α-Amino Carbanions. Preparation, Metalation, and Alkylation of Enamidines. Synthesis of Piperidine and Pyrrolidine Natural Products and Homologation of Carbonyl Compounds

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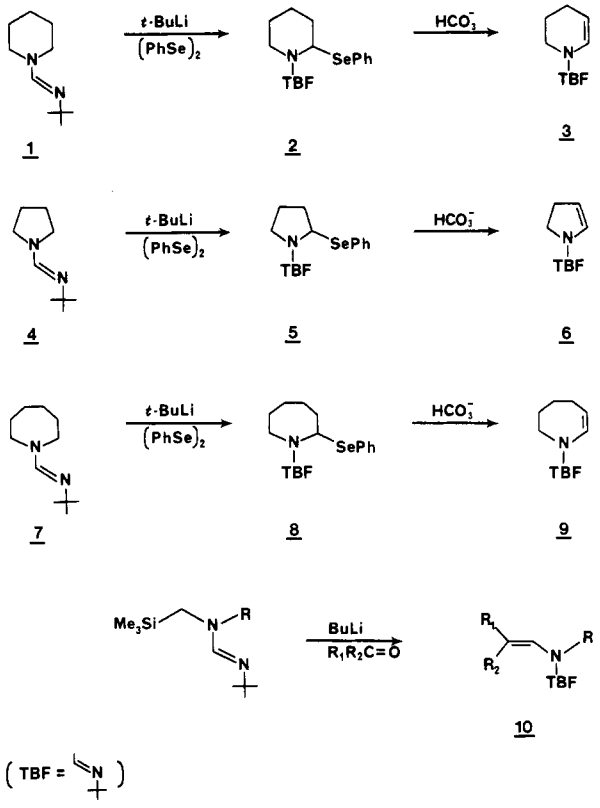
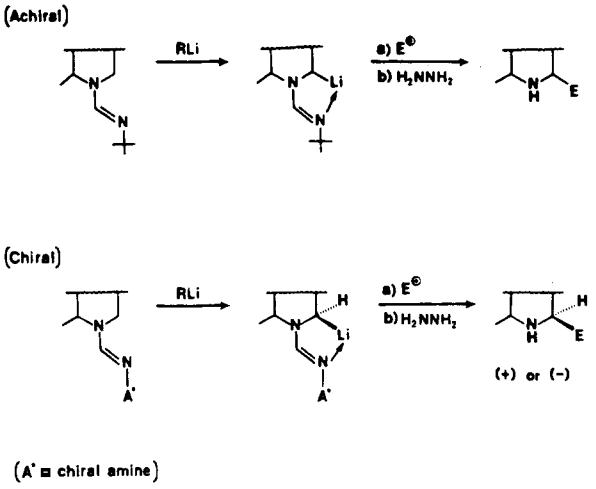
Saturated heterocycles, as their *tert*-butylformamidines, may be transformed into enamidines, by metalation–selenation–elimination. These enamidines are valuable precursors to 2-substituted, 2,4-disubstituted, and 2,4,6-trisubstituted pyrrolidines, piperidines, and perhydroazepines, prepared in a regiospecific manner. The method is demonstrated by the synthesis of solenopsin A and the red fire ant venom. The use of acyclic enamidines is displayed as a homologation reagent which converts carbonyl compounds to higher alkyl derivatives.

In our continuing studies on the synthetic utility of dipole stabilized anions derived from formamidines, which have produced α-substituted heterocycles[1] both in an achiral[2] and chiral[3] fashion (Scheme I), we have encountered another significant variation in this methodology. The ability of these α-lithio formamidines to undergo selenation and subsequent elimination provides enamidines which have proven to be rich precursors to a number of polysubstituted heterocycles as well as homologated carbonyl compounds. It is the purpose of this report to describe the chemistry of enamidines **3**, **6**, **9**, and **10**, which are readily obtainable in high yields.



Formation of *tert*-butylformamidines from simple heterocyclic bases such as piperidine, pyrrolidine, and perhydroazepine, **1**, **4**, and **7**, respectively, has already been described[2a] and their metalation–alkylation characteristics have been discussed. It was found, however, that metalation of these three heterocycles with *tert*-butyllithium followed by addition of diphenyl diselenide generates the α-selenophenyl derivatives **2**, **5**, and **8** which readily undergo elimination at or near room temperature by mere treatment with bicarbonate to give the cyclic enamidines in 70–90% yields. The facile elimination of phenylselenol is obviously due to its acetal-like nature. The enamidine, **10**, was prepared by an alternative route, also facile in nature, and will be described in full detail (vide infra).

Scheme I



Metalation of enamidine **3** was accomplished by using *n*-butyllithium or *tert*-butyllithium in 4:1 ether/THF providing complete metalation to **11** after 1 h. Addition of various electrophiles gave generally excellent yields of 2-substituted enamidine **12**. Metalation of α-*N*-vinyl compounds have been reported previously for indoles[4b] and β-(dimethylamino)acrylonitrile.[4a] When allylic halides were introduced into the α-lithio species **11**, the yields were poor (30–40%). However, transformation of **11** to its pentynylcuprate **13**, and then addition of allyl bromide gave the 2-allyl product **14** in 76% yield. Addition of enolizable compounds, whose acidity is relatively high (pK_a <25) failed to produce elaborated enamidines and only starting material **3** was recovered.

The alkylated enamidines were transformed into their tetrahydropyridine derivates **15** by removing the formamidine moiety with hydrazine, acetic acid, and ethanol and stirring at room temperature for 3–4 h. The crude

(1) For a review on dipole-stabilized carbanions adjacent to nitrogen, see: Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78* 275. Beak, P., Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471–523.

(2) (a) Meyers, A. I.; Edwards, P. D.; Reiker, W. F.; Bailey, T. R. *J. Am. Chem. Soc.* **1984**, *106*, 3270. (b) Meyers, A. I.; Loewe, M. F. *Tetrahedron Lett.* **1984**, *25*, 2642. (c) Edwards, P. D.; Meyers, A. I. *Tetrahedron Lett.* **1984**, *25*, 939.

(3) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 117. Meyers, A. I.; Fuentes, L. M.; Kubota, Y. *Tetrahedron* **1984**, *40*, 1361. Meyers, A. I.; Boes, M.; Dickman, D. A. *Angew. Chem.* **1984**, *23*, 458–459.

(4) Schmidt, R. R.; Speer, H. *Tetrahedron Lett.* **1981**, *11*, 4259. Sundberg, R. J.; Russell, H. F. *J. Org. Chem.* **1973**, *38*, 3324.

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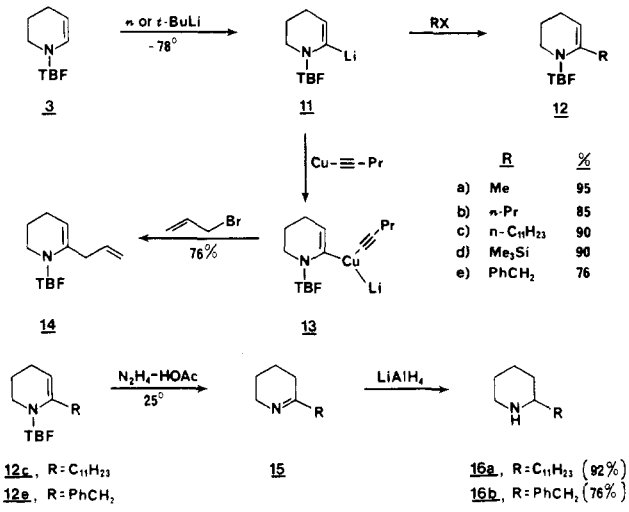
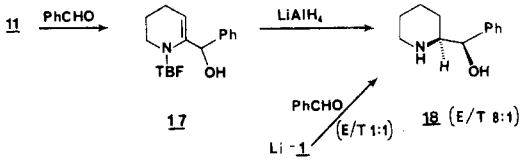
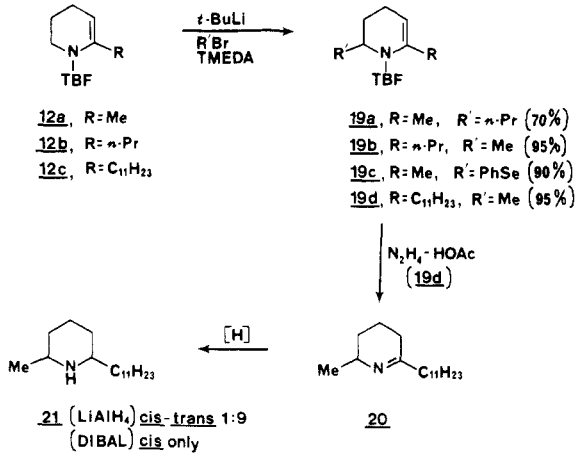


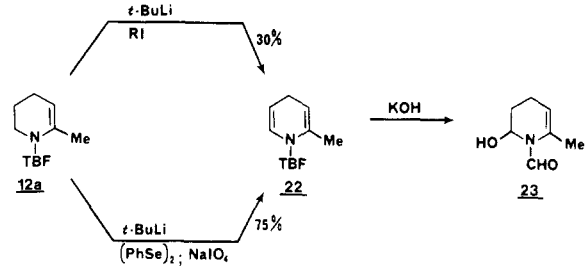
products **15** were subjected to reduction with lithium aluminum hydride affording the 2-substituted piperidines **16** in good yields. Although this transformation can be carried out by direct metalation of piperidineformamidines, via their cuprates,[2a] the route given here possesses a distinct stereochemical advantage. Thus, when **11** was treated with benzaldehyde, a 90% yield of **17** was realized and, after lithium aluminum hydride reduction, gave the amino alcohol **18** in a diastereomeric ratio of 8:1.[5] However, when the saturated piperidine formamidine **1** was lithiated and treated with benzaldehyde, only a 1:1 mixture of **18** was obtained after reduction with lithium aluminum hydride. The major difference appears to be in the intermediacy of the Δ^1-imine intermediate (e.g., **15**) which is reduced with a high degree of stereoselectivity. This is in accord with the report by Stork[5] who described high selectivity in the reduction of cyclic imines.



Further transformation of the alkylated enamidines **12** was also achieved by a second metalation which occurred at the 6-position to give, after addition of alkyl halides, excellent yields of the disubstituted products, **19**. The

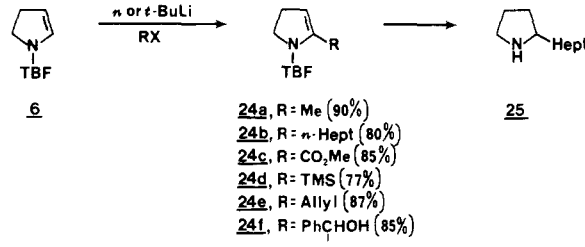


use of *tert*-butyllithum was required to effect this transformation and no metalation was detected at the allylic position in **12**. Furthermore the lithio derivative of **12** required addition of TMEDA or use of the pentynylcuprate prior to addition of alkyl bromide, otherwise, electron-transfer reactions compete, as was noted previously.[2a] In the absence of the pentynylcuprate or TMEDA, the major product (30%) was the dihydropyridine **22**. Only in the use of methyl iodide to give **19b** was it unnecessary to employ TMEDA or pentynylcopper. When the 2-undecyl-6-methyl derivative **19d** was subjected to hydrazinolysis the cyclic imine **20** was obtained in 95% yield and reduced either with lithium aluminum hydride or diisobutyl aluminum hydride producing solenopsin A, **21** (trans) in a 9:1 ratio, and the cis derivative, **21**, respectively. The stereoselectivity compares favorably with that reported by Yamamoto[6,7] for the synthesis of solenopsin A. It should be noted that Yamamoto's approach to solenopsin involved reversal of the alkyl groups on the cyclic imine.



Returning to the single election transfer observed during the alkylation of lithiated **12a** wherein the dihydropyridine **22** was formed as one of the products, the reaction could be made much more efficient if **12a** was lithiated and selenated and then oxidized with sodium periodate. In this fashion, a 76% isolated yield of dihydropyridine **22** was realized. The latter was found to be resistant to further metalation in an attempt to effect lithiation at the 2-methyl or the 6-vinyl position. However, aqueous alkali transformed **22** into the *N*-formylcarbinolamine **23**.

The enamidine **6** readily metalates with *n*- or *tert*-butyllithium and alkylates smoothly with methyl iodide, benzaldehyde, Me_3SiCl, or MeOCOCl. Similar to the



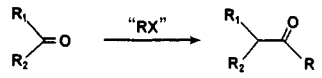
homologous enamidine, **3**, allyl bromide alkylation took place only when the pentynylcuprate was used. Hydrazinolysis of **24b**, followed by $LiAlH_4$ reduction gave 2-heptylpyrrolidine in 95% yield. For the alkylated enamidines **24**, they likewise underwent metalation at the α-methylene position and addition of ethyl iodide in the presence of TMEDA gave the disubstituted dihydropyrrole **26**. Hydrazine removal of the formamidine resulted in the cyclic imine which was reduced directly with $LAlH_4$ to the red fire ant venom, **27**[2a] as a 1:1 mixture of cis–trans isomers. Alternately, the 2-methyl enamidine **24a** was smoothly metalated with *tert*-butyllithium and treated with diphenyl diselenide. The resulting α-selenophenyl

(5) Stork, G.; Jacobson, R. M.; Levitz, R. *Tetrahedron Lett.* **1979**, 771.

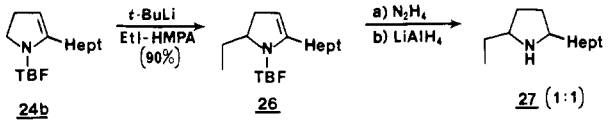
(6) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831.

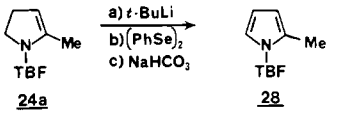
(7) MacConnell, J. G.; Blum, M. S. *Tetrahedron* **1971**, *26*, 1129.

Scheme II

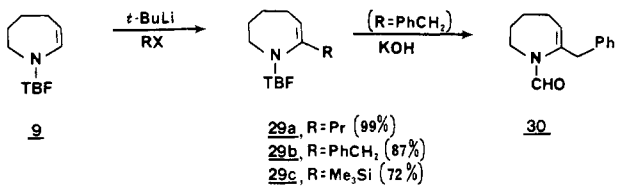


derivative was readily transformed into the pyrrole derivative **28** by bicarbonate. As in the case of the 1,4-dihydropyridine **22**, the pyrrole **28** was totally resistant to metalation under a variety of bases and solvents. The rigidity of the dihydropyridine and pyrrole probably inhibits the conformation necessary for the organolithium base, while complexed to the formamidine, to participate in proton abstraction.[8] This is in contrast to the more flexible enamidines **3** and **6** which readily undergo vinyl proton abstraction.



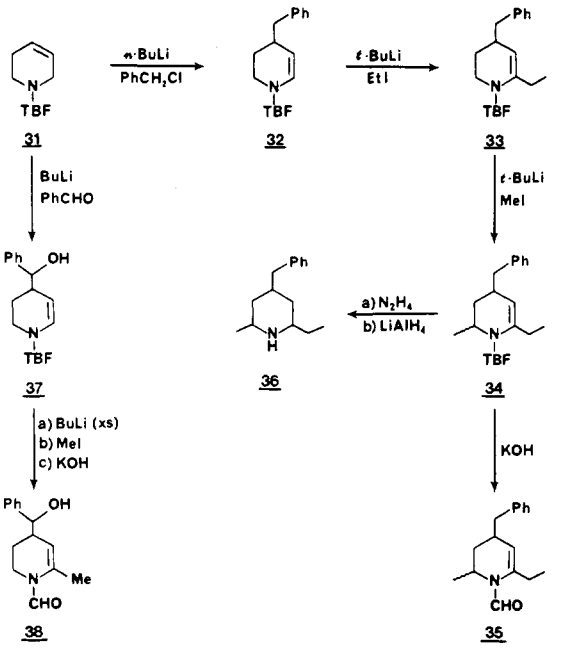


The seven-membered enamidine ring system, **9**, also displayed the expected metalation when treated with *tert*-butyllithium (ether/THF, 4:1) at −78 °C. Alkylation with several electrophiles (*n*-PrI, $PhCH_2Br$, and Me_3SiCl) proceeded in good yield. In the case of the 2-benzyl product **29b**, aqueous methanolic KOH transformed it smoothly to the *N*-formylazepine derivative **30**.



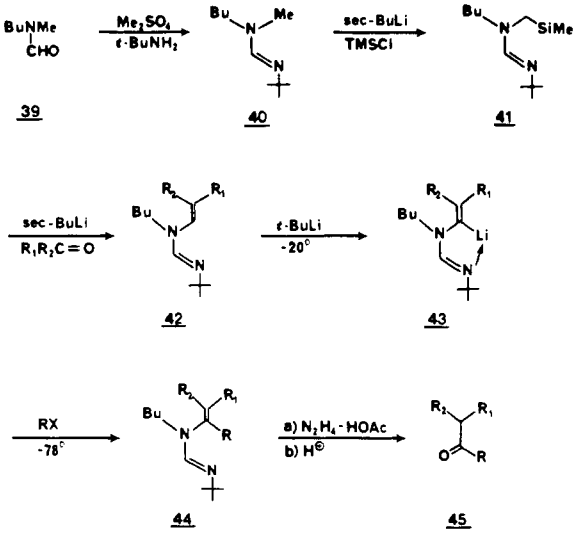
The forgoing adequately demonstrates that enamidines of various cyclic amines may be elaborated routinely to a host of alkylated derivatives under mild and convenient conditions to give alkylated products on either side of the ring nitrogen.

A further extension of the α-amino carbanion methodology was uncovered when the tetrahydropyridine formamidine, previously described,[2a] was shown to alkylate, not at the 2-position, but at the 4-position. Thus, metalation of **31**, was shown by earlier studies[2a] to metalate at the 2-position, yet alkylate predominately, via allylic transposition, to the 4-benzyl derivative **32**. The latter is now set to undergo vinyl deprotonation and indeed this occurred after metalation and treatment with ethyl iodide. The dialkyl enamidine **33** was formed in 96% yield. Once again, the α-methylene position could be metalated with *tert*-butyllithium and treatment with methyl iodide gave the trialkylated enamidine **34** as 1:1 mixture of diastereomers. Alkaline hydrolysis gave **35** in quantitative yield but the stereoisomers have not, as yet, been separated. Alternatively, hydrazinolysis of **34** gave the cyclic imine which was reduced with $LiAlH_4$ to **36** as a three component mixture (out of a possible four) in a ratio (HPLC) of 2.4:2.2:1. Thus, this methodology is capable of producing



2,4,6-trisubstituted piperidines by sequential and regiochemical substitution, albeit with poor stereoselectivity at this stage of our studies. When the tetrahydropyridine-formamidine **31** was metalated and treated with benzaldehyde, the 4-substituted carbinol **37** was produced exclusively[2a] as a mixture of erythro–threo isomers separable by radial chromatography. Metalation of a single diastereoisomer with 2.6 equiv of *t*-BuLi and 3.0 equiv of methyl iodide gave the 2-methyl derivative in 95% yield which was directly hydrolyzed to the formamide **38** in 80% yield. This sequence again demonstrated that 2- and 4-substitution on piperidine could be accomplished and presumably a third alkylation could be invoked.

Finally, a study was performed on acyclic enamidines to assess their synthetic utility. It was found that a unique homologation (Scheme II) could be carried out on a large scale in overall yields of 50–70%.[9] Commercially available formamide **39** was transformed by successive treatment

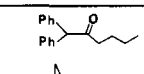
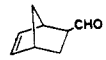
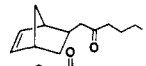
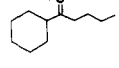
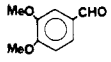
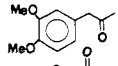
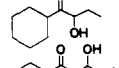
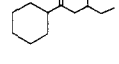
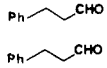
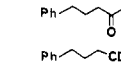
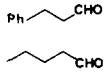
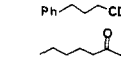
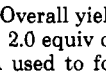
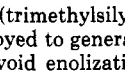


with dimethyl sulfate and *tert*-butylamine into the formamidine **40** on a 100-g scale. The latter was metalated with

(8) Meyers, A. I.; Reiker, W. F.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 2082.

(9) A preliminary report on this and other homologations of carbonyl compounds has appeared: Meyers, A. I., Jagdmann, G. E., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 877.

Table I. Homologation of Carbonyls via 41[a]

Carbonyl	Electrophile (R in 44)	Product	% Yield[a]	Mp[g], °C
$Ph_2C=O$	*n*-BuI		61[b]	155 156 SC[h]
	*n*-BuI		74	111-114 SC[i]
	*n*-BuI		64[d]	69-71 DNP[j]
	MeI		64	143-144 DNP[k]
			50	201-203 DNP[l]
			50	122-124 SC[m]
	MeI		67[e]	76-77 DNP[n]
	D_2O		87	110-112 DNP[o]
	*n*-BuI		71[f]	56-57 SC[p]

[a] (a) Overall yield based on [(trimethylsilyl)methyl]formamidine **41**. (b) 2.0 equiv of base employed to generate **43**. (c) 2.0 equiv of HMPA used to form **42**, to avoid enolization of cyclohexanone. (d) 1.8 equiv *sec*-BuLi employed in DME at −38 °C to form enamidine **42**. (e) Cleavage of **44** accomplished with 1,1-dimethylhydrazine. (f) Hydrazone from **44** cleaved with $Cu(OAc)_2 \cdot H_2O$. (g) These are for semicarbazones (SC) or 2,4-dinitrophenylhydrazones (DNP). (h) mp 159 °C [Billard, F. *Bull Soc. Chim. Fr.* **1921**, *29*, 429]. (i) Anal. Calcd for $C_{14}H_{23}NO$: C, 67.43; H, 9.30. Found: C, 6718; H, 9.49. (j) mp 70–71 °C [Nelson, N. K.; Norris, H. H. *J. Am. Chem. Soc.* **1953**. *75*, 3337]. (k) mp 144 °C [Binovic, K.; et al. *Chim. Ther.* **1968**, *3*, 313; *Chem. Abstr.* **1969**, *70*, 87171y]. (l) Anal. Calcd for $C_{16}H_{22}N_3O_5$: C, 54.85; H, 6.33. Found: C, 55.14; H, 6.46. (m) Anal. Calcd for $C_{12}H_{23}N_3O_2$: C, 59.72; H, 9.61. Found: C, 59.45; H, 9.33. (n) mp 78 °C [Clark, C. M.; Johnson, J. D. A. *J. Chem. Soc.* **1962**, 126]. (o) mp 110.5–112 °C (protio compound); 96.5% deuteriation by NMR [Overberger, C. G.; Herin, I. P. *J. Org. Chem.* **1962**, *27*, 417]. (p) mp 57–58 °C [Sharefkin, J. G.; Boghoisian, E. M. *Anal. Chem.* **1961**, *33*, 640].

sec-butyllithium at −20 °C and treated with Me_3SiCl affording the α-trimethylsilylformamidine **41** in 87–90% (50-g scale) and provided the pivotal starting material for this homologation. A variety of carbonyl compounds was introduced into the lithio salt of **41**, prepared from *sec*-butyllithium, and the Peterson olefination[10] allowed to proceed. An *E*/*Z* mixture of **42** usually resulted, but this was of no consequence since the subsequent process eliminates this stereochemical element. When **42** was treated with *tert*-butyllithium, the lithiated vinyl species **43** was produced which was alkylated with various electrophiles (Table I). The alkylation of **43** to **44** proceeded in 84–95% yields and the homologated carbonyl **45** was liberated by sequential treatment with hydrazine (to form the hydrazone of the carbonyl) and acetone. In this fashion the carbonyls **45** were produced in good yields as seen from Table I.

In summary, enamidines have shown their synthetic versatility in a number of ways described herein and in our earlier reports. Their ability to form C–C bonds both in a chiral and achiral sense prompts us to continue probing the unusual and efficient chemical characteristics which they display.

Experimental Section

General Procedure for Preparation of Enamidines 3, 6, and 9. To a 0.5 M solution of dry piperidine- (**1**)[2a] or perhydroazepine- (**7**)[2a] formamidines in 80% ether–THF, or dry pyrrolidine (**4**)[2a] in THF, cooled to −78 °C, was added 1.3 equiv of *tert*-butyllithium. The yellow solution was stirred at −20 °C for 1 h resulting in formation of a white precipitate in the case of the piperidine and perhydroazepine and a faint yellow solution in the case of the pyrrolidine formamidines. The reaction was cooled to −78 °C, 1.4 equiv of diphenyl diselenide was added, and the mixture was stirred at −78 °C for 1 h and slowly warmed to room temperature. The solution was poured into 150 mL of dichloromethane and 15 g of 1:1 potassium carbonate/sodium sulfate for each gram of starting formamidine and stirred for 24 h under argon. In the case of **8**, the solution was heated to reflux for 2 days. The solution was then filtered and the solvents removed at reduced pressure. The residue was taken up in 3 N HCl and washed with ether to remove the nonbasic impurities and the latter discarded. The aqueous layer was made basic (pH 12) with 20% NaOH and extracted several times with dichloromethane. The combined organic extracts were dried over potassium carbonate/sodium sulfate, and the solvents removed at reduced pressure. The crude enamidines were purified by bulb-bulb distillation.

3: oil, Kugelrohr, 45 °C (1.5 torr); yield 85–90%; IR (film) 2960, 2863, 1640, 1468, 1416, 1362, 1287, 1200, 1176, 1133, 1073, 995, 965, 770 cm^{-1}; ^1H NMR ($CDCl_3$) 1.17 (9 H, s), 1.5–2.3 (4 H, m), 3.50 (2 H, t, J = 6.0 Hz), 4.60 (1 H, m), 6.31 (1 H, dd, J = 2.0, 8.0 Hz), 7.32 (1 H, s); R_f 0.51 in 10% triethylamine/hexane. Anal. Calcd for $C_{10}H_{18}N_2$: C, 72.24; H, 10.91; N, 16.85. Found: C, 71.93; H, 11.26.

6: oil, Kugelrohr, 40 °C (1.5 torr); yield 60–70%; IR (film) 2970, 2865, 1640, 1615, 1412, 1365, 1203, 986, 902, 718 cm^{-1}; ^1H NMR ($CDCl_3$) 1.23 (9 H, s), 2.70 (2 H, m), 3.72 (2 H, t, J = 9.0 Hz), 4.91 (1 H, m), 6.28 (1 H, m), 7.65 (1 H, s); R_f 0.30 in 10% triethylamine/hexane. Anal. Calcd for $C_9H_{16}N_2$: C, 71.00; H, 10.60; N, 18.40. Found: C, 70.59; H, 10.86.

9: oil, Kugelrohr, 48 °C (1.5 torr); yield 99% as a pale yellow oil; IR (film) 3300, 2970, 2930, 2860, 1640, 1450, 1415, 1355, 1305, 1248, 1215, 1195, 1185, 1165, 1150, 1075, 700 cm^{-1}; ^1H NMR ($CDCl_3$) 1.14 (9 H, s), 1.67 (4 H, m), 2.13 (2 H, m), 3.53 (2 H, m), 4.76 (1 H, dt, J = 9.4 Hz), 6.34 (1 H, d, J = 9.4 Hz), 7.36 (1 H, s). Anal. Calcd for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18. Found: C, 72.96; H, 10.80.

General Procedure for Alkylation of Enamidines 3, 6, and 9 without Pentynylcopper. To a −78 °C, 0.5 M solution of the enamidines **3**, **6**, or **9** in 80% ether/THF, or THF for the alkylation of **6** with alkyl halides, was added 1.3 equiv of *n*-butyl or *tert*-butyllithium. The yellow solution was stirred at −20 °C for 1 h, resulting in formation of a white precipitate. The reaction mixture was cooled to −78 °C, 1.5 equiv of electrophile was added, and the mixture was stirred at −20 to 0 °C until TLC indicated consumption of starting material. The reaction mixture was poured into 3 N HCl and washed with ether and the latter discarded. The aqueous layer was made basic (pH 12) with 12% NaOH and was extracted several times with dichloromethane. The combined organic extracts were dried over potassium carbonate/sodium sulfate and the solvents removed at reduced pressure. The crude product was purified by bulb-bulb distillation or by preparative TLC on silica gel. For specific conditions see physical data below.

12a: oil; purified by bulb-bulb distillation (bp 65 °C (1.5 torr)); yield 95%; IR (film) 2975, 2940, 2870, 1670, 1640, 1380, 1354, 1320, 1218, 1173, 968, 843, 758, 742 cm^{-1}; ^1H NMR δ 1.18 (9 H, s), 1.70–2.10 (7 H, m), 3.60 (2 H, t, J = 6.0 Hz), 4.48 (1 H, m), 7.82 (1 H, s).

12b: oil; purified by bulb-bulb distillation (bp 68 °C (1.5 torr)); yield 85%; IR (CHCl) 2955, 2862, 1710, 1620, 1455, 1355, 1200, 1163, 904, 710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3 H, t, J = 6.0 Hz), 1.18 (9 H, s), 1.20–2.20 (8 H, m), 3.58 (2 H, t, J = 6.0 Hz), 4.55 (1 H, m), 7.73 (1 H, s).

12c: oil; purified by removal of starting material at reduced pressure (35 °C (0.5 torr)) and filtration through a pad of silica gel with 10% triethylamine/hexane; yield 90%; IR (film) 2960, 2920, 2855, 1635, 1465, 1409, 1355, 1375, 1210, 1167, 1068, 970, 880 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.92 (3 H, m), 1.18 (9 H, s), 1.30 (18 H, br s), 1.48–2.35 (6 H, m), 3.63 (2 H, m), 4.57 (1 H, t, J = 3.5 Hz), 7.78 (1 H, s); R_f 0.60 in 10% triethylamine/hexane.

12d: oil; purified by flash chromatography on silica gel, deactivating column with 10% triethylamine/hexane, eluting with 5% triethylamine/hexane; yield 90%; IR (CHCl) 2958, 1630, 1590,

(10) Hudrlik, P. F.; Peterson, D.; Chou, D. *Synth. Commun.* **1975**, *5*, 359.

1360, 1250, 1200, 1145, 1076, 1041, 835, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$) 0.24 (9 H, s), 1.24 (9 H, s), 1.47–2.27 (4 H, 7)e 3.64 (2 H, m), 5.06 (1 H, t, J = 4.0 Hz), 7.77 (1 H, s); R_f 0.59 in 10% triethylamine/hexane.

12e: oil; purified by preparative TLC on silica gel developing with 10% triethylamine/hexane; yield 76%; IR (film) 3038, 3024, 2960, 2855, 1635, 1495, 1452, 1375, 1355, 1209, 1165, 1076, 982, 883, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (9 H, s), 1.60–2.34 (4 H, m), 3.57 (4 H, m), 4.60 (1 H, t, J = 4.5 Hz), 7.12 (5 H, s), 7.57 (1 H, s); R_f 0.50 in 10% triethylamine/hexane.

24a: oil; purified by bulb-bulb distillation (bp 60 °C (1.5 torr)); yield 85–95%; IR (film) 2970, 2865, 1635, 1475, 1418, 1387, 1366, 1349, 1275, 1201, 1018, 985, 916, 713 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (9 H, s) 1.88 (3 H, br s), 2.53 (2 H, m), 3.79 (2 H, t, J = 9.0 Hz), 4.66 (1 H, m), 7.71 (1 H, s).

24b: oil; purified by removal of starting material at reduced pressure (40 °C (torr)) followed by filtration through a pad of silica gel with 10% triethylamine/hexane; yield 75–85%; IR (film) 2960, 2930, 2858, 1635, 1462, 1415, 1363, 1343, 1207, 1000, 917, 720 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, m), 1.17 (9 H, s), 1.28 (10 H, m), 1.87–2.66 (4 H, m), 3.67 (2 H, t, J = 9.0 Hz), 4.53 (1 H, m), 7.50 (1 H, s); R_f 0.45 in 10% triethylamine/hexane.

24c: oil; purification precluded by instability of compound; yield 85–90%; IR (film) 2960, 2865, 1720, 1635, 1610, 1443, 1335, 1305, 1185, 1160, 1039, 1003, 918, 780, 726 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (9 H, s), 2.42 (2 H, dt, J = 10 and 4.0 Hz), 3.62 (2 H, t, J = 10 Hz), 6.10 (1 H, t, J = 4.0 Hz), 8.63 (1 H, s).

24d: oil; purified by preparative TLC on silica gel developing with 10% triethylamine/hexane; yield 77%; IR (film) 2955, 2858, 1640, 1575, 1475, 1402, 1361, 1345, 1253, 1206, 1188, 999, 977, 926, 833, 750, 728, 687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.22 (9 H, s), 1.17 (9 H, s), 2.52 (2 H, dt, J = 10 and 2.0 Hz), 3.72 (2 H, t, J = 10 Hz), 5.10 (1 H, t, J = 2.0 Hz), 7.77 (1 H, s); R_f 0.61 in 10% triethylamine/hexane.

24f: solid; purification precluded by instability of compound; yield 85%; IR (film) 3225, 3060, 3025, 2960, 2860, 1950, 1880, 1810, 1625, 1450, 1410, 1205, 1025, 1005, 915, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.08 (9 H, s), 2.47 (2 H, dt, J = 9.0, 3.0 Hz), 3.78 (2 H, t, J = 9.0 Hz), 4.72 (1 H, t, J = 3.0 Hz) 5.32 (1 H, s), 7.22 (6 H, m).

29a: oil; purified by flash chromatography on silica gel eluting with 5% Et_3N in hexanes; IR (film) 2960, 2930, 2870, 1640, 1450, 1400, 1365, 1330, 1290, 1255, 1195, 1160, 1080, 975, 945 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 3.2 Hz), 1.16 (9 H, s), 1.60 (6 H, m), 2.13 (2 H, m), 3.56 (2 H, m), 5.09 (1 H, t, J = 5.7 Hz), 7.46 (1 H, s); ^{13}C NMR ($CDCl_3$) 13.5, 20.2, 24.6, 26.7, 27.7, 28.6, 29.2, 31.0, 37.5, 47.1, 53.0, 116.2, 144.6, 145.6.

29b: oil; purified by flash chromatography on silica gel eluting with 5% Et_3N in hexane; IR (film) 3020, 2960, 2920, 2850, 1640, 1495, 1450, 1360, 1330, 1250, 1190, 1155, 1090, 975, 945, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (9 H, s), 1.58 (4 H, m), 2.11 (2 H, m), 3.34 (2 H, m), 3.60 (2 H, s), 5.24 (1 H, t, J = 5.9 Hz), 7.21 (5 H, s), 7.39 (1 H, s).

29c: oil; purified by flash chromatography on silica gel eluting with 5% Et_3N in hexanes; IR (film) 2960, 2930, 2860, 1640, 1595, 1440, 1385, 1355, 1245, 1210, 1180, 1140, 1085, 970, 830, 775, 675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.12 (9 H, s), 1.16 (9 H, s), 1.60 (4 H, m), 2.17 (2 H, m), 3.52 (2 H, m), 5.64 (1 H, t, J = 5.7 Hz), 7.42 (1 H, s).

General Procedure for Alkylation of Formamidines 3 and 6 with Pentynylcopper. To a −78 °C, 0.5 M solution of enamidine **3** or **6** in 80% ether/THF was added 1.3 equiv of *tert*-butyllithium and the yellow solution stirred at −20 °C for 1 h resulting in formation of a white precipite. A suspension of pentynylcopper[2a] in a volume of THF equal to the volume of the original solution was added and the heterogenous mixture was stirred at −20 °C for an additional 0.5 h and cooled to −78 °C. To this mixture was added 1.6 equiv of electrophile and the mixture stirred at −20 °C for 4 h. The mixture was poured into 3 N HCl and stirred until all the *yellow* solid was digested and then the copper precipitated with a saturated solution of sodium sulfide. The aqueous mixture was filtered through Celite, washed with ether, and made basic (pH 12) with 20% NaOH. The aqueous layer was extracted with several portions of dichloromethane, and the combined organic extracts dried over potassium carbonate/sodium sulfate, filtered, and concentrated. For specific conditions on purification of the crude products see the physical data below.

14: oil; purified by preparative TLC on silica gel developing with 10% triethylamine/hexane; yield 70–75%; IR (film) 3080, 2960, 2865, 1635, 1470, 1415, 1380, 1355, 1333, 1320, 1255, 1268, 1212, 1166, 989, 913, 881, 762, 740, 711 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (9 H, s), 1.48–2.28 (4 H, m), 3.02 (2 H, d J = 5.0 Hz), 3.65 (2 H, t, J = 6.0 Hz), 4.58 (1 H t, J = 4.0 Hz), 4.95 (1 H, m), 5.18 (1 H, m), 5.48–6.22 (1 H, m), 7.78 (1 H, s); R_f 0.51 in 10% triethylamine/hexane.

24e: oil; purified by filtration through a pad of silica gel with 10% triethylamine/hexane; yield 87%; IR (film) 2960, 2855, 1635, 1407, 1363, 1345, 1259, 1204, 914 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (9 H, s), 2.50 (2 H, m), 2.93 (2 H, m), 3.73 (2 H, t, J = 9.0 Hz), 4.60 (1 H, m), 4.93 (1 H, m), 5.12 (1 H, m), 5.37–6.07 (1 H, m), 7.57 (1 H, s).

General Procedure for Alkylation of Enamidines 12a–e and 24b. To a −78 °C, 0.5 M solution of the 2-substituted enamidine **12a–e** or **24b** in THF was added *tert*-butyllithium. The yellow solution was stirred at −20 °C for 1.5 h and cooled to −78 °C. If alkyl bromides are used as electrophiles, a volume of TMEDA equal to the volume of the original solution was added and the solution stirred an additional 0.5 h prior to cooling to −78 °C. The electrophile was then added and the mixture stirred at −20 to 0 °C for 4 h. The reaction mixture was poured into 3 N HCl and washed with ether and the latter discarded. The aqueous layer was made basic (pH 12) with 20% NaOH and was extracted several times with dichloromethane. The combined organic extracts were dried over potassium carbonate/sodium sulfate and the solvents removed at reduced pressure. For specific conditions on purification of crude products see physical data below.

19a: oil; purified by preparative TLC on silica gel developing with 2/49/49 triethylamine/ether/hexane; yield 70%; IR (film) 2965, 2950, 2870, 1635, 1459, 1373, 1300, 1266, 1213, 1174, 965, 950, 755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, m), 1.17 (9 H, s), 1.80–2.18 (8 H, m), 1.95 (3 H, br s), 4.45 (1 H, m), 7.73 (1 H, s); ^{13}C NMR ($CDCl_3$) 14.25, 18.68, 19.21, 20.38, 24.11, 31.00, 32.17, 47.41, 53.36, 100.89, 132.83, 143.90; R_f 0.62 in 10% triethylamine/hexane.

19b: oil; purified by bulb-bulb distillation (bp 80 °C (1.5 torr)); yield 90%; IR ($CHCl_3$) 2961, 2865, 1625, 1460, 1378, 1357, 1200, 1175, 905, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.02 (6 H, m), 1.20 (9 H, s), 1.21–2.23 (8 H, m), 4.50 (1 H, m), 4.75 (1 H, m), 7.67 (1 H, s); R_f 0.60 in 10% triethylamine/hexane.

19c: oil; purification precluded by instability of compound; yield 80%; IR (film) 3050, 2960, 2860, 1665, 1638, 1577, 1473, 1438, 1368, 1210, 1168, 1108, 962, 888, 733, 686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (9 H, s), 1.81 (5 H, m), 2.04 (2 H, m), 4.54 (1 H, m), 6.34 (1 H, m), 7.04 (3 H, m), 7.47 (1 H, s), 7.61 (2 H, m).

19d: oil; purified by filtration through pad of silica gel with 10% triethylamine/hexane; yield 95%; IR (film) 2960, 2930, 2858, 1635, 1468, 1418, 1375, 1357, 1321, 1298, 1212, 1177 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.87 (3 H, m), 1.02 (3 H, d, J = 6.5 Hz), 1.15 (9 H, s), 1.26 (18 H, br s), 1.40–2.41 (6 H, m), 4.44 (1 H, m), 4.71 (1 H, m), 7.54 (1 H, s); R_f 0.62 in 10% triethylamine/hexane.

26: oil; purficiation precluded by instability of compound; yield 90%; IR (film) 2960, 2925, 2855, 1635, 1458, 1412, 1360, 1343, 1205, 988, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.89 (6 H, m), 1116 (9 H, s), 1.32 (10 H, m), 1.62–2.62 (6 H, m), 4.19–4.66 (2 H, m), 7.69 (1 H, s); R_f 0.54 in 10% triethylamine/hexane.

***N*-(*tert*-Butylformamidinyl)-2-methylpyrole (28).** The dihydropyrrole **24a** was subjected to the procedure described for **3**, **6**, and **9** and gave **2**, as oil: purified by bulb-bulb distillation (bp 60 °C (1.5 torr)); yield 70%; IR (film) 2962, 2865, 1669, 1638, 1618, 1488, 1417, 1371, 1335, 1304, 1210, 1198, 1118, 975, 884, 826, 780, 709 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.23 (9 H, s), 2.27 (3 H, s), 5.73 (1 H, m), 5.92 (1 H, t, J = 3.2 Hz), 7.08 (1 H, m), 7.87 (1 H, s); R_f 0.59 in 10% triethylamine/hexane. Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.12; H, 9.82; N, 17.06. Found: C, 72.80; H, 9.85.

Oxidation of Selenide 19c to Dihydropyridine 22 and Hydrolysis to Carbinolamide 23. To a 0.5 M solution of selenide **19c** in 50% aqueous THF was added 10 equiv of sodium bicarbonate, and then 5 equiv of sodium periodate and the mixture stirred at room temperature under argon for 12 h. The reaction mixture was partitioned between water and ether and the aqueous

layer extrated with several portions of ether. The combined etheral extracts were extracted with 2 portions of 3 N HCl and discarded. The aqueous extracts were washed with ether and and the latter discarded. The aqueous extracts were made basic (pH 12) with 20% NaOH, extracted several times with dichloromethane, and dried over potassium carbonate/sodium sulfate and the solvents removed at reduced pressure. The crude product was purified by bulb-bulb distillation (bp 65 °C (1.0 torr)) affording a 75% yield of **22** as a colorless oil: IR (film) 3000, 2960, 2860, 1625, 1369, 1295, 1178, 1112, 1080, 1058, 972, 912, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (9 H, s), 1.93 (5 H, m), 4.63 (1 H, m) 4.63–5.16 (1 H, m), 5.58 (1 H, t, J = 4.0 Hz), 7.38 (1 H, s). Formamidine **22** (1.0 mmol) was added to 5 mL of MeOH, 3 mL of H_2O, and 0.4 g of KOH for 12 h. The solution was partitioned between water and dichloromethane, the aqueous layer extracted several times with dichloromethane, and the solvents were removed at reduced pressure. The crude product was purified by preparative TLC on silica gel developing with 2:49:49 triethylamine/ether/hexane to afford a 65% yield of **23** as a white solid: mp 88–90 °C; IR (film) 3400, 3000, 2915, 2850, 1650, 1438, 1379, 1305, 1255, 1108, 1063, 968, 929, 690, 620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (7 H, m), 5.90 (1 H, m), 8.46 (1 H, s); ^{13}C NMR ($CDCl_3$) δ 16.93, 19.44, 26.62, 71.40, 108.48, 129.32, 160.09; R_f 0.36 in 10% triethylamine/ether acetate. Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92; O, 22.67. Found: C, 59.48; H, 7.82; N, 9.94.

General Procedure for Removal of Formamidines with N_2H_4/AcOH. To a 0.1 M solution of enamidine in 95% EtOH was added 8 equiv of hydrazine and 0.6 mL of AcOH for each mL of hydrazine. The solution was stirred at room temperature until TLC indicated consumption of starting material, usually less than 3 h. The mixture was added to 20% NaOH, extracted several times with dichloromethane, and dried over potassium carbonate/sodium sulfate, and the solvents removed at reduced pressure. The crude imines can be purified by chromatography on silica gel eluting with 10% triethyl amine/ethyl acetate, but were generally used without purification.

15 (R = $C_{11}H_{23}$): oil; yield 95%; IR (film) 2920, 1665, 1468, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, br t, J = 6.0 Hz), 1.28 (18 H, br s), 1.56 (4 H, m), 2.10 (4 H, m), 3.53 (2 H, m).

15 (R = $PhCH_2$): oil; purified by preparative TLC on silica gel developing with 10% triethylamine/ethyl acetate; yield 95%; IR (film) 3080, 3055, 3020, 2920, 2845, 1658, 1600, 1493, 1452, 1350, 730, 692 cm^{-1}; ^1H NMR ($CDCl_3$) 1.57 (4 H, m), 2.07 (2 H, m), 3.47 (2 H, s), 3.57 (2 H, m), 7.14 (5 H, s).

20: oil; yield 95%; IR (film) 2956, 2913, 2855, 1659, 1465, 1455, 1366, 1310 cm^{-1}; ^1H NMR ($CDCl_3$) 0.87 (3 H, br t, J = 5.0 Hz), 1.22 (23 H, m), 1.42–1.85 (4 H, m), 1.86–2.32 (4 H, m), 3.28 (1 H, m).

25: oil; purified by flash chromatography on silica gel eluting with 10% triethylamine/ethyl acetate; yield 97%; IR (film) 2950, 2920, 2850, 1645, 1468, 1430, 1377, 1300, 1005, 960, 715 cm^{-1}; ^1H NMR ($CDCl_3$) 0.90 (3 H, br t, J = 6 Hz), 1.06–2.07 (10 H, m), 2.40 (4 H, m), 3.80 (2 H, m); R_f 0.54 in 10% triethylamine/ethyl acetate. Anal. Calcd for $C_{11}H_{21}N$: C, 78.97; H, 12.65; N, 8.37. Found: C, 78.80; H, 12.92.

General Procedure for Reduction of Imines. To a 0.01 M solution of imine **15** or **25** in ether was added 4.0 equiv of lithium aluminium hydride and the mixture stirred at room temperature for 3 h. The mixture was quenched by the method described in Fieser and Fieser.[11] After stirring for 1 h, potassium carbonate/sodium sulfate was added to dry the solution, and after filtration, the solvents were removed under reduced pressure. The crude products were purified either by flash chromatography on silica gel or bulb-to-bulb distillation. For the disubstituted imine **20**, reduction was performed with $LiAlH_4$ or Dibal according to the procedure of Yamamoto.[6]

16a: oil; purified by flash chromatography on silica gel eluting with 10% triethylamine/ethyl acetate; yield 97%; IR (film) 2920, 2852, 2791, 1467, 1328, 1119, 1050, 714 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6.0 Hz), 1.30 (20 H, s), 1.31–1.88 (6 H, m), 2.20–3.20 (3 H, m); R_f 0.17 in 10% triethylamine/ethyl acetate. Anal. Calcd for $C_{16}H_{30}N$: C, 80.26; H, 13.89; N, 5.85. Found: C, 80.20; H, 13.91; N, 5.92.

16b: oil; purified by preparative TLC on silica gel developing with 10% triethylamine/ethyl acetate; yield 77%; IR (film) 3300, 3080, 3055, 3015, 2930, 2845, 2795, 2730, 1950, 1870, 1800, 1670, 1495, 1440, 1332, 1318, 1120, 1050, 985, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.90 (6 H, m), 1.90 (1 H, s), 1.90 (1 H, s), 2.26–3.30 (5 H, m), 7.15 (5 H, s); R_f 0.20 in 10% triethylamine/ethyl acetate; mp of HCl salt 135–137 °C (lit.[12] mp 136–137 °C).

***cis*-21**: oil; purified by flash chromatography on silica gel eluting with 10% triethylamine/ethyl acetate; yield 90% pure *cis*-**21**; IR (film) 2950, 2920, 2850, 1465, 1440, 1373, 1330, 1320, 1128, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6.1 Hz), 1.06 (3 H, d, J = 5.9 Hz), 1.25 (20 H, br, s), 1.36–1.62 (6 H, m), 2.44 (1 H, m), 2.61 (1 H, m); R_f 0.44 in 10% triethylamine/ethyl acetate; VPC t_R 6.59 on 3% SE-30 130–200 °C at 8 °C/min; mp of HCl salt 142–143 °C (lit.[7] mp 153–154 °C).

***trans*-21**: oil; purified by flash chromatography on silica gel eluting with 10% triethylamine/ethyl acetate; yield 85% pure *trans*-**21**; IR (film) 2945, 2920, 2850, 1465, 1445, 1375, 1335, 1140, 1063, 713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, J = 6.1 Hz), 1.07 (3 H, d, J = 6.3 Hz), 1.26 (20 H, br s), 1.38–1.62 (6 H, m), 2.87 (1 H, m), 3.05 (1 H, m); ^{13}C NMR ($CDCl_3$) 14.07, 19.62, 21.25, 22.65, 26.51, 29.37, 29.66, 30.88, 31.88, 33.05, 34.10, 45.77, 50.79; R_f 0.22 in 10% triethylamine/ethyl acetate; VPC t_r 6.95 on 3% SE-30 130–200 °C at 8 °C/min. Spectral properties identical to an authentic sample.[7]

27: oil; purified by bulb-bulb distillation (bp 60 °C (0.05 torr)); yield 87%; IR (film) 3350, 2955, 2920, 28.50, 1555, 1460, 1400, 1130, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (6 H, m), 1.06–2.00 (18 H, m), 2.60–3.27 (2 H, m); mp of HCl salt 88–90 °C (lit.[13] 85–90 °C).

$LiAlH_4$ Reduction of Enamidine 17 to 18. To a 0.1 M solution of **17** in THF was added 4 molar equiv of lithium aluminum hydride and the mixture heated at 60 °C for 12 h, cooled to room temperature, and worked up as for the imine reductions above. The crude product was purified by bulb-bulb distillation (bp 140 °C (0.1 torr)) to afford an 83% yield of an amorphous white solid: IR ($CHCl_3$) 3320, 3060, 3010, 2940, 2860, 1490, 1455, 1330, 1305, 1205, 1115, 1020, 915, 885, 720, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.00–1.86 (6 H, m), 2.26–3.06 (3 H, m), 4.30 (0.12 H, d, J = 8.0 Hz, threo), 4.55 (0.87 H, J = 5.5 Hz, erythro), 7.20 (5 H, s). Spectral properties identical with an authentic sample.[5]

Alkylation of 32 to 33. To a 0.5 M solution of dry **32**[2a] in THF under argon and cooled to −78 °C was added 1.5 equiv of *tert*-butyllithium. The reddish-orange solution was allowed to warm to −20 °C and maintained at this temperature for 2 h. The mixture was cooled to −78 °C, 1.5 equiv of ethyl iodide was added, and the mixture allowed to warm slowly to room temperature. The mixture was diluted with an equal volume of ether, wshed with saturated sodium bicarbonate, dried (K_2CO_3), and concentrated. The residual oil was purified (95%) by flash chromatography on silica gel eluting with 5% triethylamine in hexane: IR (film) 3025, 2965, 2930, 2860, 1635, 1490, 1450, 1410, 1370, 1355, 1315, 1195, 1175, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.07 (3 H, t, J = 7.3 Hz), 1.18 (9 H, s), 1.70 (2 H, m), 2.27 (2 H, q, J = 7.3 Hz), 2.55 (3 H, m), 3.40 (1 H, m), 3.85 (1 H, m), 4.46 (1 H, m), 7.23 (5 H, m), 7.83 (1 H, s).

Alkylation of 33 to 34. In a similar fashion to the alkylation of **32** to **33**, the latter was metalated (1.5 equiv of *tert*-butyllithium) and alkylated with 5 eqiv of methyl iodide. The product was purified by flash chromatography with 5% triethylamine and hexane affording 0.64 g (98%) of a light yellow oil: IR (film) 3025, 2960, 2925, 2860, 1635, 1455, 1375, 1210, 1180, 730, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88, 1.19 (6 H, m), 1.17 and 1.18 (9 H, 2 s), 1.80–2.69 (7 H, m), 4.49 (1 H, m), 4.65 (1 H, m), 7.23 (5 H, m), 7.71 (1 H, s). This product was taken directly to the formamide **35** described below.

Reduction of 34 to Trisubstituted Piperidine 36. A solution of 0.464 g (1.60 mmol) of formamidine **34**, 0.4 mL (8 eq) of hydrazine and 0.3 mL of glacial acetic acid in 15 mL of 95% EtOH was heated at 50 °C under argon for 24 h. Upon cooling, the solvent was removed under vacuum and the crude product was dissolved in diethyl ether. The ethereal phase was washed with saturated $NaHCO_3$ solution and dried over anhydrous K_2CO_3.

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Radial chromatography of the crude product on a 4 mm silica gel plate eluting with a 60:15:25 hexane/Et_3N/acetone solution afforded 0.23 g (67%) of the imine as a light yellow oil: IR (film) 3020, 2960, 2920, 1660, 1490, 1450, 1365, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.05 (3 H, m), 7.19 (5 H, m). The reduction to **36** was performed in the manner described for **15** and **25** to give an oily product (72%) and purified by bulb-to-bulb distillation (140 °C (0.5 torr)). The product was subjected to HPLC analysis as the *p*-nitrobenzamide derivative and showed three isomers in the ratio of 2.1:2.4:1 (10% ethyl acetate/hexane).

Methylation of 37 to 38. After the alkylation procedure of **32** to **33**, except that 2.6 equiv of butyllithium and 3.0 equiv of methyl iodide was used, the carbinol **37**[2a] was alkylated to give the intermediate [(2-methyl-4-hydroxyphenyl)methylene]formamidine, which was transformed by the procedure below to the formamide **38**.

Hydrolysis of Formamidines 34, 37, and 29h into Formamides. A solution of 1 mmol of the above formamidine and 0.4 g (7 mmol) of KOH in 5 mL of MeOH and 2.5 mL of water was heated at 50 °C under argon for 5 h (room temperature overnight was also sufficient). Upon cooling, the solvent was removed under vacuum, and the residue was dissolved into CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$ solution and dried over anhydrous K_2CO_3. Flash or radial chromatography on silica gel eluting with 1:1 hexane/EtOAc afforded the products as viscous oils.

35: oil; purified by flash chromatography on silica gel eluting with 5% Et_3N in hexanes; IR (film) 3020, 2970, 2920, 1680, 1655, 1600, 1490, 1380, 1330, 1180, 740, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1 (3 H, m), 1.3 (3 H, d, J = 6 Hz), 1.4–2.9 (7 H, m), 4.7 (1 H, m), 4.9 (1 H, m), 7.2 (5 H, s), 8.4 (1 H, s). Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70. Found: C, 78.60; H, 8.63.

38: mp 109–111 °C; purified by flash chromatography on silica gel eluting with 1:1 hexane/EtOAc followed by recrystallization from ether/hexane; IR (film) 3400 (v br), 3050, 3020, 2950, 2920, 2860, 1640, 1450, 1370, 1305, 1190, 1170, 780, 755, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.89 (2 H, m), 1.96 (3 H, s), 2.53 (2 H, m), 3.30 (1 H, m), 3.92 (1 H, m), 4.50 (2 H, m), 7.32 (5 H, m), 8.41 (1 H, s). The product was a single diastereomer (HPLC) of undetermined stereochemistry. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.76; H, 7.38; N, 6.04.

30: oil; purified by bulb-to-bulb distillation (0.05 torr, 100 °C); ^1H NMR ($CDCl_3$) δ 1.62 (4 H, m), 2.12 (2 H, m), 2.99 and 3.30 (2 H, m), 3.54 and 3.70 (2 H, s), 5.58 (1 H, m), 7.23 (5 H, m), 8.03 and 8.22 (1 H, s). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.86; H, 7.98; N, 6.64.

***N'-tert*-Butyl-*N*-*n*-butyl-*N*-methylformamidine (40).** A mixture of 0.50 mol of *N*-methyl-*N*-formyl-*n*-butylamine and 0.50 mol of dimethyl sulfate was stirred at 80–90 °C under nitrogen for 3 h, then cooled to 0 °C, and treated with 0.55 mol of *tert*-butylamine in 100 mL of dichloromethane over 30 min, keeping the temperature below 15 °C. An additional 100 mL of dichloromethane was added and the mixture heated to reflux for 18–20 h. After cooling the mixture was poured into 600 mL of 20% KOH and the organic layer separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 120 mL) and the combined organic layers were washed with 300 mL of water and brine, dried (Na_2SO_4), and concentrated. Distillation of the residue gave 76.5 g (90%) (bp 74–75 °C (8.0 torr)) which was pure by VPC (t_R 2.8 min, SE-52, 115 °C): ^1H NMR ($CDCl_3$) δ 7.33 (1 H, s), 3.10 (2 H, J = 6.5 Hz, t), 2.78 (3 H, s), 1.18 (9 H, s), 0.70–1.70 (7 H, m).

***N'-tert*-Butyl-*N*-*n*-butyl-*N*-[(trimethylsilyl)methyl]formamidine (41).** A solution of 200 mmol of formamidine **40** in 400 mL of THF, cooled to −78 °C (N_2) was treated with 205 mmol of *sec*-butyllithium in cyclohexane or *tert*-butyllithium in pentane, and the mixture allowed to warm to −20 °C. It was stirred at −20 ± 3 °C for 1 h to effect complete metalation and then recooled to −78 °C. Addition of 200 mmol of trimethylchlorosilane followed and the mixture was allowed to warm slowly to room temperature. After quenching in 600 mL of water, the organic phase was separated and the aqueous layer extracted (3 × 150 mL) with dichlomethane, combined with the organic phase, washed with brine, dried (Na_2SO_4), and concentrated. The residue was distilled, bp 60–65 °C (0.20 torr), to give 43 g (87.1%) of pure material (VPC, 10% SE-52, 150 °C, t_R 2.2 min): IR (film) 1638 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.28 (1 H, s), 3.10 (2 H, t, J = 6.1 Hz), 2.69 (2 H, s), 1.15 (9 H, s), 0.80–1.70 (7 H, m), 0.10 (9 H, s).

General Procedure for Preparation of Enamidines 42. A solution of 5 mmol of *N*-[(trimethylsilyl)methyl]formamidine (**41**) in 10 mL of anhydrous THF at −78 °C under nitrogen was treated with 5.75 mmol of *sec*-butyllithium/cyclohexane. The solution was warmed to −20 °C over 30 min and stirred at −20 ± 5 °C for 1.0–1.5 h and then the pale yellow mixture was recooled to −78 °C. (If an enolizable ketone or aldehyde was used, then 2.0 equiv of HMPA was added.) A solution of 5.75 mmol of the ketone or aldehyde in 2–4 mL of THF was added dropwise and the mixture maintained at −78 °C for at least 30 min and then warmed to 0 °C or room temperature over 2 h. Following a minimum 30-min stirring period at 0 °C or room temperature, the reaction solution was poured into a rapidly stirred ice mixture of 20 mL of saturated aqueous $NaHCO_3$ and 40 mL of methylene chloride or chloroform. The organic layer was separated and the aqueous layer extracted with 2 × 20 mL of methylene chloride (or chloroform). The combined organic layers were washed with 40 mL of brine, dried (Na_2SO_4), and concentrated in vacuo to afford the crude enamidine, which may be purified or used in further steps as obtained. In all cases, the enamidines **42** were bulb-to-bulb distilled and the *E*/*Z* mixtures were observed on VPC (SE-52, 150–200 °C) as either two distinct peaks or overlapping peaks. The infrared peaks all showed the characteristic formamidine stretch at 1625–1640 cm^{-1} as neat films while the ^1H NMR spectra all exhibited the proton (HC=N) of the formamidine at 7.2–7.5, unless obscured by aromatic protons. The vinylamine moiety appeared in all cases at 5.4–5.9 (α-proton) coupled to the β-proton at 3.5–4.8. Since many of the enamidines were *E*/*Z* mixtures, the vinyl signals were complex.

General Procedure for the Metalation and Alkylation of *N*-*n*-Butyl Enamidines 42 to 44. A solution of 2 mmol of the starting *N*-*n*-butyl enamidine in 5 mL of the THF at −78 °C under N_2 is treated via syringe with 2.6 mmol of *tert*-butyllithium/pentane (or *sec*-butyllithium–cyclohexane) and warmed over 20–30 min to −25 °C. After 1 h at −25 ± 5 °C (longer if *sec*-BuLi was employed), the solution was recooled to −78 °C and treated dropwise with 2.6 mmol of the appropriate electrophile in 2 mL of THF. The solution was warmed to room temperature over 1–2 h and added at once to a rapidly stirred ice-cold mixture of 10 mL of water and 20 mL of methylene chloride. The organic layer was separated and the aqueous layer was extracted with 2 × 15 mL of methylene chloride. The combined organic layers were washed with 20 mL of brine, dried (Na_2SO_4), and concentrated in vacuo to afford crude alkylated product, **44**, which was hydrolyzed directly to the homologated carbonyls, **45**, by the procedure given below.

Hydrolysis of Enamidines 44 to Carbonyls 45. The crude alkylated enamidine is converted to its hydrazone with 0.50 mL of hydrazine (as described for NH_2NMe_2 on a 2-mmol scale) and 0.40 mL of glacial acetic acid in EtOH/H_2O; the intermediate hydrazone was dissolved in 20 mL of acetone[14] and treated with 3 mL of water, followed by 0.40 mL of boron trifluoride etherate. After a 12–24-h stirring period at room temperature (may be followed by TLC), the mixture was neutralized with saturated aqueous $NaHCO_3$ and most of the acetone was removed in vacuo and replaced with water. The aqueous mixture was extracted with 3 × 50 mL of methylene chloride and the combined organic extracts were washed with 50 mL of brine, dried (Na_2SO_4), and concentrated in vacuo to afford crude material, which was purified as appropriate (preparative TLC or bulb-to-bulb distillation). All purities were checked with VPC (10% SE-52, 130–160 °C). See Table I for physical data.

Hydrolysis of Enamidines 42 to Aldehydes (4-Phenylbutanal and 4-Phenylbutanal-*1*-*d*). Any of the enamidines **42** could be cleaved directly to the homologated aldehydes by the following procedure. A solution of 2.0 mmol of the enamidine **42** in 3.0 mL of the enamidine **42** in 3.0 mL of 70% EtOH/H_2O was treated with 1.5 mL of 1,1-dimethylhydrazine, followed by a solution of 0.40 mL of glacial acetic acid in 3.0 mL of 70% EtOH/H_2O. The mixture was stirred for 6–16 h at 55–60 °C and then diluted to 25 mL total volume with water. The aqueous solution was saturated with NaCl and extracted with 3 × 30 mL

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of chloroform, and the combined organic layers were washed with 25 mL of brine, dried (Na_2SO_4), and concentrated in vacuo. The crude hydrazone obtained above was dissolved in 2 mL of methyl iodide and refluxed under N_2 for 3–5 h. The mixture was concentrated in vacuo and suspended in 25 mL of ether, which was treated with 12 mL of 1 N HCl. The two-phase mixture was rapidly stirred for 1–2 h and separated. The aqueous layer was extracted with 3 × 25 mL of methylene chloride, and the combined organics were washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and concentrated in vacuo to afford crude material, which was purified as appropriate.

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Manganese(III)-Mediated Spirodilactonization

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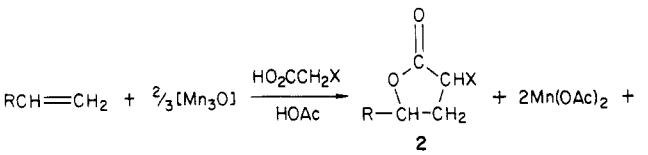
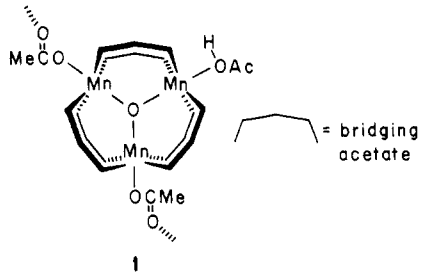
Manganese(III) oxidation of malonic acid in the presence of alkenes results in the formation of spiro-fused lactones, 2,7-dioxaspiro[4.4]nonane-1,6-diones. Terminal alkenes produce a mixture of the three possible diastereomers. The stereochemistry of the diastereomeric spirodilactones was determined by NMR and corroborated by the intensity of the coupled IR carbonyl stretching frequencies. 1,1,6,6-Tetrasubstituted 1,5-hexadienes give in one step tricyclic dilactones. Mechanistic and synthetic aspects of this reaction are discussed.

Manganese(III) acetate, **1**, oxidation of acetate ion in the presence of alkenes is known to produce lactones with high efficiency according to eq 1, X = H.[1-3] This reaction was



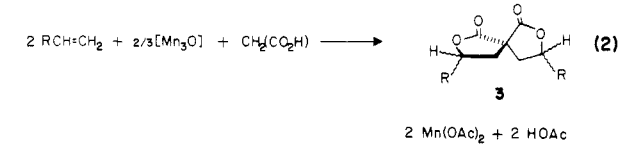


particularly intriguing to us because of its requirement of a trinuclear manganese oxidant to effect on overall two-electron oxidation of the organic moieties. In addition, the reaction is synthetically very useful, and we wished to expand on this synthetic utility.

Manganese(III) acetate is an easily prepared,[4] stable cinnamon brown solid when prepared as the hydrate. When manganese(III) was reduced to manganese(II) during a lactonization, the solution changed from dark brown to colorless. Thus, the course of all the present oxidations with manganese(III) were easily followed by inspection.

While investigating the mechanism of this lactonization reaction, we found that rapid ligand exchange occurred with the solvent which allowed substituted acetic acids to become incorporated into the manganese triangle.[5] Electron-withdrawing substituents on the acetic acid ligand greatly enhanced the reactivity of these ligands, allowing selective oxidation of these substituted ligands to take place. The rate of manganese(III) reduction was found to increase in the following order: acetic < chloroacetic < malonic < cyanoacetic acid by factors 1.3×10^1, 1.4×10^4, and 4.0×10^5, respectively at 120 °C.[1] In particular, cyanoacetic acid and 1-octene gave the α-cyanolactone, **2**, X = CN, R = *n*-hexyl, which crystallized out of the crude reaction workup in 69% yield. This prompted us to oxidize malonic acid in the anticipation of producing **2**, X = COOH, which should be capable of further functionalization or decarboxylation to the parent lactone **2**, X = H.

The lactone **2**, X = COOH, was indeed formed when 1 molar equiv of malonic acid was added to the lactonization mixture; however, it further reacted to yield the spirodilactone **3**, R = *n*-hexyl, in quantitative yield, eq 2. Thus,



(2)

the intermediate carboxy lactone **2**, X = COOH, proved more reactive to manganese(III) oxidation than malonic acid itself. This unusually facile spirodilactonization is the subject to this report.[6,7] During the final stages of this

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