On the Mechanism of Pd^0-Initiated Coupling−Cyclization of γ-Aminoalkynes

Peter A. Jacobi* and Hui Liu†

Burke Chemical Laboratory, Dartmouth College, Hanover, New Hampshire 03755

peter.a.jacobi@dartmouth.edu

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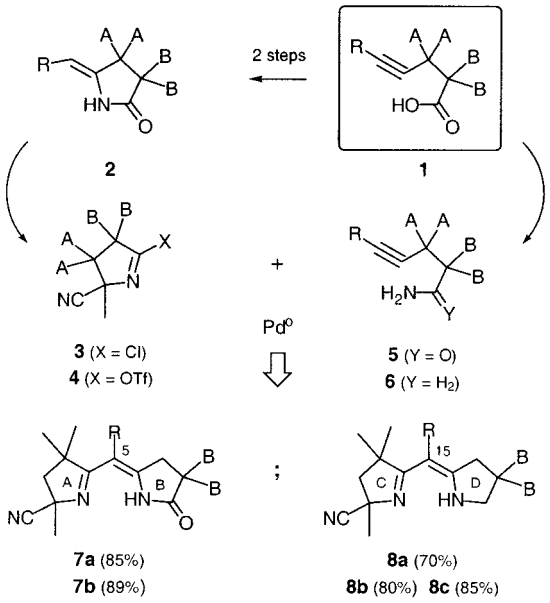
Introduction

Recently, we have been investigating the synthetic utility of alkyne acids of general structure **1**, which are useful precursors to a variety of natural product skeletons (Scheme 1).[1] The versatility of these species derives partly from their bifunctional structure, which incorporates both a nucleophilic and an electrophilic component in the same synthon. In addition, acids of type **1** can frequently be prepared in enantiomerically pure form.[1f,2] A particularly useful transformation of **1** involves 5-*exo-dig* cyclization, which we employed in a two-step synthesis of cyclic enamides **2** [Pd(II)-induced cyclization followed by aminolysis[1b] or amidation followed by F^--catalyzed ring closure[1h]]. Enamides **2** are important building blocks for the synthesis of hydroporphyrins,[3a] employing the Eschenmoser sulfide contraction methodology.[3b] Also, we have developed an iterative synthesis of dipyrrin derivatives that takes advantage of the ready availability of imidoyl chlorides **3** and triflates **4**, each derived in two steps from **2**.[1b] For example, semicorrins **7a**,**b** were prepared by Pd^0-initiated coupling−cyclization of imidoyl chloride **3a** with the alkyne acid/amide derivatives **1a** or **5b**, depending upon the *meso*-substitution pattern at C_5 (85−89% yields).[1b,c] In similar fashion, Pd^0-initiated coupling-cyclization of triflate **4a** with the alkyne amines **6a**−**c** afforded good-excellent yields of the (H_6)-dipyrrins **8a**−**c**.[1d] Interestingly, steric hindrance was not a problem in these transformations, even though the reactive C−X bond is adjacent to a quaternary center. In fact, in some cases this proved to be beneficial (*vide infra*). Finally, it is worth noting that imidoyl chlorides **3** were much more reactive than triflates **4** in Pd^0-initiated coupling−cyclizations with alkyne *acids* **1**.[1b,c] Conversely, imidoyl triflates **4** were better substrates for coupling−cyclization with alkyne *amines* **6**.[1d] These observations are discussed further below.

Scheme 1



a: A = H, B,R = Me. **b**: A,R = H, B = Me. **c**: A,B,R = H.

Results and Discussion

Semicorrins **7** and (H_6)-dipyrrins **8** are suitably constituted for preparing corrins of type **9** (Figure 1), and the methodology for accomplishing this transformation is well established.[3b,c] However, most naturally occurring hydroporphyrins have a substitution pattern related to that found in cobyric acid (**10**), in which the quaternary carbons are located at C_2, C_7, C_{12}, and C_{17} (i.e., regioisomeric to **9**).[3a] In principle, the "natural" corrin regiochemistry can be obtained by altering the substitution pattern of the starting imidoyl chlorides/triflates **3**, **4** and alkyne acids/amines **1**, **6**. This worked well for a number of semicorrin derivatives **11**, beginning with acids **1**.[1c] For example, the ring-A,B precursor **11d** was readily derived from the imidoyl chloride **3d** and the alkyne acid **1d** by a two-step sequence involving Pd^0-initiated coupling−cyclization, followed by aminolysis of the resultant enol lactone (Figure 1).

In contrast, the construction of ring-C,D dipyrrins **12** incorporating the "natural" regiochemistry was not so straightforward (Scheme 2). This synthesis was based upon the Pd^0-initiated coupling−cyclization of alkyne amines **6** with imidoyl triflate **4d**, a seemingly minor variation to our syntheses of dipyrrins **8** (cf. Scheme 1). However, with **4d** the geminal methyl groups are well removed from the C−OTf bond and provide little steric shielding. Consequently, nucleophilic displacement by the amino group competes effectively with the Pd^0-initiated process, a pathway that was not observed with imidoyl triflate **4a**. In the most favorable case, coupling of **4d** with the alkyne amine **6a** gave a 52% yield of the meso-substituted (H_6)-dipyrrin **12a** (A = H; B, R = Me), accompanied by 37% of amidine **13a**, the product of amine displacement. In analogous fashion, the more sterically hindered alkyne **6d** afforded only 31% of the desired (H_6)-dipyrrin **12d** (A = Me; B, R = H), and 62% of amidine **13d**. Finally, alkyne amine **6e**, which contains the most shielded triple bond (A, R = Me) and the least

† Current Address: ChemRx Advanced Technology, San Diego, CA.

(1) (a) Jacobi, P. A.; Coutts, L. D.; Guo, J.; Hauck, S. I.; Leung, S. *J. Org. Chem.* **2000**, *65*, 205. (b) Jacobi, P. A.; Liu, H. *J. Am. Chem. Soc.* **1999**, *121*, 1958. (c) Jacobi, P. A.; Liu, H. *J. Org. Chem.* **1999**, *64*, 1778. (d) Jacobi, P. A.; Liu, H. *Org. Lett.* **1999**, *1*, 341. (e) Jacobi, P. A., Herradura, P. *Tetrahedron Lett.* **1997**, *38*, 6621. (f) Jacobi, P. A.; Guo, J.; Rajeswari, S.; Zheng, W. *J. Org. Chem.* **1997**, *62*, 2907, and references therein. (g) Jacobi, P. A.; Murphree, S.; Rupprecht, F. Zheng, W. *J. Org. Chem.* **1996**, *61*, 2413. (h) Jacobi, P. A.; Brielmann, H. L.; Hauck, S. I. *J. Org. Chem.* **1996**, *61*, 5013, and references therein.

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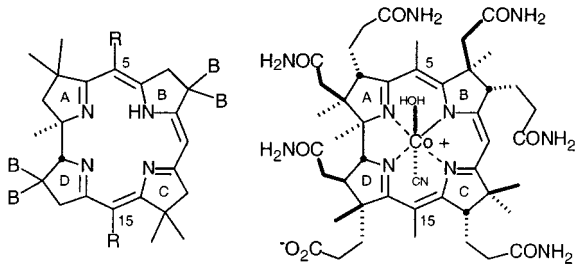
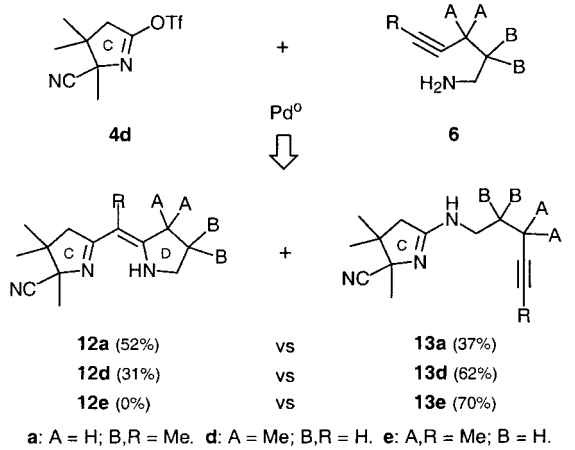


Figure 1. Cobyric acid (**10**): corrin skeleton of vitamin B_{12}.

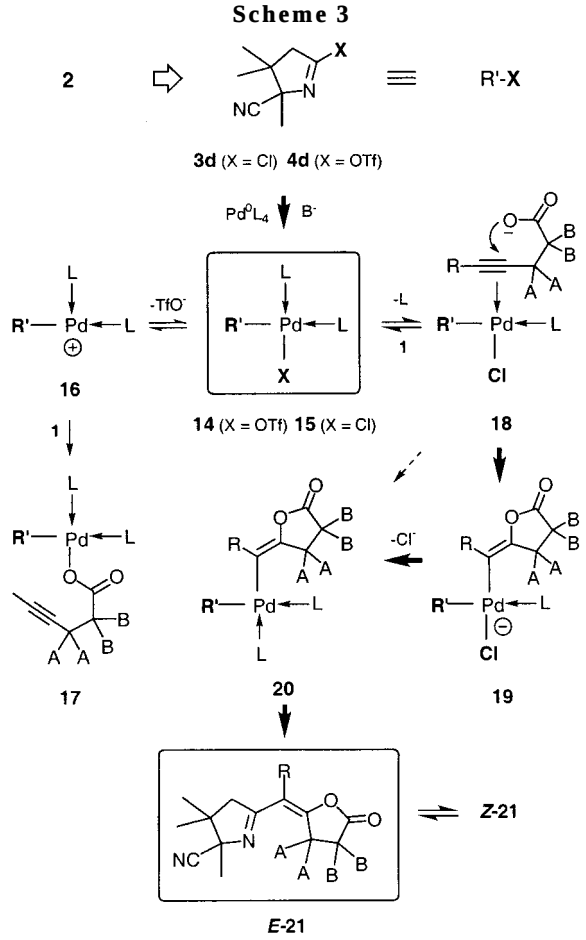
Scheme 2



hindered amine (B = H), gave amidine **13e** as the exclusive product (70% yield). Once again, imidoyl chloride **3d** was relatively unreactive toward both coupling and direct displacement with alkyne amines **6**.[1d]

Clearly, different mechanisms operate in the Pd^0-initiated coupling−cyclization of alkyne amines **6** and alkyne acids **1**. The reactivity pattern of acids **1** is best explained on the basis of the relative Pd(II) ligand bond strengths of Cl^-, TfO^-, and RCO_2^-. This is illustrated in Scheme 3, employing imidoyl chloride **3d** (X = Cl) and imidoyl triflate **4d** (X = OTf) as substrates. In both examples, Pd^0-initiated coupling reactions were carried out under weakly alkaline conditions, in which the alkyne acid **1** is completely ionized ($B^- = NEt_3$). Beginning with **4d**, syn-oxidative addition leads initially to the square-planar Pd(II) complex **14**, which is likely in equilibrium with the cationic species **16**.[4] However, a dissociative mechanism is not required. As pointed out by Arcadi *et al.*,[5a] carboxylate anions readily displace the labile triflate ligand from Pd(II) complexes. The resultant σ-Pd(II)−

Scheme 3



carboxylate complex **17** is then effectively removed from the catalytic cycle, and little or no enol lactone (*E*)-**21** is formed. In contrast, under identical conditions the imidoyl chloride **3d** efficiently produces the desired lactones **21**. This change in reaction pathway is most likely due to the greater stability of the Pd−Cl bond in **15**,[4a] which is inert to both heterolytic cleavage (**15** → **16**) and direct anionic substitution (**15** → **17**). Instead, π-complexation takes place by dissociation of a neutral ligand L to form the alkyne complex **18**.[4,5] Ligand substitution is then followed by nucleophilic capture, affording the σ-vinylpalladium intermediate **20** either by direct displacement of Cl^- (**18** → **20**)[5a,b] or via an anionic, associative process (**18** → **19** → **20**).[6] In either case, σ-bond formation is facilitated by the high nucleophilicity of the participating carboxylate anion. Finally, cis-reductive elimination leads initially to the *E*-enol lactone **21**,[5] which undergoes rapid equilibration to the observed *E*,*Z* mixture (some bond isomerizations have been omitted for clarity).

A similar analysis applies to the Pd^0-initiated coupling−cyclization of alkyne amines **6**, which is sluggish when effected with imidoyl chloride **3d**, but rapid with triflate **4d** (Scheme 4, below). This is the opposite chemoselectivity to that exhibited with alkyne acids **1**, and presumably reflects the greatly reduced nucleophilicity of the alkyne amine π-complex **22**, as compared to the alkyne carboxylate π-complex **18** (cf. Scheme 3). Thus, the amino alkyne group in **22** is slow to substitute Cl^- by either direct displacement (**22** → **24**) or by an associative process (**22** → **23** → **24**).

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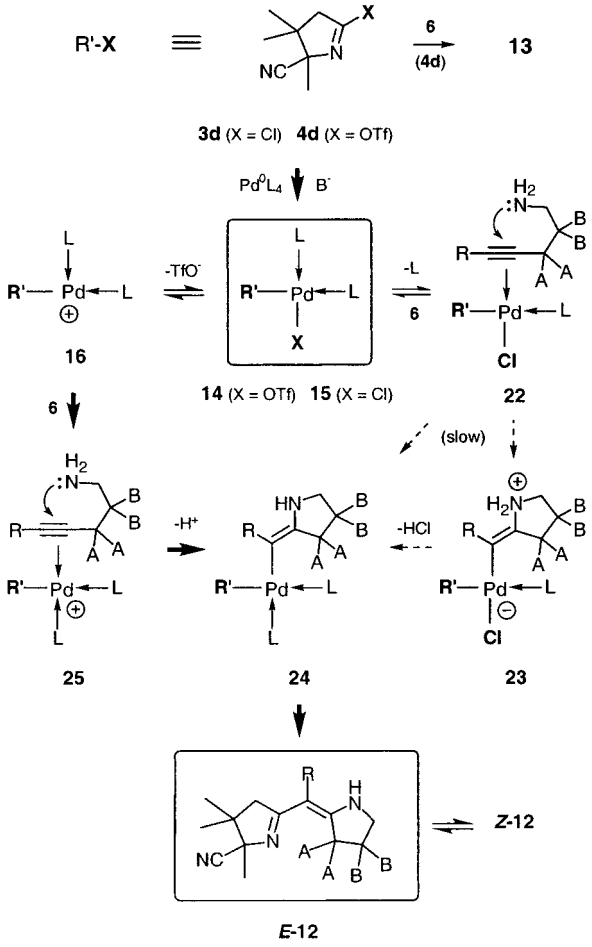
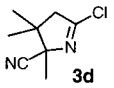
Scheme 4



Last, we consider the coupling of imidoyl triflate **4d** and alkyne amines **6**, which is important for the synthesis of (H_6)-dipyrrins **12** (Scheme 4). As described above, this transformation was much faster than that observed with chloride **3d** and afforded mixtures of dipyrrins **12** and amidines **13**.[1d] We briefly explored the possibility that amidines **13** were derived by a Pd^0-catalyzed process.[7] However, control experiments demonstrated that TfO^- substitution occurred by direct nucleophilic displacement and was not catalyzed by Pd^0 when L = PPh_3. The more favorable Pd^0-initiated coupling of triflate **4d** and alkyne amines **6** is consistent with a mechanism in which syn-oxidative addition of Pd^0 affords the square planar complex **14**, followed by dissociation of the labile TfO^- ligand to give cation **16**. An identical sequence was postulated for steps 1−2 in the attempted coupling-cyclization of alkyne acids **1** and imidoyl triflate **4d** (cf. Scheme 3). At this point, however, the reaction pathways diverge. With carboxylate anions **1**, ion-pair bonding with cation **16** affords the neutral Pd(II)−σ-complex **17**, a

Table 1



12a + 13a

Entry	Ligand[2]	Solvent	°C	Time	% 12a	% 13a	% 3d
1	TFP	MeCN	75	3 h	30%	0%	70%
2	TFP	MeCN	75	19 h	30%	0%	0%
3	PCy_3	MeCN	75	5 h	0%	0%	>90%
4	*t*-Bu_2PØ-Ø	MeCN	70	16 h	0%	0%	>90%
5	None	MeCN	75	3 h	0%	0%	>90%

(1) All reactions run in presence of $BnNEt_3Cl$
(2) Ligands added to $Pd_2(dba)_3$ (ligand-free Pd)

favorable, albeit nonproductive step (Scheme 3).[5a] In contrast, primary alkyne amines **6** are less likely to undergo Pd(II)−σ-bond formation. This type of association typically requires concomitant deprotonation by strong base ($LiNR_2$, NaOR, etc.) or additional activating functionality ($SnNR_2$).[7a−d] In the present case, π-complexation of **6** with **16** is more favorable (Scheme 4) and affords the cationic species **25** which is highly activated toward nucleophilic capture (**25** → **24**).[4] The resultant σ-vinylpalladium complex **24** then undergoes cis-reductive elimination, followed by *E*,*Z* equilibration, to give the (H_6)-dipyrrins **12**.

A number of observations support the mechanistic pathway(s) outlined in Scheme 4. The most important of these pertain to the effect of ligands L on the course of the Pd^0-initiated coupling−cyclization. With imidoyl chloride **3d**, the nature of L had only a marginal impact on the rate of formation of dipyrrins **12**. Low reactivity was observed across a wide range of experimental conditions (Table 1). Employing alkyne amine **6a**, the best results were obtained with L = tri(2-furyl)phosphine (TFP),[8a−c] which afforded 30% of dipyrrin **12a** and 70% of recovered **3d** after 3 h at 75 °C (entry 1). Unfortunately, however, the yield of **12a** showed no improvement with increasing time, which instead led to extensive decomposition of **3d** (entry 2). Also, little or no dipyrrin **12a** was formed employing electron-rich and/or bulky phosphine ligands (entries 3 and 4; PCy_3 = tricyclohexylphosphine; *t*-Bu_2PØ-Ø = 2-[di-*tert*-butylphosphino]biphenyl),[7] or under "ligand-free" conditions (entry 5; dba = dibenzylideneacetone).[8d] These data are in agreement with a rate-determining step involving Pd−σ-bond formation (**22** → **24**), as opposed to substitution of L (**15** → **22**). Interestingly, at temperatures <80 °C we could detect no trace of amidines **13**, the product of noncatalyzed nucleophilic displacement. Rouden et al. have recently noted a similar lack of reactivity of primary amines with heteroaryl imidoyl chlorides.[7h] Finally, we obtained closely related results with other alkyne amines **6**.

The reactivity pattern of imidoyl triflate **4d** is more complex, owing to the exceptional leaving group ability of TfO^-.[4] In this case, amidine formation competes effectively with the Pd^0-initiated coupling−cyclization. We devoted considerable effort to differentiating these

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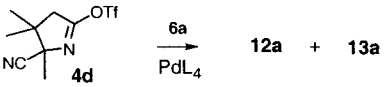
Table 2

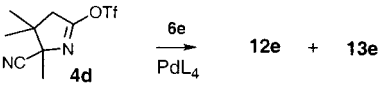


Entry	Ligand[2]	Solvent	°C	Time	% 12a	% 13a	% 4d
1	TFP[1]	MeCN	80	1 h	52%	37%	0%
2	PCy_3[1]	MeCN	70	4 h	0%	0%	d.
3	*t*-Bu_2PØ-Ø[1]	MeCN	70	1 h	<10%	50%	0%
4	None	MeCN	70	3 h	75%	10%	0%
5	None	THF	70	3 h	75%	10%	0%
6	None	Dioxane	70	3 h	79%	7%	0%
7	None	DMF	70	3 h	18%	72%	0%
8	None	DMF	rt	60 h	10%	80%	0%
9	-	MeCN	80	3 h	0%	95%	0%

(1) Reaction run in presence of $BnNEt_3Cl$

(2) Ligands added to $Pd_2(dba)_3$ (ligand-free Pd)

Table 3



Entry	Ligand[2]	Solvent	°C	Time	% 12e	% 13e	eq Pd
1	TFP[1]	MeCN	80	1 h	0%	70%	0.15
2	-	MeCN	80	3 h	0%	70%	0
3	None	MeCN	70	3 h	40%	48%	0.10
4	None	MeCN	70	3 h	40%	25%	0.20
5	None	MeCN	70	3 h	38%	16%	0.30
6	None	MeCN	70	3 h	19%	0%	0.50

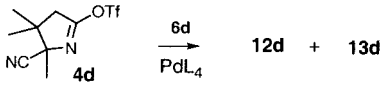
(1) Reaction run in presence of $BnNEt_3Cl$

(2) Ligands added to $Pd_2(dba)_3$ (ligand-free Pd)

pathways and, in particular, to adjusting the reactivity of cation **16** (cf. Scheme 4). If sufficiently activated, we believed that π-complexation of **16** with alkyne amines **6** might be accelerated (**16** → **25**), thereby favoring the cyclization process. Several experiments designed to probe this possibility are summarized in Table 2 for the reaction of triflate **4d** and alkyne amine **6a**. Our original conditions employed TFP as ligand,[8a−c] which gave a 52% yield of dipyrrin **12a** together with 37% of amidine **13a** (entry 1). In this case, electron-rich and/or sterically hindered ligands had a deleterious effect on dipyrrin formation, since cation **16** is stabilized by such groups (cf. Scheme 4). Typically, we observed either increased decomposition (entry 2) or higher proportions of amidines **13** (entry 3).[7e] In contrast, the ratio of **12a**:**13a** improved significantly employing "ligand-free" Pd^0 (Pd_2dba_3).[8] This was especially true with weakly coordinating solvents, which afforded ratios of **12a**:**13a** on the order of 8:1 (entries 4−6). However, in DMF this selectivity was reversed, affording only 18% of **12a** and 72% of amidine **13a** (entry 7). This result is understandable since DMF coordinates strongly to cation **16** and inhibits the π-complexation necessary to give intermediate **25** (cf. Scheme 4). Conversely, polar solvents accelerated the formation of amidine **13a** by nucleophilic displacement, which took place readily at room temperature in DMF (entry 8).

The use of "ligand-free" conditions was particularly beneficial for the synthesis of (H_6)-dipyrrin **12e** (Table 3). In our original studies, we were unable to prepare this key corrin precursor utilizing the Pd-cyclization methodology.[1d] For example, attempted catalysis with $Pd(TFP)_4$

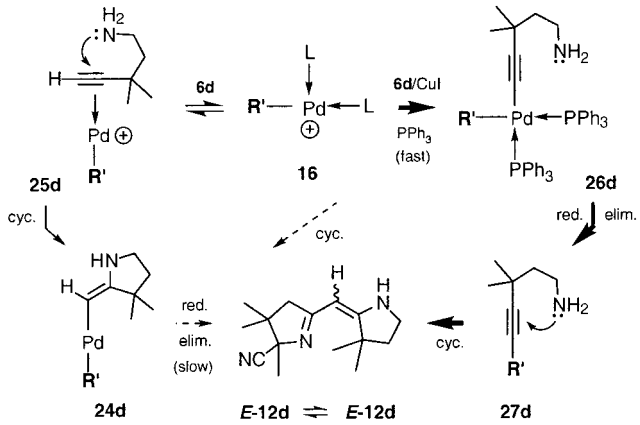
Table 4



Entry	Ligand[2]	Solvent	°C	Time	% 12d	% 13d	eq Pd
1	Ph_3P	THF	rt	16 h	31%	62%	0.15
2	-	THF	rt	16 h	0%	>90%	0
3	Ph_3P	MeCN	rt	16 h	18%	70%	0.15
4	TFP	MeCN	rt	16 h	48%	15%	0.15
5	None	THF	rt	16 h	0%	>90%	0.15
6	Ph_3P/CuI	THF	rt	16 h	68%	0%	0.15

(2) Ligands added to $Pd_2(dba)_3$ (ligand-free Pd)

Scheme 5



gave the same results as the corresponding blank reaction (entries 1 and 2; see also Scheme 2). In both cases, we isolated amidine **13e** as the only identifiable product. In contrast, employing Pd_2dba_3, we obtained an approximately 1:1 ratio of **12e**:**13e** under otherwise identical conditions (entry 3). The success of this reaction is remarkable given the steric hindrance of the alkyne bond in **6e**. In addition, we observed a clear trend favoring the formation of **12e** upon increasing the catalyst concentration (entries 3−5). The ratio of **12e**:**13e** reached a maximum at 0.5 equiv of Pd_2dba_3 (>95:5, entry 6), at which point decomposition became prevalent. However, we are hopeful that with further study this reaction might be improved.

Finally, the terminal alkyne amine **6d** represented a special case (Table 4), since this substrate suffers cyclization and/or polymerization with Pd catalysts. Therefore, all reactions were carried out at room temperature, where amidine formation is very competitive (entry 2). By way of summary, employing Ph_3P as ligand we obtained ratios of **12d**:**13d** ranging from 31:62 (THF, entry 1) to 18:70 (MeCN, entry 3). These results improved greatly using TFP as ligand,[8a−c] which afforded 48% of dipyrrin **12d** and 15% of amidine **13d**. Surprisingly, however, we obtained none of the desired **12d** employing "ligand-free" Pd^0 (entry 5), our most effective catalyst system with the internal alkyne amine **6e** (cf. Table 3). This experiment points toward a different rate determining step in the formation of **12d**, as compared to that with dipyrrins **12a** (Table 2) and **12e** (Table 3). The reasons for this change are not clear. Steric hindrance is not likely to be a factor, since π-complex **25d** is less crowded than the case with internal alkyne **6e** (Scheme 5; see also Scheme 4). Also, it is doubtful that the cyclization of **25d** to **24d** would be significantly slower than with **6e**

(Scheme 4). Most likely this rate difference derives from the reductive elimination step (**24d** → **12d**), a process that is well-known to be strongly influenced by ligands L.[7]

In any event, this difficulty was circumvented using a relatively minor modification. Thus, with PPh_3/CuI/NEt_3 as co-reactants (entry 6), we obtained dipyrrin **12d** as the exclusive product under conditions otherwise identical to those employed in entry 1. This transformation is a variant of a Sonogashira coupling,[9] which is initiated by the Pd/NEt_3-catalyzed production of Cu-acetylides, followed by trans-metalation. In the case of alkyne amine **6d** this affords the Pd−σ-alkyne complex **26d**, which can produce the desired dipyrrin **12d** by either of two pathways: Reductive elimination to the alkyne amine **27d**, followed by 5-*exo*-*dig* cyclization;[10] or alternatively, initial cyclization of **26d** to **24d**, followed by reductive elimination. Both of these processes should be favorable with Ph_3P as ligand, which facilitates reductive elimination.[8] At present we cannot conclusively differentiate these pathways, although we have some evidence for the transient formation of alkyne amine **27d**.

Currently we are extending this methodology to the synthesis of *meso*-substituted corrins of type **10**, as well as to chlorins and bacteriochlorins of potential use in photodynamic therapy (PDT). The results of these studies will be reported in future papers.

Experimental Section

Melting points were determined on a Fisher-Johns microscope melting point apparatus and are not corrected. ^{1}H NMR and ^{13}C NMR were recorded at 300 MHz and are expressed as ppm downfield from Me_4Si as an internal standard.[11]

2-((4,4-Dimethylpyrrolidin-2-ylidene)ethyl)-4,4,5-trimethyl-1-pyrroline-5-carbonitrile (12a). A solution of 35 mg (0.12 mmol) of imidoyl triflate **4d**, 20 mg (0.15 mmol) of alkyne amine **6a**, and 0.18 mL (1.2 mmol) of NEt_3 in 10 mL of MeCN was degassed with argon for 5 min and was then treated with 26 mg (0.024 mmol) of $Pd_2(dba)_3$·$CHCl_3$ under an argon atmosphere. The reaction was then heated to 70 °C, with vigorous stirring, for a period of 3 h and then concentrated to dryness. The residue was diluted with 100 mL of CH_2Cl_2, washed with saturatedd $NaHCO_3$ and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel) to give 23 mg (75%) of **12a** as a yellow solid: mp 86−7 °C; R_f 0.23 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.17 (s, 3H), 1.18 (s, 3H), 1.33 (s, 3H), 1.51 (s, 3H), 1.74 (s, 3H), 2.43 (s, 2H), 2.52/2.57/2.63/2.68 (AB, J = 16.2 Hz, 2H), 3.30/3.33/3.34/3.37 (AB, J = 9.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 22.5, 23.2, 26.1, 27.8 (two signals), 37.0, 43.3, 46.5, 50.3, 61.2, 73.2, 88.0, 123.0, 160.8, 175.6; MS (EI) m/z 259 (M^+, 21), 258 (M^+ − H, 100); HRMS (EI) calcd for $C_{16}H_{24}N_3$ (M^+ − H) 258.1970, found 258.1966.

Amidine **13a** was obtained in 10% yield: R_f 0.39 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.34 (s, 6H0, 1.37 (s, 3H), 1.53 (s, 3H), 1.86 (s, 3H), 1.89 (t d, J = 6.9, 3.0 Hz, 2H), 2.56/2.61/2.67/2.72 (AB, J = 16.2 Hz, 2H), 3.48 (t, J = 6.9 Hz, 2H); MS (EI) m/z 259 (M^+, 21), 258 (M^+ − H, 100); HRMS (EI) calcd for $C_{16}H_{24}N_3$ (M^+ − H) 258.1970, found 258.1973.

5-(3,3-Dimethylpyrrolidin-2-ylidenemethyl)-2,3,3-trimethyl-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (12d). A solution of 70 mg (0.24 mmol) of imidoyl triflate **4d**, 32 mg (0.29 mmol) of alkyne amine **6d**, and 0.34 mL (2.4 mmol) of NEt_3 in 4 mL of THF was degassed with argon for 5 min and was then treated with 9.2 mg (0.048 mmol) of CuI, immediately followed by a solution of 28 mg (0.024 mmol) of $Pd(Ph_3P)_4$ in 2 mL of THF under an argon atmosphere. After being stirred for an additional 16 h at room temperature, the reaction mixture was quenched with 10 mL of 10% $Na_2S_2O_3$ and then diluted with 100 mL of CH_2Cl_2, washed with 10% $Na_2S_2O_3$, saturated $NaHCO_3$ and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, EtOAc/hexane/NEt_3 = 10:100:1 to 50:50:1) to give 40 mg (68%) of **12d** as a colorless solid: mp 89−90 °C; R_f 0.51 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.21 (s, 3H), 1.22 (s, 3H), 1.33 (s, 3H), 1.52 (s, 3H), 1.85 (t, J = 6.6 Hz, 2H), 2.44/2.50/2.61/2.66 (AB, J = 16.2 Hz, 2H), 3.54 (t, J = 6.6 Hz, 2H), 4.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.4, 23.1, 25.8, 27.1, 27.2, 38.6, 43.4, 43.8, 44.6, 52.0, 73.7, 79.1, 123.0, 170.4, 176.0; MS (EI) m/z 245 (M^+, 51), 230 (100); HRMS (EI) calcd for $C_{15}H_{23}N_3$ 245.1892, found 245.1892.

2-((3,3-Dimethylpyrrolidin-2-ylidene)ethyl)-4,4,5-trimethyl-1-pyrroline-5-carbonitrile (12e). A solution of 35 mg (0.12 mmol) of imidoyl triflate **4d**, 20 mg (0.15 mmol) of alkyne amine **6e**, and 0.18 mL (1.2 mmol) of NEt_3 in 10 mL of MeCN was degassed with argon for 5 min and was then treated with 26 mg (0.024 mmol, 0.2 equiv) of $Pd_2(dba)_3$·$CHCl_3$ under an argon atmosphere. The reaction was then heated to 70 °C, with vigorous stirring, for a period of 3 h and then concentrated to dryness. The residue was diluted with 100 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel) to give 13 mg (40%) of **12e** as a yellow oil: R_f 0.39 (25% EtOAc/hexane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.34 (s, 6H, 1.37 (s, 3H), 1.53 (s, 3H), 1.86 (s, 3H), 1.89 (t, J = 6.9 Hz, 2H), 2.56/2.61/2.67/2.72 (AB, J = 16.2 Hz, 2H), 3.48 (t, J = 6.9 Hz, 2H); MS (EI) m/z 259 (M^+, 21), 258 (M^+ − H, 100); HRMS (EI) calcd for $C_{16}H_2N_3$ (M^+ − H) 258.1970, found 258.1973.

Amidine **13e** was obtained in 25% yield: R_f 0.12 (25% EtOAc/hexane); IR (neat) 3225, 3060, 2966, 2919, 2226, 1608 (vs), 1472, 1449; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.19 (s, 6H), 1.31 (s, 3H), 1.48 (s, 3H), 1.62 (t, J = 7.5 Hz, 2H), 1.78 (s, 3H), 2.21/2.26/2.55/2.60 (AB, J = 15.0 Hz, 2H), 3.41 (br m, 2H), 4.70 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 4.2, 22.5, 23.6, 25.6, 29.1, 30.4, 30.6, 34.1, 41.5, 43.0, 45.3, 48.2, 77.0, 86.9, 123.7, 168.0. MS (EI) m/z 259 (M^+, 6), 258 (M^+ − H, 18), 244 (M^+ − CH_3, 46), 217 (M^+ − CH_3 − HCN, 100); HRMS (EI) calcd for $C_{16}H_{24}N_3$ (M^+ − H) 258.1970, found 258.1966.

5-(3,3-Dimethylhex-4-ynylamino)-2,3,3-trimethyl-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (13e). A solution of 31 mg (0.11 mmol) of imidoyl triflate **4d**, 20 mg (0.16 mmol) of alkyne amine **6e**, and 0.15 mL (1.1 mmol) of NEt_3 in 4 mL of CH_3CN was heated to 80 °C for a period of 3 h. The reaction mixture was then concentrated to dryness. The residue was diluted with 100 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was then purified by flash chromatography (silica gel, EtOAc/hexane/NEt_3 = 30:90:1) to give 20 mg (70%) of **13e** as a yellow oil, identical in all respects to **13e** isolated as described above.

5-(2,2-Dimethyl-hex-4-ynylamino)-2,3,3-trimethyl-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (13a). This material was prepared in 95% yield from 70 mg (0.25 mmol) of imidoyl triflate **4d**, 62 mg (0.50 mmol) of alkyne amine **6a**, and 0.34 mL (2.5 mmol) of NEt_3, following a procedure identical to that described above for **13e**: yellow oil; R_f 0.12 (28% EtOAc/hexane); IR (neat) 3389, 3248, 3083, 2966, 2919, 2226, 1614 (vs), 1466; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 6H), 1.05 (s, 3H), 1.33 (s, 3H), 1.46 (s, 3H), 1.80 (s, 3H), 2.06 (s, 2H), 2.06/2.12/2.57/2.62 (AB, J = 15.0 Hz, 2H), 3.20 (br s, 2H), 4.55 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 3.7, 22.0, 23.1, 24.8, 25.2 (two signals), 25.3, 29.7, 35.4, 44.8, 52.2, 71.3, 76.9, 78.1, 122.6, 168.0; MS (EI) m/z 259 (M^+, 12), 244 (M^+ − CH_3, 64), 217 (M^+ − CH_3, − HCN, 100); HRMS (EI) calcd for $C_{16}H_{25}N_3$ (M^+) 259.2048, found 259.2043.

5-(3,3-Dimethylpent-4-ynylamino)-2,3,3-trimethyl-3,4-dihydro-2*H*-pyrrole-2-carbonitrile (13d). A solution of 70 mg (0.25 mmol) of imidoyl triflate **4d**, 56 mg (0.50 mmol) of alkyne amine **6d**, and 0.34 mL (2.5 mmol) of NEt_3 in 6 mL of THF was

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(11) Copies of NMR spectra for compounds **12a**,**d**,**e** and **13a**,**e** are available in the Supporting Information for ref 1d.

stirred at room temperature for a period of 16 h. The reaction mixture was then concentrated to dryness. The residue was diluted with 100 mL of CH_2Cl_2, washed with saturated $NaHCO_3$ and saturated brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 59 mg (97%) of **13d** as a colorless oil: R_f 0.10 (25% EtOAc/hexane); IR (neat) 3295, 3213, 3037, 2966, 2226, 2108, 1602 (vs), 1472, 1449, 1367; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.26 (s, 6H), 1.32 (s, 3H), 1.49 (s, 3H), 1.69 (t, J = 6.0 Hz, 2H), 2.15 (s, 1H), 2.22/2.28/2.55/2.61 (AB, J = 18.0 Hz, 2H), 3.47 (br m, 2H), 4.59 (br s, 1H); MS (EI) m/z 246 (M^+ + H, 14), 219 (M^+ − CN, 100); HRMS (EI) calcd for $C_{15}H_{24}N_3$ (M^+ + H) 246.1970, found 246.1964.

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