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General and Regioselective Synthesis of Substituted Pyrroles by Metal-Catalyzed or Spontaneous Cycloisomerization of (*Z*)-(2-En-4-ynyl)amines

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A general and regioselective synthesis of substituted pyrroles **2** by cycloisomerization of readily available (*Z*)-(2-en-4-ynyl)amines **1** is reported. Spontaneous cycloisomerization leading to **2** occurred in the course of preparation of enynamines bearing a terminal triple bond or a triple bond substituted with a phenyl or a CH_2OTHP group. When the triple bond was substituted with an alkyl or alkenyl group, enynamines were stable and could be converted into the corresponding pyrroles by metal catalysis. $CuCl_2$ was found to be an excellent catalyst for cycloisomerization of substrates substituted at C-3, while PdX_2 in conjunction with KX (X = Cl, I) turned out to be a superior catalyst for the reaction of enynamines unsubstituted at C-3.

Introduction

Pyrroles are a very important class of heterocyclic compounds. The pyrrole ring is present in many natural products, and a large number of pyrrole derivatives have displayed interesting biological activity.[1] Moreover, pyrroles have found broad application in the field of material chemistry.[2]

Recently, there has been considerable interest in the development of new regioselective methods for the synthesis of substituted pyrroles, either by cyclization or cycloaddition of suitably functionalized acyclic precursors or by functionalization of the pyrrole ring.[3]

We recently reported the Pd-catalyzed cycloisomerization of (*Z*)-2-en-4-yn-1-ols, (*Z*)-2-en-4-yne-1-thiols, and 2-alkynylbenzyl alcohols to substituted furans,[4] thiophenes,[5] and 1-alkylidene-1,3-dihydroisobenzofurans or 1*H*-isochromenes,[6] respectively. On the other hand, the Pd-catalyzed cycloisomerization of (*Z*)-(2-en-4-ynyl)-amines **1** to pyrroles **2** has only been disclosed in a preliminary communication.[7] In this work, we report a full account on the synthesis of substituted pyrroles **2** by transition-metal-catalyzed (eq 1) or spontaneous (eq 2; square brackets indicate that the compound is unstable) cycloisomerization of readily available **1**.

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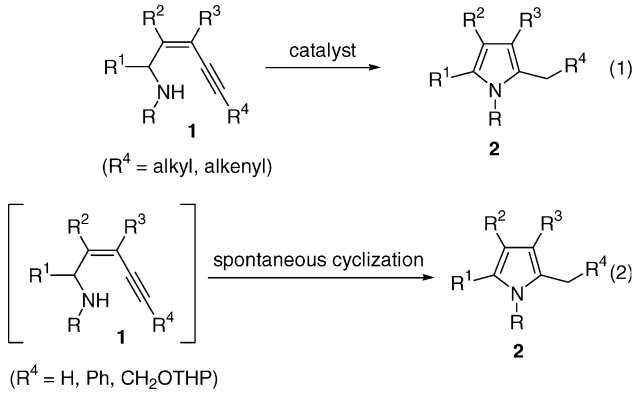
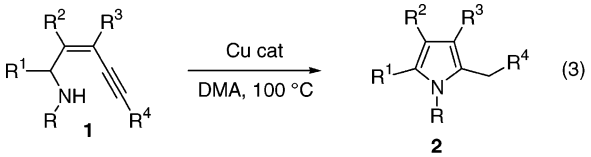


Results and Discussion

Enynamines Substituted at C-3. Enynamines (*Z*)-R⁴C≡CC(R³)=CHCH₂NHR. We began our investigation with enynamines bearing a substituent at C-3 and C-5 and bearing a secondary amino group, such as (*Z*)-benzyl(3-methylnon-2-en-4-ynyl)amine **1a** (R = CH_2Ph, R^3 = Me, R^4 = Bu). The reaction of this substrate was initially carried out under conditions similar to those employed for enynols[4] and enynethiols,[5] i.e., with PdI_2 (1 mol %) in conjunction with KI (2 mol %) as catalyst in anhydrous *N*,*N*-dimethylacetamide (DMA) as the solvent (2 mmol of **1a** per mL of DMA) at 100 °C under nitrogen. After 6 h, GLC analysis revealed the formation of 1-benzyl-3-methyl-2-pentylpyrrole **2a** in 53% yield; formation of unidentified heavy products, as showed by TLC analysis, accounted for substrate conversion (90%, Table 1, entry 1). The reaction did not occur in the absence of catalyst, as confirmed by blank experiments. The nature of alkaline metal cation as well as that of the halide anion (entries 1−7) did not affect substrate conversion and the yield of **2a** significantly, even though slightly higher yields were observed with chloride rather than iodide; modest results were instead obtained by using $Pd(OAc)_2$ (entry 8). Remarkably, a virtually quantitative yield was achieved by changing the metal catalyst to $CuCl_2$ (entry 9 and eq 3) or CuI + 2KI (entry 10).

Similar results were observed using (*Z*)-butyl(3-methylnon-2-en-4-ynyl)amine **1b** and (*Z*)-butyl(3-butylnon-2-en-4-ynyl)amine **1c**, which were somewhat more reactive than **1a** (Table 1, entries 11−16 and eq 3).



a R=Bn, R^1=R^2=H, R^3=Me, R^4= Bu: 91%
b R=R^4=Bu, R^1=R^2=H, R^3=Me: 80%
c R=R^3=R^4=Bu, R^1=R^2=H: 75%
d R=*t*-Bu, R^1=R^2=H, R^3=Me, R^4=Bu: 63%
e R=R^1=R^2=H, R^3=Me, R^4=Bu: 88%
f R=Bn, R^1=R^4=Bu, R^2=H, R^3=Me: 90%
g R=R^4=Bu, R^1=H, R^2=Et, R^3=Ph: 90%
h R=Bn, R^1=R^2=H, R^3=Me, R^4=CH=CMe_2: 83%

Interestingly, using Cu(II) as catalyst the cycloisomerization reaction could also be effected on substrates bearing a bulky substituent on nitrogen, such as *tert*-butyl, even though the reaction rate was decreased. The results obtained with (*Z*)-*tert*-butyl(3-methylnon-2-en-4-ynyl)amine **1d** are reported in Table 1, entries 17−19. With 5% $CuCl_2$ at 100 °C, after 26 h the GLC yield of the corresponding pyrrole **2d** reached 72% (63% isolated) at total substrate conversion (entry 17 and eq 3). Substrate conversion was quantitative after only 8 h working with 10% $CuCl_2$, with a 66% GLC yield of **2d** (entry 19). No reaction occurred under conditions similar to those reported in entries 17−19 using $PdCl_2$ + 2KCl or PdI_2 + 2KI as catalyst.

The cycloisomerization procedure also worked well with substrates substituted at C-3 and C-5 with alkyl groups and bearing a primary amino group. The results obtained with (*Z*)-3-methylnon-2-en-4-ynylamine **1e** are shown in Table 1, entries 20−27. As for **1a**−**d**, Cu-based catalysts ensured a higher yield of pyrrole **2e** [93% GLC yield (88% isolated) using $CuCl_2$, entry 20 and eq 3], with respect to Pd-based catalysts.

Enynamines (*Z*)-R⁴C≡CC(R³)=CHCHR¹NHR. Additional substitution at C-1 with respect to substrates **1a**−**e** resulted in a slight decrease of the substrate conversion rate, both with Cu(II)- and Pd(II)-based catalysts, as exemplified by the results obtained with (*Z*)-benzyl(1-butyl-3-methylnon-2-en-4-ynyl)amine **1f** (Table 2, entries 28−30, to be compared with the results reported in Table 1 for **1a**). As for **1a**−**e**, the best yield in the corresponding pyrrole **2f** (95% GLC yield, 90% isolated) was obtained with $CuCl_2$ as catalyst (entry 28 and eq 3), even though an 86% GLC yield (80% isolated) could also be obtained using $PdCl_2$ + 2KCl (entry 29).

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TABLE 1. Synthesis of Pyrroles 2a−e by Cu- or Pd-Catalyzed Cycloisomerization of Enynamines 1a−e[a]

entry	catalyst	1	R	R^1	R^2	R^3	R^4	*t* (h)	conversion of **1** (%)[b]	yield of **2** (%)[c]
1	PdI_2 + 2KI	**1a**	Bn	H	H	Me	Bu	6	90	53 (48)
2	PdI_2 + 2NaI	**1a**	Bn	H	H	Me	Bu	6	96	55
3	PdI_2 + 2LiI	**1a**	Bn	H	H	Me	Bu	6	99	53
4	$PdCl_2$ + 2KCl	**1a**	Bn	H	H	Me	Bu	6	100	65
5	$PdCl_2$ + 2NaCl	**1a**	Bn	H	H	Me	Bu	6	100	60
6	$PdCl_2$ + 2LiCl	**1a**	Bn	H	H	Me	Bu	6	100	55
7	$(PhCN)_2PdCl_2$	**1a**	Bn	H	H	Me	Bu	6	100	57
8	$Pd(OAc)_2$	**1a**	Bn	H	H	Me	Bu	6	46	20
9	$CuCl_2$	**1a**	Bn	H	H	Me	Bu	6	100	100 (91)
10	CuI + 2KI	**1a**	Bn	H	H	Me	Bu	6	100	98
11	$CuCl_2$	**1b**	Bu	H	H	Me	Bu	3	100	85 (80)
12	$PdCl_2$ + 2KCl	**1b**	Bu	H	H	Me	Bu	14	100	49 (43)
13	PdI_2 + 2KI	**1b**	Bu	H	H	Me	Bu	14	100	52 (47)
14	$CuCl_2$	**1c**	Bu	H	H	Bu	Bu	3	100	81 (75)
15	$PdCl_2$ + 2KCl	**1c**	Bu	H	H	Bu	Bu	3	45	25
16	PdI_2 + 2KI	**1c**	Bu	H	H	Bu	Bu	3	48	26
17[d]	$CuCl_2$	**1d**	*t*-Bu	H	H	Me	Bu	26	100	72 (63)
18[d]	CuI + 2KI	**1d**	*t*-Bu	H	H	Me	Bu	26	61	59
19[e]	$CuCl_2$	**1d**	*t*-Bu	H	H	Me	Bu	8	100	66
20	$CuCl_2$	**1e**	H	H	H	Me	Bu	2	100	93 (88)
21	CuI + 2KI	**1e**	H	H	H	Me	Bu	2	100	87
22	$PdCl_2$ + 2KCl	**1e**	H	H	H	Me	Bu	2	30	23
23	$PdCl_2$ + 2KCl	**1e**	H	H	H	Me	Bu	6	100	75 (69)
24	$(PhCN)_2PdCl_2$	**1e**	H	H	H	Me	Bu	2	42	36
25	PdI_2 + 2KI	**1e**	H	H	H	Me	Bu	2	40	28
26	PdI_2 + 2KI	**1e**	H	H	H	Me	Bu	6	100	73 (68)
27	$Pd(OAc)_2$	**1e**	H	H	H	Me	Bu	2	80	61

[a] Unless otherwise noted, all reactions were carried out under nitrogen at 100 °C using 1 mol % of catalyst in anhydrous DMA (2 mmol of **1**/mL DMA, 3−6 mmol scale based on **1**). [b] Based on starting **1**, by GLC. [c] GLC yield (isolated yield) based on **1**. [d] The reaction was carried out using 5 mol % of catalyst. [e] The reaction was carried out using 10 mol % of catalyst.

TABLE 2. Synthesis of Pyrroles 2f−h by Cu- or Pd-Catalyzed Cycloisomerization of Enynamines 1f−h[a]

entry	catalyst	1	R	R^1	R^2	R^3	R^4	*t* (h)	conversion of **1** (%)[b]	yield of **2** (%)[c]
28[d]	$CuCl_2$	**1f**	Bn	Bu	H	Me	Bu	12	100	95 (90)
29[d]	$PdCl_2$ + 2KCl	**1f**	Bn	Bu	H	Me	Bu	12	100	86 (80)
30[d]	PdI_2 + 2KI	**1f**	Bn	Bu	H	Me	Bu	12	100	42 (35)
31	$CuCl_2$	**1g**	Bu	H	Et	Ph	Bu	1.5	100	100 (90)
32	CuI + 2KI	**1g**	Bu	H	Et	Ph	Bu	1.5	100	100
33	$PdCl_2$ + 2KCl	**1g**	Bu	H	Et	Ph	Bu	1.5	60	35
34	$(PhCN)_2PdCl_2$	**1g**	Bu	H	Et	Ph	Bu	1.5	71	40
35	PdI_2 + 2KI	**1g**	Bu	H	Et	Ph	Bu	1.5	85	68
36	$Pd(OAc)_2$	**1g**	Bu	H	Et	Ph	Bu	1.5	40	22
37	$CuCl_2$	**1h**	Bn	H	H	Me	$CH{=}CMe_2$	5	100	92 (83)
38	$PdCl_2$ + 2KCl	**1h**	Bn	H	H	Me	$CH{=}CMe_2$	5	99	48
39	$(PhCN)_2PdCl_2$	**1h**	Bn	H	H	Me	$CH{=}CMe_2$	5	100	52
40	PdI_2 + 2KI	**1h**	Bn	H	H	Me	$CH{=}CMe_2$	5	68	31
41	$Pd(OAc)_2$	**1h**	Bn	H	H	Me	$CH{=}CMe_2$	5	89	18

[a] Unless otherwise noted, all reactions were carried out under nitrogen at 100 °C using 1 mol % of catalyst in anhydrous DMA (2 mmol of **1**/mL DMA, 3−6 mmol scale based on **1**). [b] Based on starting **1**, by GLC. [c] GLC yield (isolated yield) based on **1**. [d] The reaction was carried out using 2 mol % of catalyst.

Enynamines (*Z*)-$R^4C{\equiv}CC(R^3){=}CR^2CH_2NHR$. $CuCl_2$ turned out to be the catalyst of choice also for enynamines bearing an internal triple bond and a substituent on both olefinic carbons, as in the case of (*Z*)-butyl(2-ethyl-3-phenylnon-2-en-4-ynyl)amine **1g** (Table 2, entries 31−36). A virtually quantitative GLC yield of the corresponding pyrrole **2g** was obtained after only 1.5 h using either $CuCl_2$ (entry 31 and eq 3) or CuI + 2KI (entry 32), whereas under similar conditions the Pd-based catalysts were less active (entries 33−36).

Enynamines (*Z*)-$R^5{}_2C{=}CHC{\equiv}CC(R^3){=}CHCHR^1NHR$. Enynamines with the triple bond conjugated with a double bond behaved similarly to the analogous substrates with the triple bond substituted with an alkyl group. Thus, (*Z*)-benzyl(3,7-dimethylocta-2,6-dien-4-ynyl)amine **1h** was smoothly converted into pyrrole **2h** in 5 h using $CuCl_2$ as catalyst, with a GLC yield as high as 92% (83% isolated, Table 2 entry 37 and eq 3). As before, under analogous conditions, Pd-based catalysts led to lower yields of **2h** (Table 2, entries 38−41).

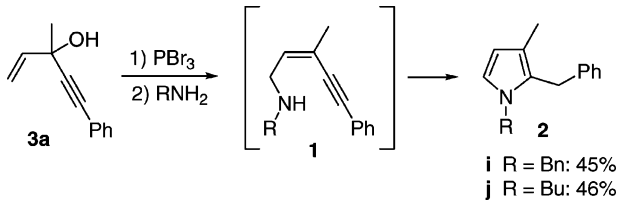
Enynamines (*Z*)-$PhC{\equiv}CC(R^3){=}CHCH_2NHR$. Interestingly, enynamines bearing a triple bond conjugated with a phenyl group turned out to be unstable and underwent spontaneous cyclization to the corresponding pyrroles without need of metal catalysis. Thus, column chromatography of the crude product deriving from bromination of 3-methyl-5-phenylpent-1-en-4-yn-3-ol **3a** followed by nucleophilic substitution with benzylamine or butylamine led to the corresponding pyrroles **2i** and **2j** in 45% and 46% isolated yield based on starting enynol (Scheme 1; allylic isomerization occurred during the bromination step, see Experimental Section for details).

TABLE 3. Synthesis of Pyrroles 2m−o by Cu- or Pd-Catalyzed Cycloisomerization of Enynamines 1m−o[a]

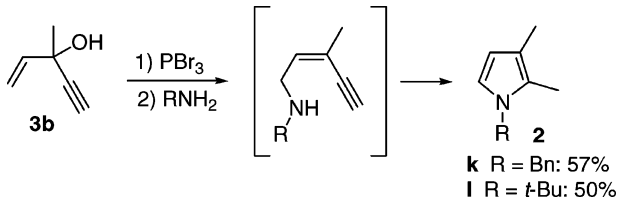
entry	catalyst	1	R	R^1	R^2	R^3	R^4	*t* (h)	conversion of **1** (%)[b]	yield of **2** (%)[c]
42	$PdCl_2$ + 2KCl	**1m**	Bu	H	Et	H	Bu	7	100	90 (85)
43[d]	$PdCl_2$ + 2KCl	**1m**	Bu	H	Et	H	Bu	25	75	69
44	$(PhCN)_2PdCl_2$	**1m**	Bu	H	Et	H	Bu	7	62	47
45	PdI_2 + 2KI	**1m**	Bu	H	Et	H	Bu	7	100	87 (80)
46[d]	PdI_2 + 2KI	**1m**	Bu	H	Et	H	Bu	25	100	89 (83)
47	$Pd(OAc)_2$	**1m**	Bu	H	Et	H	Bu	7	58	52
48	$CuCl_2$	**1m**	Bu	H	Et	H	Bu	7	49	45
49	CuI + 2KI	**1m**	Bu	H	Et	H	Bu	7	90	73
50	$PdCl_2$ + 2KCl	**1n**	Bn	H	Et	H	Bu	6	100	94 (85)
51	PdI_2 + 2KI	**1n**	Bn	H	Et	H	Bu	5	100	92 (82)
52[d]	PdI_2 + 2KI	**1n**	Bn	H	Et	H	Bu	15	100	89 (80)
53	$PdCl_2$ + 2KCl	**1o**	Bu	H	Ph	H	Bu	4	100	93 (86)
54	PdI_2 + 2KI	**1o**	Bu	H	Ph	H	Bu	4	100	95 (86)
55[d]	PdI_2 + 2KI	**1o**	Bu	H	Ph	H	Bu	15	100	96 (87)

[a] Unless otherwise noted, all reactions were carried out under nitrogen at 25 °C using 1 mol % of catalyst in anhydrous DMA (2 mmol of **1**/mL DMA, 3−6 mmol scale based on **1**). [b] Based on starting **1**, by GLC. [c] GLC yield (isolated yield) based on **1**. [d] The reaction was carried out using 0.2 mol % of catalyst.

SCHEME 1



SCHEME 2

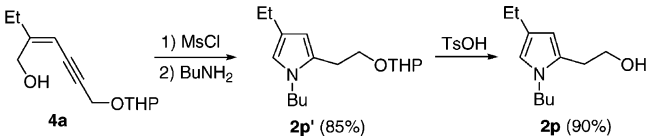


From these reactions, it has also been possible to isolate (*E*)-benzyl(3-methyl-5-phenylpent-2-en-4-ynyl)-amine **1i′** (13% yield based on **3a**) and (*E*)-butyl(3-methyl-5-phenylpent-2-en-4-ynyl)amine **1j′** (10%). Cycloisomerization of these latter compounds did not occur even in the presence of catalyst.

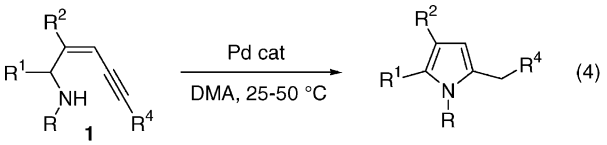
Enynamines (*Z*)-HC≡CC(R^3)=CHCH_2NHR. Spontaneous annulation also occurred in the case of enynamines bearing a terminal triple bond, as shown in Scheme 2 for the synthesis of pyrroles **2k** and **2l**. It is worth noting that cyclization occurred readily even with a sterically hindered amine such as *tert*-butylamine.

Enynamines Unsubstituted at C-3. Enynamines (*Z*)-R^4C≡CCH=C(R^2)CH_2NHR. Enynamines substituted at C-2 and C-5 and unsubstituted at C-3 were considerably more reactive than analogous substrates substituted at C-3, and cycloisomerization reactions could be carried out at 25 °C. Moreover, with these substrates, PdX_2 + 2KX (X = Cl, I) turned out to be more active than Cu-based catalysts, as exemplified by the results obtained with (*Z*)-butyl(2-ethylnon-2-en-4-ynyl)amine **1m**, which are shown in Table 3 (entries 42−49, to be compared with the results reported above for **1a**−**c**). By using $PdCl_2$ + 2KCl (1 mol % of $PdCl_2$) at 25 °C for 7 h, the yield of pyrrole **2m** reached 90% by GLC (85% isolated, entry 42 and eq 4) at total substrate conversion. Interestingly, when the substrate to catalyst molar ratio was raised to 500, the cycloisomerization process was appreciably faster with PdI_2 + 2KI (entry 46) rather than $PdCl_2$ + 2KI (entry 43).

SCHEME 3



Similar results were obtained with (*Z*)-benzyl(2-ethylnon-2-en-4-ynyl)amine **1n** (Table 3, entries 50−52), which was somewhat more reactive than **1m**. Under conditions analogous to those reported in entry 42 for **1m**, substrate conversion reached 100% after 6 h, with a yield of the corresponding pyrrole **2n** of 94% by GLC (85% isolated, entry 50 and eq 4). (*Z*)-Butyl(2-phenylnon-2-en-4-ynyl)-amine **1o**, bearing a phenyl rather than an alkyl substituent at C-2, was also more reactive than **1m**, as shown by the results reported in Table 3 (entries 53−55).



m R=R^4= Bu, R^1=H, R^2=Et : 85%
n R=Bn, R^1=H, R^2=Et, R^4 = Bu: 85%
o R=R^4= Bu, R^1=H, R^2=Ph: 87%
r R=Bn, R^1=R^2=H, R^4=Bu: 88%
s R=Bn, R^1=R^4=Bu, R^2=H: 86%

Interestingly, when R^4 was CH_2OTHP rather than a simple alkyl group, spontaneous cycloisomerization to the corresponding pyrrole occurred. Thus, mesylation of (*Z*)-2-ethyl-6-(tetrahydropyran-2-yloxy)hex-2-en-4-yn-1-ol **4a** followed by nucleophilic substitution with butylamine afforded directly pyrrole **2p′** in 85% isolated yield. After deprotection, 1-butyl-4-ethyl-2-(2-hydroxyethyl)pyrrole **2p** could be recovered in 90% yield with respect to **2p′** (Scheme 3).

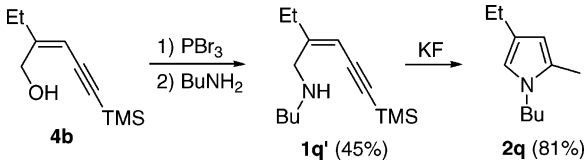
Enynamines (*Z*)-HC≡CCH=CHCH_2NHR. As expected, spontaneous cyclization also took place when the triple bond was terminal, as exemplified by the direct formation of 4-ethyl-2-methylpyrrole **2q** by deprotection

TABLE 4. Synthesis of Pyrroles 2r,s by Cu- or Pd-Catalyzed Cycloisomerization of Enynamines 1r,s[a]

entry	catalyst	1	R	R^1	R^2	R^3	R^4	*t* (h)	conversion of **1** (%)[b]	yield of **2** (%)[c]
56	PdI_2 + 2KI	**1r**	Bn	H	H	H	Bu	15	100	89 (80)
57[d]	PdI_2 + 2KI	**1r**	Bn	H	H	H	Bu	7	100	95 (88)
58	$PdCl_2$ + 2KCl	**1r**	Bn	H	H	H	Bu	15	70	64
59	$(PhCN)_2PdCl_2$	**1r**	Bn	H	H	H	Bu	15	26	21
60	$Pd(OAc)_2$	**1r**	Bn	H	H	H	Bu	15	44	40
61	$CuCl_2$	**1r**	Bn	H	H	H	Bu	15	32	30
62	CuI + 2KI	**1r**	Bn	H	H	H	Bu	15	68	59
63	$PdCl_2$ + 2KCl	**1s**	Bn	Bu	H	H	Bu	26	100	91
64[e]	$PdCl_2$ + 2KCl	**1s**	Bn	Bu	H	H	Bu	8	100	91 (86)
65	$(PhCN)_2PdCl_2$	**1s**	Bn	Bu	H	H	Bu	26	59	50
66	PdI_2 + 2KI	**1s**	Bn	Bu	H	H	Bu	28	100	88
67	$Pd(OAc)_2$	**1s**	Bn	Bu	H	H	Bu	26	52	43
68	$CuCl_2$	**1s**	Bn	Bu	H	H	Bu	26	35	25

[a] Unless otherwise noted, all reactions were carried out under nitrogen at 25 °C using 1 mol % of catalyst in anhydrous DMA (2 mmol of **1**/ mL DMA, 3−6 mmol scale based on **1**). [b] Based on starting **1**, by GLC. [c] GLC yield (isolated yield) based on **1**. [d] The reaction was carried out at 50 °C. [e] The reaction was carried out at 40 °C.

SCHEME 4



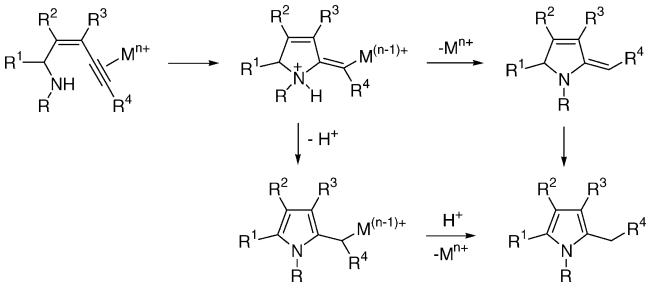
of (*Z*)-butyl(2-ethyl-5-trimethylsilanylpent-2-en-4-ynyl)-amine **1q′** (Scheme 4).

Enynamines (*Z*)-$R^4C{\equiv}CCH{=}CHCH_2NHR$. The cycloisomerization procedure was also successfully applied to substrates unsubstituted at C-2 and C-3 for the synthesis of 2-substituted pyrroles. Actually, the present reaction represents one of the few examples of direct synthesis of 2-susbtituted pyrroles by metal-catalyzed annulation of acyclic precursors.[8] Enynamines unsubstituted at C-2 were slightly less reactive than the analogous ones bearing a substituent at C-2 and required a longer reaction time to achieve complete conversion under analogous conditions. This is evident, for example, by comparing the results obtained with (*Z*)-benzyl(non-2-en-4-ynyl)amine **1r**, reported in Table 4 (entries 56−62) with those shown in Table 3 for **1m**. Using PdI_2 + 2KI at 25 °C, substrate conversion was quantitative after 15 h, with formation of pyrrole **2r** in 89% GLC yield (80% isolated, entry 56). By working at 50 °C, reaction time could be shortened to 7 h with a GLC yield of **2r** of 95% (88% isolated, entry 57 and eq 4).

Enynamines (*Z*)-$R^4C{\equiv}CCH{=}CHCHR^1NHR$. As expected, additional substitution at C-1 with respect to **1r** resulted in a slight decrement of reactivity, as in the case of (*Z*)-benzyl(1-butylnon-2-en-4-ynyl)amine **1s** (Table 4, entries 63−68). The best results in terms of substrate conversion rate and product yield were observed by working with either $PdCl_2$ + 2KCl or PdI_2 + 2KI, while the other Pd-based catalysts tested as well as $CuCl_2$ were less active. Using $PdCl_2$ + 2KCl, GLC yield of pyrrole **2s** was as high as 91% either after 26 h at 25 °C (entry 63) or after 8 h at 40 °C, with an isolated yield of 86% (entry 64 and eq 4).

(8) CuI-assisted cycloisomerization of alkynyl imines (30 mol % of CuI with respect to the substrate) to 2-substituted pyrroles, carried out at 110 °C under basic conditions (1:7 Et_3N/DMA), has been recently reported: Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074−2075.

SCHEME 5



On the basis of the results obtained above the following observations can be made on cycloisomerization of (*Z*)-(2-en-4-ynyl)amines to substituted pyrroles:

(a) Spontaneous cycloisomerization occurred when the triple bond of (*Z*)-(2-en-4-ynyl)amines was either (i) terminal, (ii) conjugated with a phenyl group, or (iii) substituted with a CH_2OTHP group. This is conceivable, since uncatalyzed nitrogen attack on the triple bond becomes possible when the triple bond is less hindered or made more electrophilic by conjugation to a phenyl group or substitution with an alkyl group bearing an electron-withdrawing substituent.

(b) When the triple bond was substituted with an alkyl or alkenyl group, (*Z*)-(2-en-4-ynyl)amines were stable and isolable and could be smoothly converted into the corresponding pyrroles in high yields through catalysis by copper or palladium.

(c) No cycloisomerization occurred in the case of (*E*)-(2-en-4-ynyl)amines, either spontaneous or catalyzed. This means that, analogously to what we have previously observed for 2-en-4-yn-1-ols,[4] no *E* → *Z* isomerization occurred under the reaction conditions.

(d) For stable enynamines requiring metal catalysis for cycloisomerization to occur, substrate reactivity was much higher in the absence of a substituent at C-3. This is in agreement with an *anti* 5-*exo*-*dig* mechanism, with the triple bond activated by coordination to the metal cation from the opposite site with respect to the CHR^1NHR moiety (Scheme 5, unreactive ligands are omitted for clarity). Clearly, such coordination is more favored in the absence of substitution at C-3 for steric reasons. The resulting vinylmetal intermediate then undergoes protonolysis and aromatization or vice versa to give the pyrrole with regeneration of the catalyst.

(e) Palladium catalysis was significantly more sensitive to the steric effects exerted by the substituent at C-3 than copper catalysis. This can be due to the larger ionic radius of Pd^{2+} with respect to both Cu^{2+} and Cu^{+},[9] although other effects (such as a different coordination environment) might also be at work. As a consequence, in the presence of C-3 substitution, both $CuCl_2$ and CuI + 2KI turned out to be more active catalysts than Pd-based catalysts, either neutral (as in the case of $(PhCN)_2PdCl_2$ or $Pd(OAc)_2$) or anionic (as in the case of PdX_4^{2-}, formed in situ from PdX_2 + 2 KX, X = Cl or I). $CuCl_2$ usually gave slightly better results than CuI + 2KI, which is in agreement with the diminished steric requirements of a complex bearing chlorides rather than iodides as ligands. This effect is partially counterbalanced by the higher electron-releasing power of I^- as compared with Cl^-, which tends to favor protonolysis when X = I rather than Cl.

(f) For substrates unsubstituted at C-3, PdX_4^{2-} (X = Cl, I) catalysts were more active than CuI + 2KI, which was in its turn significantly more active than $CuCl_2$. On the other hand, neutral palladium catalysts (such as $(PhCN)_2PdCl_2$ or $Pd(OAc)_2$) showed low reactivity, comparable to that of $CuCl_2$. These results indicate that, in the absence of a steric hindrance at C-3, active catalytic species are actually favored by halide ligands. Moreover, although $PdCl_2$ + 2KCl and PdI_2 + 2KI showed a level activity with a substrate to Pd molar ratio of 100, PdI_2 + 2KI was somewhat more active when this ratio was raised to 500. The higher electron-releasing power of I^- as compared with Cl^-, which tends to favor protonolysis when X = I rather than Cl, can be responsible for this effect.

(g) As expected in view of a mechanism involving intramolecular nucleophilic attack by the nitrogen of the NHR moiety to the triple bond, the cycloisomerization reaction was sensitive to the steric effect exerted by the substituent on nitrogen. For example, other substituents and reaction conditions being the same, reactivity decreased passing from R = H to R = Bu or Bn and even more to R = *t*-Bu. Also, nitrogen nucleophilicity was affected by α-substitution, as shown by the fact that slower reactions were usually observed for substrates bearing an additional substituent at C-1 with respect to the analogous ones unsubstituted at C-1.

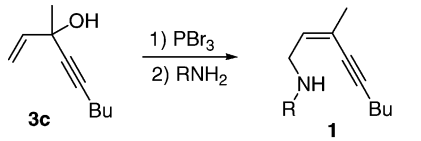
(h) Substitution at C-2 tended to enhance substrate reactivity. This effect is clearly related to the steric assistance exerted by the R^2 group; in fact, the unfavorable steric repulsion between the substituent and the CHR^1NHR moiety is relieved going through the transition state leading to cyclization.

(i) Phenyl rather than alkyl substitution on olefinic carbons resulted in higher reactivity. This is apparently due to the stabilizing effect exerted by the phenyl group by conjugation in the transition state leading to final pyrrole.

Conclusions

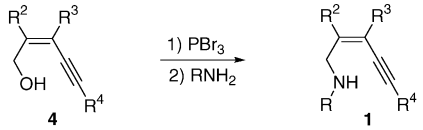
We have shown that spontaneous or catalyzed cycloisomerization of readily available (*Z*)-(2-en-4-ynyl)amines is a powerful technique for the construction of the pyrrole ring with the desired substitution pattern. The methodology is quite general and allows the regioselective synthesis of substituted pyrroles in high yields under mild conditions. The amino group of the substrate can be either primary or secondary, and the nitrogen can be substituted even with a very bulky group such as *tert*-butyl. The triple bond can be terminal or internal, and in the latter case alkyl, aryl, and alkenyl, as well as functionalyzed groups, can be present as substituents.

SCHEME 6



a R=Bn: 79%
b R=Bu: 51%
d R=t-Bu: 81%

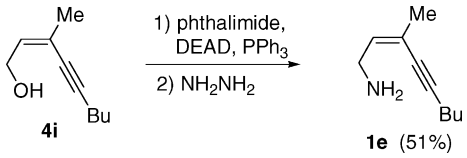
SCHEME 7



c R^2=H, R^3=R^4=Bu
d R^2=Et, R^3=Ph, R^4=Bu
e R^2=H, R^3=Me, R^4=CH=CMe_2
f R^2=Et, R^3=H, R^4=Bu
g R^2=Ph, R^3=H, R^4=Bu
h R^2=R^3=H, R^4=Bu

c R=R^3=R^4=Bu, R^2=H: 68%
g R=R^4=Bu, R^2=Et, R^3=Ph: 74%
h R=Bn, R^2=H, R^3=Me, R^4=CH=CMe_2: 66%
m R=R^4=Bu, R^2=Et, R^3=H: 66%
n R=Bn, R^2=Et, R^3=H, R^4=Bu: 52%
o R=R^4=Bu,R^2=Ph, R^3=H: 78%
r R=Bn, R^2=R^3=H, R^4=Bu: 74%

SCHEME 8



Experimental Section

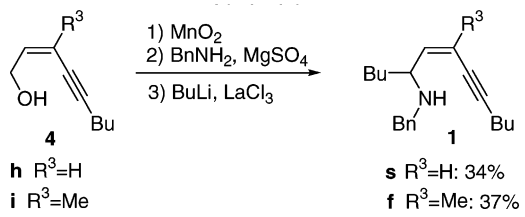
Synthesis of (*Z*)-(2-en-4-ynyl)amines 1. Enynamines **1a**−**d**, **1g,h**, **1m**−**o**, and **1r**, bearing a secondary amino group, were easily prepared by bromination of either 3-methylnon-1-en-4-yn-3-ol **3c** or (*Z*)-2-en-4-yn-1-ols **4c**−**h** with PBr_3 followed by nucleophilic substitution with RNH_2 (Schemes 6 and 7). Allylic isomerization occurred in the course of bromination of **3c** to give a ca. 20:1 (by GLC and GC−MS) *Z*:*E* mixture of the more stable allylic primary bromide. Following the reaction with RNH_2, (*Z*)-(2-en-4-ynyl)amine **1a**, **1b**, or **1d** could be easily isolated in the pure state by column chromatography, as detailed below.

Enynamine **1e** bearing a primary amino group was prepared from (*Z*)-3-methylnon-2-en-4-yn-1-ol **4i** by reaction with phthalimide under Mitsunobu conditions,[10] followed by cleavage with hydrazine (Scheme 8). Enynamines **1f** and **1s** bearing a substituent α to the amino group were prepared from **4i** or (*Z*)-non-2-en-4-yn-1-ol **4h**, respectively, through oxidation with MnO_2 to give (*Z*)-2-en-4-ynals, reaction with RNH_2 to the corresponding imines, and regioselective addition of BuLi in the presence of $LaCl_3$ (Scheme 9).

(9) Shannon, R. D.; Prewitt, C. T. *Acta Crystallogr.* **1969**, *B25*, 925−946.

(10) Mitsunobu, O. *Synthesis* **1981**, 1−28.

SCHEME 9



Preparation of Enynols 3c and 4c−h. Enynols **3c**, **4e−h** were prepared as we already reported.[4] Enynol **4c,d** were prepared by Pd/Cu-catalyzed coupling between (*Z*)-3-iodohept-2-en-1-ol[11] or (*Z*)-2-ethyl-3-iodo-3-phenylprop-2-en-1-ol, respectively, and 1-hexyne, as described below. (*Z*)-2-Ethyl-3-iodo-3-phenylprop-2-en-1-ol was prepared by addition of EtMgBr to 3-phenylprop-2-yn-1-ol[12] followed by iodolysis according to Duboudin.[13] To a cooled solution (0 °C) of 3-phenylprop-2-yn-1-ol (10.0 g, 75.8 mmol) and CuI (1.44 g, 7.6 mmol) in Et_2O (100 mL) was added dropwise a solution of EtMgBr [prepared from 20.6 g (189 mmol) of EtBr, 5.0 g (206 mmol) of Mg and 100 mL of Et_2O]. After being stirred at room temperature for 3 h, the reaction mixture was cooled to 0 °C and iodine (25.9 g, 102 mmol) was added in small portions. The mixture was then allowed to stir at 0 °C for 1 h and then at room temperature for 1 h. After cooling to 0 °C, the reaction mixture was quenched with saturated NH_4Cl, and phases were separated. The aqueous layer was extracted with Et_2O, and the collected organic phases were washed with saturated $Na_2S_2O_3$ and water and eventually dried over Na_2SO_4. The solvent was evaporated, and the crude iodide was used for the next step without further purification.

The method of Alami[14] was employed for the coupling. To a cooled (0 °C), stirred mixture of $Pd(PPh_3)_4$ (2.86 g, 2.5 mmol) and CuI (950 mg, 5.0 mmol) in pyrrolidine (10 mL) was added dropwise a solution of the vinyl iodide (12.0 g, 50 mmol of (*Z*)-3-iodohept-2-en-1-ol, or crude (*Z*)-2-ethyl-3-iodo-3-phenylprop-2-en-1-ol obtained as above) in pyrrolidine (50 mL), followed by stirring for 5 min. A solution of BuC≡CH (8.1 g, 98.6 mmol) in pyrrolidine (10 mL) was then added dropwise at 0 °C. After stirring at room temperature for 2 h, the reaction mixture was diluted with Et_2O and quenched at 0 °C with saturated NH_4Cl. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The residue then was purified by column chromatography on silica gel: **4c** was a yellow oil (8:2 hexane−AcOEt, 9.0 g, 93% based on (*Z*)-3-iodohept-2-en-1-ol); **4d** was a colorless oil (9:1 hexane−AcOEt, 10.4 g, 57% based on starting 3-phenylprop-2-yn-1-ol).

General Procedure for Bromination of 3c or 4c−h Followed by Reaction with RNH_2 (Schemes 6 and 7). To a cooled (−15 °C) solution of **3c** or **4c−h** (30.0 mmol) in anhydrous Et_2O (5.2 mL) and pyridine (490 μL) was added dropwise a solution of PBr_3 (3.2 g, 11.8 mmol) in Et_2O (18 mL). After being stirred at room temperature for 0.5 h, the reaction mixture was quenched with water, and the phases were separated. The aqueous layer was extracted with Et_2O, and the collected organic phases were washed with saturated $NaHCO_3$, washed with water to neutral pH, dried over Na_2SO_4, and evaporated. The crude allylic primary bromide thus obtained was then used for the next step without further purification. The procedure described by Nussbaumer[15] was employed for the amination. To a cooled solution of RNH_2 (490 mmol) in EtOH (60 mL) maintained at 0 °C was added dropwise a solution of the bromide in anhydrous DMF (16 mL). After being stirred at 0 °C for 1 h, the mixture was allowed to stir at room temperature overnight. The solvent was evaporated, and the residue was quenched with water and extracted several times with Et_2O. The aqueous layer was basified to pH 9 with 1 N NaOH and then extracted several times with Et_2O. The basic organic layer was analyzed by TLC and GLC; in some cases it only contained RNH_2 and was discarded, otherwise it was added to the previously obtained organic phase. After drying over Na_2SO_4, the solvent was evaporated, and crude enynamines were purified by column chromatography on silica gel: **1a** was a pale yellow oil (hexane−AcOEt from 9:1 to 8:2, 5.72 g, 79% based on starting **3c**); **1b** was a yellow oil (hexane−AcOEt from 9:1 to 7:3, 3.17 g, 51% based on starting **3c**); **1c** was a colorless oil (hexane−AcOEt from 9:1 to 8:2, 5.09 g, 68% based on starting **4c**); **1d** was a yellow oil (hexane−AcOEt from 9:1 to 7:3, 5.04 g, 81% based on starting **3c**); **1g** was a yellow oil (hexane−AcOEt from 9:1 to 7:3, 6.60 g, 74% based on starting **4d**); **1h** was a yellow oil (hexane−AcOEt from 98:2 to 90:10, 4.74 g, 66% based on starting **4e**); **1m** was a yellow oil, hexane−AcOEt from 9:1 to 7:3, 4.38 g, 66% based on starting **4f**); **1n** was a pale yellow oil (hexane−AcOEt from 9:1 to 7:3, 3.98 g, 52% based on starting **4f**); **1o** was a yellow oil (hexane−AcOEt from 9:1 to 7:3, 6.30 g, 78% based on starting **4g**); **1r** was a pale yellow oil, 9:1 hexane−AcOEt, 5.05 g, 74% based on starting **4h**).

(*Z*)-(3-Methylnon-2-en-4-ynyl)amine 1e (Scheme 8). The method of Hegedus[16] was employed. To a stirred solution of phthalimide (13.2 g, 90 mmol) and PPh_3 (23.6 g, 90 mmol) in anhydrous THF (382 mL) was added dropwise a mixture of (*Z*)-3-methylnon-2-en-4-yn-1-ol **4i**[4] (11.6 g, 76.2 mmol) and DEAD (15.7 g, 90 mmol). During the addition, the reaction flask was suitably cooled so that the reaction temperature would not exceed 25 °C. The mixture was allowed to stir at room temperature for 3 days. After elimination of the solvent in vacuo, a pale yellow semisolid was obtained, which was dissolved in MeOH (380 mL). Hydrazine monohydrate (7.7 g, 154 mmol) was added slowly, and the resulting mixture was refluxed overnight. After cooling to room temperature, concentrated HCl (11.5 mL) was added, and the mixture refluxed overnight. The solvent was evaporated to obtain a pale yellow solid, which was washed several times with 90 mL of a HCl solution prepared from 13.4 mL of concentrated HCl and 383 mL of water. After filtration, the collected aqueous phases were collected and washed with $CHCl_3$ (7 × 58 mL) and Et_2O (3 × 58 mL). The aqueous phase was cooled to 0 °C and basified with saturated NaOH to pH 13. Phases were separated, the aqueous phase was extracted with Et_2O (10 × 60 mL), and the collected organic layers were washed with brine (4 × 95 mL) and dried (Na_2SO_4). After evaporation of the solvent, the brown residue was distilled under reduced pressure (28−29 °C/47 × 10^{-2} mmHg) to give **1e** as a colorless oil (5.9 g, 51% based on **4i**).

(*Z*)-Benzyl-(1-butyl-3-methylnon-2-en-4-ynyl)amine 4f and (*Z*)-Benzyl-(1-butylnon-2-en-4-ynyl)amine 4s (Scheme 9). The method of Dixneuf[17] was employed for the oxidation of enynols **4h,i**. To a stirred suspension of MnO_2 (20.0 g, 230 mmol) in CH_2Cl_2 (75 mL) was added enynol **4h** or **4i** (30.0 mmol) in 15 min, and the mixture was allowed to stir at room temperature for 16 h. After filtration through Celite, the solvent was evaporated, and the crude aldehyde thus obtained was used as such for the next step. The method of Martin[18]

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was used for the formation of imines. To a cooled (0 °C) solution of $MgSO_4$ (3.30 g, 27.4 mmol) and benzylamine (2.94 g, 27.5 mmol) in anhydrous Et_2O (34 mL) was added dropwise the crude aldehyde. The mixture was allowed to stir for 0.5 h at 0 °C and then at room temperature for 15 h. After filtration, the solvent was evaporated, and the crude imine thus obtained was used as such for the next step. The method of Qian[19] was employed for the regioselective addition of BuLi to the imino group. A mixture of $LaCl_3$ (7.3 g, 29.8 mmol) in anhydrous THF (60 mL) was allowed to stir at room temperature for 2 h. The resulting white slurry suspension was then cooled to −78 °C, and a 1.6 M solution of BuLi in hexane (18.6 mL, 29.8 mmol) was added dropwise. After stirring for 1 h at −78 °C, a solution of the imine in THF (15 mL) was added dropwise, and the resulting mixture was allowed to stir at −78 °C for 4 h. The reaction was quenched with a saturated solution of NaF (150 mL) and filtered to remove lanthanum fluoride. Phases were separated, and the aqueous phase was extracted 5 times with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. The crude product was then purified by column chromatography on silica gel: **1f** was a yellow oil (9:1 hexane−AcOEt, 3.30 g, 37% based on **4i**); **1s** was a yellow oil (9:1 hexane−AcOEt, 2.89 g, 34% based on **4h**).

General Procedure for Cycloisomerization of Enynamines 1a−h, 1m−o, 1r,s. Reactions were carried out on a 3−6 mmol scale based on enynamine **1**. Catalyst composition, substrate to catalyst molar ratio, reaction temperature and time, and yields of pyrroles **2** are indicated in Tables 1−4. In a typical experiment, the catalyst was added to a solution of **1** (5 mmol) in anhydrous DMA (2.5 mL) in a Schlenk flask. The resulting mixture was stirred at the temperature and for the time indicated in Tables 1−4. Solvent was evaporated and the crude product purified by column chromatography on silica gel: **2a** was a yellow oil (99:1 hexane−AcOEt); **2b** was a colorless oil (pure hexane); **2c** was a colorless oil (90:10 hexane−AcOEt); **2d** was a colorless oil (97:3 hexane−AcOEt); **2e** was a yellow oil (pure Et_2O); **2f** was a pale yellow oil (97:3 hexane−AcOEt); **2g** was a coloress oil (99:1 hexane−AcOEt); **2h** was a yellow oil (98:2 hexane−AcOEt); **2m** was a colorless oil (pure hexane); **2n** was a yellow oil (pure Et_2O); **2o** was a yellow oil (pure hexane); **2r** was a pale yellow oil (98:2 hexane−AcOEt); **2s** was a yellow oil (97:3 hexane−AcOEt).

Spontaneous Cycloisomerization to Pyrroles 2i,j (Scheme 1). Starting 3-methyl-5-phenylpent-1-en-4-yn-3-ol **3a** was prepared as we already reported.[4] Bromination of **3a** followed by reaction with RNH_2 was carried out as described above in the general procedure, starting from 5.17 g (30.0 mmol) of the enynol. As above, bromination occurred with allylic isomerization to give a ca. 4:1 (by GLC and GC−MS) mixture of (*Z*)- and (*E*)-(5-bromo-3-methylpent-3-en-1-ynyl)-benzene. The Et_2O extracts deriving from amination of the mixture of bromides with $BnNH_2$ contained a ca. 45:30:25 mixture of 1,2-dibenzyl-3-methylpyrrole (**2i**)/(*Z*)-benzyl(3-methyl-5-phenylpent-2-en-4-ynyl)amine (**1i**)/(*E*)-benzyl(3-methyl-5-phenylpent-2-en-4-ynyl)amine **1i′**, as shown by GC−MS analysis. Column chromatography (SiO_2, hexane−AcOEt from 9:1 to 3:7) of the crude mixture afforded 3.53 g of **2i** (yellow oil, 13.51 mmol, 45% yield based on **3a**) and 1.01 g of **1i′** (yellow oil, 3.86 mmol, 13% based on **3a**). This result clearly shows that further conversion of **1i** into **2i** occurred during the purification procedure.

Similar results were obtained from amination of the crude mixture of the bromides with $BuNH_2$: column chromatography (SiO_2, hexane−AcOEt from 85:15 to 0:100) afforded 3.12 g of 2-benzyl-1-butyl-3-methylpyrrole **2j** (pale yellow oil, 13.72 mmol, 46% based on **3a**) and 680 mg of (*E*)-butyl(3-methyl-5-phenylpent-2-en-4-ynyl)amine **1j′** (yellow oil, 2.99 mmol, 10% based on **3a**).

Spontaneous Cycloisomerization to Pyrroles 2k,l (Scheme 2). Starting 3-methylpent-1-en-4-yn-3-ol **3b** was commercially available; alternatively, it could be prepared as we already reported.[4] Bromination of **3b** followed by reaction with RNH_2 was carried out as described above in the general procedure, starting from 2.88 g (30.0 mmol) of the enynol. The Et_2O extracts, containing a ca. 20:1 (by GLC and GC−MS) mixture of (*Z*)- and (*E*)-5-bromo-3-methylpent-3-en-1-yne, were distilled at atmospheric pressure rather than in vacuo to eliminate the solvent. Column chromatography (SiO_2, 9:1 hexane−AcOEt) of the reaction crude deriving from amination with $BnNH_2$ afforded 3.17 g of 1-benzyl-2,3-dimethylpyrrole **2k** (17.11 mmol, 57% yield based on **3b**) as a low-melting (36−37 °C) colorless solid. In the case of amination with *t*-$BuNH_2$, the Et_2O extracts were distilled at atmospheric pressure rather than in vacuo to eliminate the solvent. Transfer distillation of the residue finally afforded 2.25 g of 1-*tert*-butyl-2,3-dimethylpyrrole **2l** as a pale yellow oil (14.88 mmol, 50% based on **3b**).

Synthesis of 2-(1-Butyl-4-ethylpyrrol-2-yl)ethanol 2p (Scheme 3). Starting (*Z*)-2-ethyl-6-(tetrahydropyran-2-yloxy)-hex-2-en-4-yn-1-ol **4a** was prepared by Pd/Cu-catalyzed coupling between (*Z*)-2-ethyl-3-iodoprop-2-en-1-ol[4] and commercially available 2-prop-2-ynyloxytetrahydropyran employing the method of Alami.[14] To a cooled (0 °C), stirred mixture of $Pd(PPh_3)_4$ (1.32 g, 1.14 mmol) and CuI (435 mg, 2.28 mmol) in pyrrolidine (4.5 mL) was added dropwise a solution of the vinyl iodide (4.78 g, 22.6 mmol) in pyrrolidine (18 mL), followed by stirring for 5 min. A solution of $HC{\equiv}CCH_2OTHP$ (6.41 g, 45.7 mmol) in pyrrolidine (4.0 mL) was then added dropwise at 0 °C. After being stirred at room temperature for 1 h, the reaction mixture was quenched with saturated NH_4Cl and extracted several times with CH_2Cl_2. The combined organic layers were washed with brine and water, dried ($CaCl_2$), and evaporated. The residue then was purified by column chromatography on silica gel using hexane−AcOEt from 9:1 to 8:2 to give **4a** (4.55 g, 20.3 mmol, 90%) as a pale yellow oil.

The method of Marshall[20] was used for mesylation of **4a**. To a cooled (−78 °C), stirred solution of **4a** (1.84 g, 8.20 mmol) in anhydrous CH_2Cl_2 (41 mL) were added Et_3N (2.3 mL) and MsCl (1.41 g, 12.31 mmol). The resulting mixture was allowed to stir at −78 °C for 1 h to obtain a suspension. The reaction was quenched at −78 °C with saturated $NaHCO_3$, allowed to warm to room temperature, stirred at room temperature for additional 15 min, and finally extracted several times with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. The crude mesylate thus obtained was then used as such for the next step. To a cooled solution of $BuNH_2$ (12.2 g, 166.8 mmol) in EtOH (21 mL) maintained at 0 °C was added dropwise a solution of the mesylate in anhydrous DMF (5 mL). After being stirred at 0 °C for 1 h, the mixture was allowed to stir at room temperature for 1 h. The solvent was evaporated, and the residue was quenched with water and extracted several times with Et_2O. After drying over Na_2SO_4, the solvent was evaporated, and the residue was purified by column chromatography on silica gel using 8:2 hexane−AcOEt as eluent to give 1.94 g of 1-butyl-4-ethyl-2-[2-(tetrahydropyran-2-yloxy)ethyl]pyrrole **2p′** as a colorless oil (6.94 mmol, 85% based on starting **4a**).

Deprotection of **2p′** was effected using the method of Ueda.[21] To a stirred solution of **2p′** (1.69 g, 6.05 mmol) in MeOH (100 mL) was added *p*-toluenesulfonic acid monohydrate (115 mg, 0.60 mmol), and the resulting mixture was allowed to stir at room temperature for 1 h, then diluted with CH_2Cl_2, and washed with brine. After driying over Na_2SO_4, the solvent was evaporated, and the residue was purified by column chromatography on silica gel using hexane−AcOEt from 8:2 to 7:3 to give 1.06 g of **2p** as a yellow oil (5.43 mmol, 90% based on **2p′**).

Spontaneous Cycloisomerization to 1-Butyl-4-ethyl-2-methylpyrrole 2q (Scheme 4). Starting (*Z*)-2-ethyl-5-

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trimethylsilanylpent-2-en-4-yn-1-ol **4b** was prepared as we already reported.[4] Bromination of **4b** followed by reaction with $BuNH_2$ was carried out as described above in the general procedure, starting from 5.47 g (30.0 mmol) of the enynol. Column chromatography (SiO_2, hexane−AcOEt from 9:1 to 7:3) afforded 3.21 g of (*Z*)-butyl(2-ethyl-5-trimethylsilanylpent-2-en-4-ynyl)amine **1q′** as a pale yellow oil (13.52 mmol, 45% based on **4b**).

To a stirred solution of **1q′** (622 mg, 2.62 mmol) in MeOH (4.8 mL) was added KF (228 mg, 3.93 mmol), and the resulting mixture was allowed to stir at room temperature overnight. The reaction mixture was diluted with Et_2O and quenched with water. Phases were separated, and the aqueous phase was extracted several times with Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated. Column chromatography (SiO_2, 95:5 hexane−AcOEt) afforded 350 mg of **2q** as a yellow oil (2.12 mmol, 81% based on **1q′**).

Supporting Information Available: General experimental methods and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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