoride.[9] The large sensitivity to nonpolar organic cosolvents (Table I) and the entropies of activation for the hydrolysis of methyl halides suggest that fluoride ion requires strong solvation in the transition state for solvolysis. The entropy of activation for the hydrolysis of **1**, −12 eu, calculated from rate constants at five different temperatures between 10 and 45 °C, could be accounted for mainly by solvation of the leaving fluoride ion. The entropy of activation due only to the molecularity of the transition state could be zero or positive, which is consistent with a monomolecular mechanism.

The rate constants for hydrolysis are 10^4k_o = 39 s^{-1} for **1**, 2.6 s^{-1} for **2**, and 18 s^{-1} for **3**.[7] The negative ρ value for **1** and **2**, the effects of fluoride ion, and the solvent isotope effects show that **1** behaves differently than **2** and **3**. The hydrolysis of **1** exhibits the characteristics that are expected for hydrolysis through an acylium ion mechanism (eq 1).

(8) (a) Gordon, J. E. *The Organic Chemistry of Electrolyte Solutions*; Wiley: New York, 1975; pp 174-209. (b) Collins, K. D.; Washabaugh, M. W. *Q. Rev. Biophys.* **1985**, *18*, 323-422.

(9) Robertson, R. E *Prog. Phys. Org. Chem.* **1967**, *4*, 213-280.

A Reductive Cyclization of 1,6- and 1,7-Enynes

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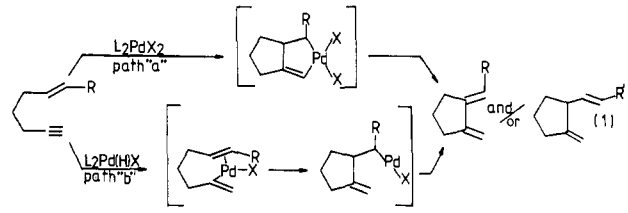
Intramolecular carbametalation reactions of enynes and diynes appear to be highly promising approaches for cyclization under extremely mild conditions.[1-4] A palladium-based method has the advantage of being truly catalytic and offering the prospect of controlling the regioisomeric nature of the product (i.e., a 1,3- or 1,4-diene) as in eq 1 depending largely upon the olefin sub-



stituent R.[5] As illustrated in eq 1, two mechanisms appear to

(1) Intramolecular carbalkylation–carbonylation using stoichiometric cobalt complexes has become known as the Pauson–Khand reaction. See: Khand, I. U.; Knox, G. R.; Pauson, P. L.; Watts, W. E.; Foreman, M. I. *J. Chem. Soc., Perkin Trans. 1* **1973**, 977. Schore, N. E.; Croudace, M. C. *J. Org. Chem.* **1981**, *46*, 5436. Billington, D. C.; Pauson, P. L. *Organometallics* **1982**, *1*, 1560. Magnus, P.; Principe, L. M. *Tetrahedron Lett.* **1985**, *26*, 4851.

(2) For stoichiometric titanium-mediated reductive cyclizations, see: Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422. This method is reported to fail with terminal acetylenes.

(3) For a stoichiometric zirconium-mediated reductive cyclization, see: Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, 107, 2568. Negishi, E.; Cederbaum, F. E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.

(4) For Pd- and Rh-catalyzed cyclizations of dienes, see: Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubbu, A.; Scott, R. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1745. In the Pd reactions, use of HCl in refluxing chloroform is required. The same group has reported cyclizations of vinyl bromides onto olefins by using Pd catalysts. See: Grigg, R.; Stevenson, P.; Worakun, T. *Chem. Commun.* **1984**, 1073.

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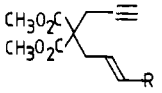
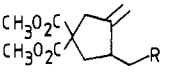
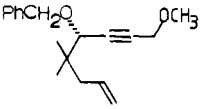
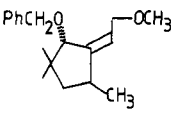
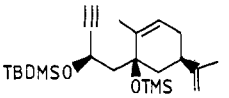
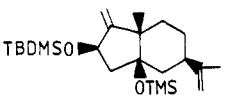
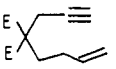
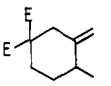
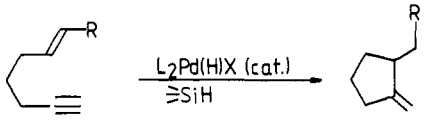
Table I. Reductive Cyclization of 1,6-Enynes[a]

entry	enyne	silane	solvent	product[e]	yield
	 **6**			 **7**	
1	**6**, R = 	PMHS	C_6H_6	**7**, R = 	96%
2	**6**, R = $CH_2OTBDMS$	PMHS	C_6H_6	**7**, R = $CH_2OTBDMS$	88%
3	**6**, R = $CH_2OTBDMS$	$(C_2H_5)_3SiH$	C_6H_6	**7**, R = $CH_2OTBDMS$	59%
4	**6**, R = $CH(OAc)_2$	PMHS	C_6H_6	**7**, R = $CH(OAc)_2$	75%
5	**6**, R = $CH(OAc)_2$	$(C_2H_5)_3SiH$	C_6H_6	**7**, R = $CH(OAc)_2$	83%
6[b]		PMHS	$ClCH_2CH_2Cl$		73%[d]
7[b]		PMHS	$ClCH_2CH_2Cl$		90%
8[c]		PMHS	C_6H_6		79%

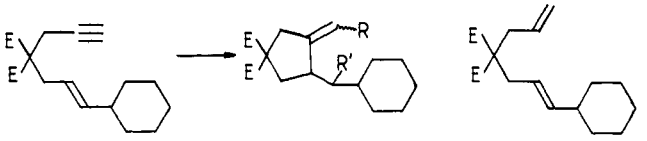
[a] All reactions employed 2.5 mol % $(dba)_3Pd_2{\cdot}CHCl_3$, 5 mol % ligand, 1 equiv HOAc, and 10 equiv of hydride from PHMS in the indicated solvent at room temperature in which the acetic acid was added by syringe pump over a 6-h period unless otherwise indicated. Tri-*o*-tolylphosphine was employed as lignd unless otherwise stated. [b] *N,N'*-Bis(benzylidene)ethylenediamine (**5**) employed as ligand. [c] No ligand employed but two additional portions of catalyst required due to deposition of Pd black. [d] The product is a single diastereomer which is tentatively assigned as trans based upon mechanistic consideration and NOE experiments. [e] All new compounds have been fully characterized and elemental composition has been determined by combustion analysis and/or high resolution mass spectroscopy.

be the most likely candidates to account for the observations to date and we set about to test the feasibility of each. In the course of studying the feasibility of path "b", we uncovered a facile reductive cyclization according to eq 2 that apparently is initiated by the addition of $L_2Pd(H)X$ to the acetylene.



(2)

In order to identify the nature of the C–Pd bonding in the intermediates of the initial enyne cyclization, we chose to effect reduction with a hydride source that would not reduce $Pd(OAc)_2$ but would effect hydride transfer at a later stage. Thus, we treated enyne **1** with 2.5 mol % $Pd(OAc)_2$ and 5 mol % tri-*o*-tolylphosphine in the presence of 10 equiv of hydride from polymethylhydrosiloxane (PMHS) and 2 equiv of allyl acetate (CH_2Cl_2, room temperature). Two products formed, the desired reductive cyclization product **2a** (55%) and the simple acetylation reduction product **3** (15%). To check the possibility that Pd(0)



1

2a R = R' = H
2b R = H, R' = D
2c R = D, R' = H
2d R = R' = D

3

was the active catalyst, $(dba)_3Pd_2{\cdot}CHCl_3$ (**4**) was substituted for palladium acetate. In the absence of allyl acetate, little, if any, reductive cyclization occurred. Addition of 2 equiv of allyl acetate to the Pd(0) reaction restored reactivity with production of **2a** and **3** in 62% and 26% yields, respectively. The requirement for stoichiometric quantities of allyl acetate suggests that a Pd(2+) rather than Pd(0) species is the active catalyst. At first glance, it would appear the two hydrogens should derive from the silicon hydride. Nevertheless, the same reaction using **4** as the source of palladium but replacing the polymethylhydrosiloxane with $(C_2H_5)_3SiD$ gave the reductive cyclization product with only 8% *d* at the vinyl position (δ 4.90 and 4.80) and 47% *d* at the saturated methylene carbon (δ 1.48, i.e., 1 D). Clearly, a mechanism via a palladacyclopentene as in path a, eq 1, was not responsible for the reductive cyclization of eq 2.

A dramatic effect occurred by adding 2 equiv of acetic acid to a reaction of enyne **1** and using 2.5 mol % **4**, 5 mol % tri-*o*-tolyphosphine, and 10 equiv of hydride from PMHS with or without additional allyl acetate. A single product **2a** was formed in nearly quantitative yield. In contrast to the effect of acetic acid, addition of HCl[4] led to almost no reaction at all. Use of acetic acid-*O-d* led to incorporation, on average, of 1 D per molecule in the vinyl position *only*. Using this new set of conditions but replacing PMHS with triethylsilane-d_1 gave **2b** with high incorporation of deuterium at only one of the diasterotopic methylene group hydrogens since the ^1H signal at δ 1.48 almost completely disappeared.

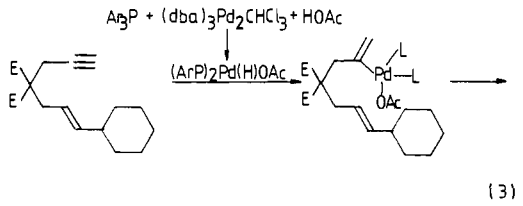
These results are in accord with a catalyst invoking the addition of acetic acid to Pd(0) as in eq 3. The absence of simple acetylene or olefin reduction products under these conditions suggests that the hydrosilane reduction of palladium occurs after cyclization as shown in eq 3. Assuming a cis addition[7] and a reductive elimination with retention of configuration accounts for the observation that only one of the two diastereotopic protons of the side-chain methylene group is replaced by deuterium when a silicon deuteride is employed.

The synthetic utility of this reductive cyclization was explored as summarized in Table I. Several features are notable. First, in addition to tri-*o*-tolylphosphine, *N,N'*-bis(benzylidene)-ethylenediamine (**5**) is an excellent ligand.[8] Second, equivalent

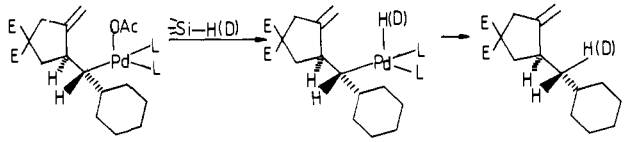
(5) (a) Trost, B. M.; Lautens, M. *J. Am. Chem. Soc.* **1985**, *197*, 1781; *Tetrahedron Lett.* **1985**, *26*, 4887. (b) Trost, B. M.; Chen, S.-F. *J. Am. Chem. Soc.* **1986**, *108*, 6053. (c) Trost, B. M.; Chung, J. Y. L. *J. Am. Chem. Soc.* **1985**, *107*, 4586.

(6) For a reduction using PMHS in a Pd(0) reaction, see: Keinan, E.; Greenspoon, N. *J. Org. Chem.* **1983**, *48*, 3545.

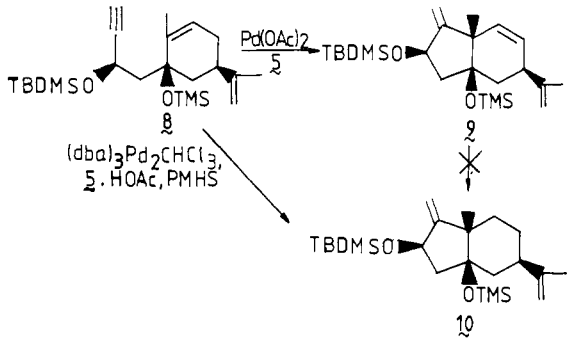
(7) Cf. Heck reaction, see: Heck, R. F. *Org. React.* **1982**, *27*, 345.



(3)



results are obtained by using triethylsilane or PMHS. In entry 3, some problems encountered in the chromatographic separation of dba resulted in a slightly lower yield. Third, allylic acetates are compatible (entries 4 and 5)—an observation also consistent with Pd(0) not being the active catalyst. Fourth, substituents on the acetylene (entry 6) as well as olefin (entries 1–5 and 7) are tolerated. Fifth, high diastereoselectivity may be observed. The product of entry 6 is a single diastereomer which has been tentatively assigned as trans on the basis of mechanistic considerations. Sixth, six-membered rings may be formed (entry 8). Seventh, the best yields are derived by a slow addition of 1 equiv of acetic acid via syringe pump to a reaction mixture containing the enyne, silane, catalyst, and ligand, all at room temperature. Normally, this reaction is complete within 6 h. This approach for reductive cyclization nicely complements the previous Pd(2+) enyne cyclizations to dienes by permitting chemoselective adjustment of the oxidation pattern. For example, it is now easy to convert **8** to either **9** or **10** but it would not be trivial to try to chemoselectively reduce **9** to **10**. The method also provides



diastereoselective incorporation of deuterium into methylene groups and can serve as a diastereoselective approach to highly substituted cyclopentanes. Mechanistically, this reaction is most consistent with involving a $L_2Pd(H)OAc$ (**11**) species which forms from **4** and acetic acid. To our knowledge, addition of a weak acid like acetic to Pd(0) has not been reported although the additions of strong acids are well-known.[9] An attempt to detect such a species by NMR spectroscopy by simply mixing **4**, ligand, and HOAc led to no observable differences in the spectrum from the reactants—a fact implying **11** can only form in an equilibrium which favors starting materials.

Acknowledgment. We thank the National Science Foundation and the National Institutes of Health General Medical Sciences for their generous support of our programs. A NATO Science Fellowship administered by the Royal Norwegian Council for Scientific and Industrial Research and a leave of absence from the University of Oslo provided support for part of the stay of F.R.

(8) D. Jebaratnam has established the utility of this ligand in other work; unpublished observations in these laboratories. Also see ref 5b.

(9) Maitlis, P. M.; Espinet, P.; Russell, M. J. H.; *Compr. Organomet. Chem.* **1982**, *6*, 250–252, 340–342.

N-Hydroxypyridine-2-thione Carbamates as Aminyl and Aminium Radical Precursors. Cyclizations for Synthesis of the Pyrrolidine Nucleus

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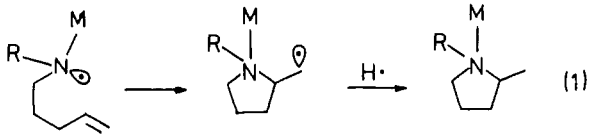
Received January 14, 1987

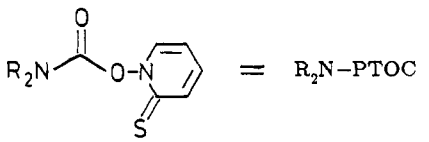
Recently there has been a growing interest in the applications of radical cyclization reactions in organic synthesis. Intramolecular C–C bond-forming reactions involving attack of a carbon radical on an alkene or alkyne have been used in the preparation of various carbocyclic and heterocyclic systems.[1] Neutral (aminyl, **1**) and protonated or complexed (aminium, **2**) nitrogen-centered radicals with δ-ϵ double bonds, while less well studied, can cyclize to give pyrrolidines (eq 1).[2] In this paper we demonstrate that *N*-



(1)

1 M = lone pair
2 M = H^+ or metal ion

hydroxypyridine-2-thione carbamates (**3**) are convenient sources



3, PTOC = ((1H)–pyridine–2–thione)oxycarbonyl

for both aminyl radicals and aminium cation radicals for intramolecular N–C bond-forming reactions. The ease of preparation of these precursors[3] and the mild conditions under which they produce either type of nitrogen-centered radical offer advantages over other routes to these radicals.[5]

The cyclization of *N*-butyl-4-pentenylaminyl radical (**5**) was studied as a model reaction.[7] Reactions were initiated by visible irradiation (150 W, tungsten filament lamp); after initiation, the radical chain processes shown in Scheme I were possible. Precursor **4** can react with a carbon-, tin-, sulfur-, or silicon-centered radical to give, after a decarboxylation step, radical **5**. Aminyl radical **5** can cyclize, apparently reversibly (see below), to carbon

(1) Examples are given in the following: *Selectivity and Synthetic Applications of Radical Reactions, Tetrahedron Symposium in Print, No. 22*; *Tetrahedron* **1985**, *41*, 3887–4303. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*; Pergamon: Oxford, 1986.

(2) (a) Stella, L. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 337–350. (b) Surzur, J.-M. In *Reactive Intermediates*, Abramovitch, R. A., Ed.; Plenum: New York, 1982; Vol. 2, Chapter 2. (c) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangements in Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980; Vol. 1, Essay 4.

(3) The preparation of carbamates **3** has been reported;[4a] the synthetic reactions are similar to those used in the preparation of *N*-hydroxypyridine-2-thione esters.[4b]

(4) (a) Newcomb, M.; Park, S.-U.; Kaplan, J.; Marquardt, D. J. *Tetrahedron Lett.* **1985**, *26*, 5651–5654. (b) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901–3924.

(5) Other routes to nitrogen-centered radicals involve radical chain reactions of *N*-chloroamines,[2a,b,6a] or *N*-nitrosamines,[6b] often in the presence of Brønsted or Lewis acids, the decomposition of tetrazenes,[6c] or the anodic oxidation of lithium dialkylamides.[6d]

(6) (a) Neale, R. S. *Synthesis* **1971**, 1–15. (b) Chow, Y. L.; Perry, R. A.; Menon, B. C.; Chen, S. C. *Tetrahedron Lett.* **1971**, 1545–1549. (c) Michejda, C. J.; Campbell, D. H.; Sieh, D. H., Koepke, S. R. In *Organic Free Radicals*; Pryor, W. A., Ed.; ACS Symposium Series 69, American Chemical Society: Washington, DC, 1978, pp 292–308. (d) Bauer, R.; Wendt, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 202–203.

(7) Alkylpentenylaminyl radicals from reactions of *N*-chloramines,[2a,b,8a] a tetrazene,[6c,8b] and lithium dialkylamides[8c,d] have been studied.

(8) (a) Broka, C. A.; Eng, K. K. *J. Org. Chem.* **1986**, *51*, 5043–5045. (b) Maeda, Y.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 328–331. (c) Tokuda, M.; Yamada, Y., Takagi, T.; Suginome, H.; Furusaki, A. *Tetrahedron Lett.* **1985**, *26*, 6085–6088. (d) Tokuda, M.; Yamada, Y.; Takagi, T.; Suginome, H. *Tetrahedron* **1987**, *43*, 281–296.

0002-7863/87/1509-3163$01.50/0