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Versatile Synthesis of Pyrrole-2-acetic Esters and (Pyridine-2-one)-3-acetic Amides by Palladium-Catalyzed, Carbon Dioxide-Promoted Oxidative Carbonylation of (*Z*)-(2-En-4-ynyl)amines

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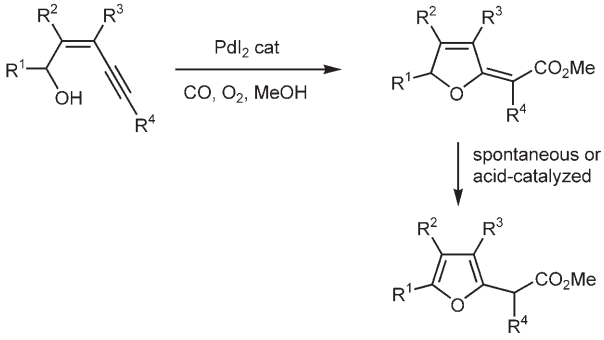
Abstract: The oxidative carbonylation of readily available (*Z*)-(2-en-4-ynyl)amines, catalyzed by the PdI_2-KI system, selectively afforded in satisfactory yields (40–95%) either pyrrole-2-acetic ester or (pyridine-2-one)-3-acetic amide derivatives, depending on the susbtitution pattern of the substrate and the reaction conditions. The presence of an excess of carbon dioxide proved in most cases to be beneficial to both the reaction rate and product selectivity.

Keywords: carbon dioxide; carbonylations; palladium; pyridinones; pyrroles

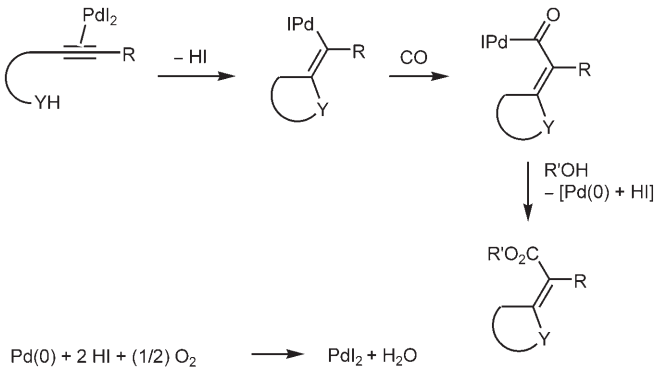
Introduction

Palladium-catalyzed heterocyclization-carbonylation of suitably functionalized alkynes has become a powerful methodology for the direct, one-step synthesis of carbonylated heterocycles.[1] In this respect, we have recently reported several new syntheses of heterocycles by PdI_2-catalyzed 5-*exo-dig* cyclization-alkoxycarbonylation, as shown in Scheme 1 (in this and in the following schemes unreactive ligands on palladium are omitted for clarity).[2–4]

In some cases, the initially formed product may undergo spontaneous or acid-promoted isomerization to give an aromatic derivative, as exemplified by the synthesis of furanacetic esters starting from (*Z*)-2-en-4-yn-1-ols (Scheme 2).[5]

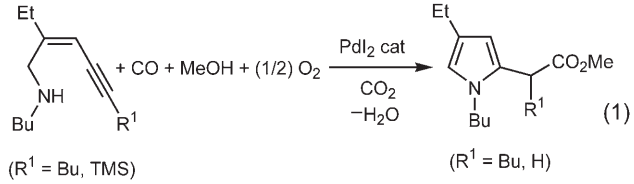


Scheme 2.

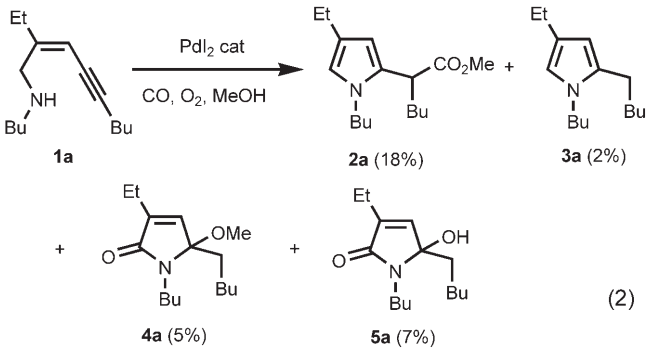


Scheme 1.

Recently, we have also communicated that some (*Z*)-(2-en-4-ynyl)amines can undergo PdI_2-catalyzed, CO_2-promoted oxidative heteroannulation-alkoxycarbonylation-aromatization to give pyrrole-2-acetic esters, according to Eq. (1).[6]



In this work, we present a full account of the PdI_2-catalyzed oxidative carbonylation of (*Z*)-(2-en-4-ynyl)amines. We have found that, depending on the substitution pattern of the substrate and on the reaction conditions, the process can selectively lead to pyrrole-2-acetic ester or (pyridine-2-one)-3-acetic amide derivatives, in satisfactory yields.[7] In most cases, working in the presence of an excess of CO_2 had a beneficial effect on both the reaction rate and product selectivity.

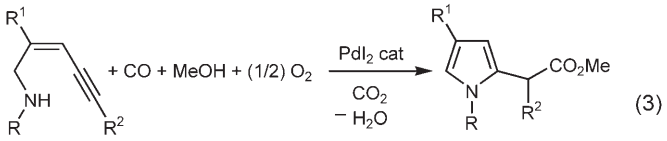


(2)

Results and Discussion

The oxidative carbonylation reaction was initially carried out using butyl-(2-ethylnon-2-en-4-ynyl)amine **1a** as the substrate, under conditions analogous to those already successfully employed for the synthesis of furan-2-acetic esters starting from (*Z*)-2-en-4-yn-1-ols,[5] that is, under 90 atm of a 9:1 mixture of CO-air at 70 °C for 15 h, in the presence of PdI_2-KI as the catalytic system (**1a**/KI/PdI_2 molar ratio = 1000:50:1, substrate concentration = 0.22 mmol mL^{-1} of MeOH). Under these conditions, however, the expected 2-(1-butyl-4-ethyl-1*H*-pyrrol-2-yl)hexanoic acid methyl ester **2a** was obtained in only 18% GLC yield, together with small amount of 1-butyl-4-ethyl-2-pentyl-1*H*-pyrrole **3a** (2% GLC yield, deriving from a competitive cycloisomerization process)[8] and its oxidation products, 1-butyl-3-ethyl-5-methoxy-5-pentyl-1,5-dihydropyrrol-2-one **4a** (5% GLC yield) and 1-butyl-3-ethyl-5-hydroxy-5-pentyl-1,5-dihydropyrrol-2-one **5a** [7% GLC yield, Eq. (2) and Table 1, entry 1].[9,10]

In order to improve the reaction selectivity towards the formation of **2a**, we have carried out a systematic study on the influence of the reaction conditions on substrate conversion and product distribution (Table 1, entries 2–8). From these data, it is clear that selectivity toward **2a** could be improved: a) by working with a lower substrate-to-catalyst ratio; b) by decreasing the substrate concentration; c) by increasing the KI/PdI_2 molar ratio and d) by working in the presence of added CO_2. Under the optimized conditions shown in Table 2, entry 9 (70 °C for 5 h in MeOH as the solvent, substrate concentration = 0.05 mmol mL^{-1} of MeOH, **1e**:KI:PdI_2 molar ratio = 100:200:1, under 90 atm of a 3:1:5 mixture of CO:air:CO_2), the desired pyrrole-2-acetic derivative **2a** was selectively obtained in 71% GLC yield [63% isolated, Eq. (3)].[11]



(3)

1a: R = R^2 = Bu, R^1 = Et
1b: R = Bu, R^1 = Et, R^2 = SiMe$_3$
1c: R = R^2 = Bu, R^1 = Ph

2a: R = R^2 = Bu, R^1 = Et (71%)
2b: R = Bu, R^1 = Et, R^2 = H (75%)
2c: R = R^2 = Bu, R^1 = Ph (70%)

Table 1. Reactions of butyl-(2-ethylnon-2-en-4-ynyl)amine **1a** with CO and O_2 in MeOH at 70 °C in the presence of the PdI_2-KI catalytic system.

Entry	PdI_2:KI:**1a** Molar Ratio	P_{CO} [atm]	P_{air} [atm]	Concentration of **1a**[a]	*t* [h]	Conversion of **1a** [%][b]	Yield of **2a** [%][c]	Yield of **3a** [%][c]
1[d]	1:50:1000	90	10	0.22	15	100	18	2
2[e]	1:50:1000	90	10	0.22	5	54	8	17
3	1:50:1000	60	10	0.22	5	50	10	23
4	1:50:1000	30	10	0.22	5	40	5	30
5	1:50:100	30	10	0.22	5	77	27	27
6	1:50:100	30	10	0.05	5	63	26	22
7	1:200:100	30	10	0.05	5	100	50 (40)	9
8[f]	1:50:100	30	10	0.05	5	100	56	

[a] Mmol of **1a**/mL of MeOH.
[b] Based on starting **1a**, by GLC.
[c] GLC yield (isolated yield) based on **1a**.
[d] The reaction also led to the formation of 1-butyl-3-ethyl-5-methoxy-5-pentyl-1,5-dihydropyrrol-2-one **4a** (5%) and 1-butyl-3-ethyl-5-hydroxy-5-pentyl-1,5-dihydropyrrol-2-one **5a** (7%).
[e] The reaction also led to the formation of **4a** (1%) and **5a** (1%).
[f] The reaction was carried out under 30 atm of CO, 10 atm of air and 50 atm of CO_2.

Table 2. Synthesis of pyrrole-2-acetic esters **2a–c** by Pd-catalyzed, CO_2-promoted oxidative methoxycarbonylation of secondary (*Z*)-(2-en-4-ynyl)amines substituted at C-2 and at C-5.[a]

Entry	1	R	R^1	R^2	Yield of **2** [%][b]	Yield of **3** [%][c]
9	**1a**	Bu	Et	Bu	71 (63)	
10	**1b**	Bu	Et	TMS	75 (65)[d]	
11	**1c**	Bu	Ph	Bu	70 (61)	8
12[e]	**1b**	Bu	Et	TMS	36[d]	3[d]
13[e]	**1c**	Bu	Ph	Bu	46	28

[a] Unless otherwise noted, all reactions were carried out in MeOH at 70 °C using 1 mol % of PdI_2 in conjunction with 200 equivs. of KI under 90 atm (at 25 °C) of a 3:1:5 mixture of CO:air:CO_2 for 5 h (1–2 mmol scale based on **1**, 0.05 mmol of **1** mL of MeOH). Substrate conversion was quantitative in all cases. Formation of unidentified heavy products accounted for substrate conversion in all cases.

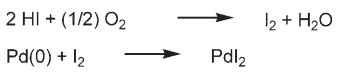
[b] GLC yield (isolated yield) based on starting **1**.

[c] GLC yield based on starting **1**.

[d] $R^2 = H$ in the final product **2b**.

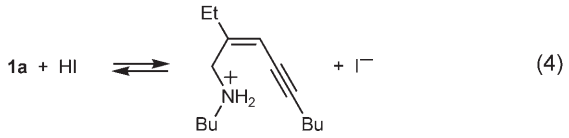
[e] The reaction was carried out under 30 atm of CO and 10 atm of air.

The beneficial effect exerted by the excess of iodide anions and by CO_2 on the carbonylation process can be related to the easier reoxidation of Pd(0) occurring under these conditions. In fact, according to the mechanism we demonstrated several years ago in the case of oxidative dicarbonylation of alkynes,[12] Pd(0) reoxidation under our conditions occurs through oxidation of HI by oxygen, followed by oxidative addition of iodine to Pd(0) (Scheme 3). Clearly,

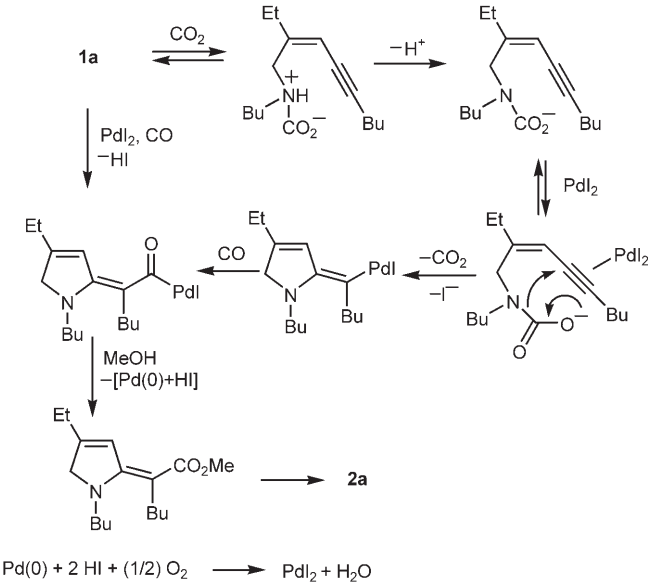


Scheme 3.

in the presence of a basic substrate such as an amine, an acid-base equilibrium takes place [Eq. (4)], which lowers the concentration of free HI in solution thus making the Pd(0) reoxidation less easy and therefore hampering the overall carbonylation process.



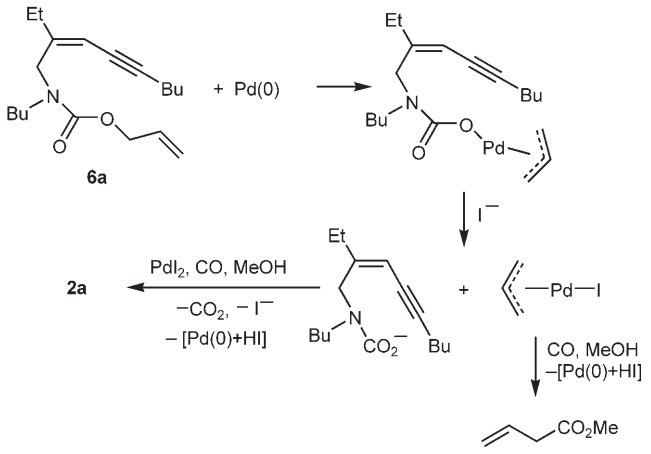
However, in the presence of a large excess of iodide anions, the acid-base equilibrium can be shifted to the left, thus allowing a higher concentration of HI in solution. On the other hand, CO_2 may act by "buffering" the basicity of the substrate, with formation of a carbamate species, thus "freeing" the HI necessary for Pd(0) reoxidation. The nitrogen of the carbamate, while less basic than in the starting amine, may still act as a nucleophile since CO_2 can be eliminated during the cyclization step leading to the 5-membered product (Scheme 4).



Scheme 4.

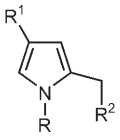
In order to verify this mechanistic hypothesis we have synthesized butyl-(2-ethylnon-2-en-4-ynyl)carbamic acid allyl ester **6a** by the reaction between **1a** and commercially available allyl chloroformate. Indeed, working under the same conditions as optimized for **1a**, but in the absence of CO_2, Pd-mediated cleavage of the allyl moiety of **6a** was expected to afford the same carbamate species as obtained from **1a** in the presence of CO_2, eventually leading to **2a** and methyl but-3-enoate (Scheme 5). The cleavage of the allyl moiety could occur by oxidative addition to a Pd(0) species (formed *in situ* from PdI_2, for example by decarboxylation of an I–Pd–CO_2H species formed in the presence of traces of water), as shown in Scheme 5, or directly to PdI_2, to give a Pd(II) or Pd(IV) allylic intermediate, respectively. According to our hypotheses, when **6a** was allowed to react under the same conditions of entry 7, **2a** and methyl but-3-enoate were obtained in a *ca.* 1:1 ratio, with no formation of pyrrole **3a**. The substrate conversion rate was however rather slow, probably due to the kinetics of cleavage of the allyl moiety (after 48 h, the conversion of **6a** was 35 % with a 22 % GLC yield of **2a**).

The reaction was then extended to other secondary (*Z*)-(2-en-4-ynyl)amines **1b** and **c** substituted at C-2 and at C-5. Under the optimized conditions found for



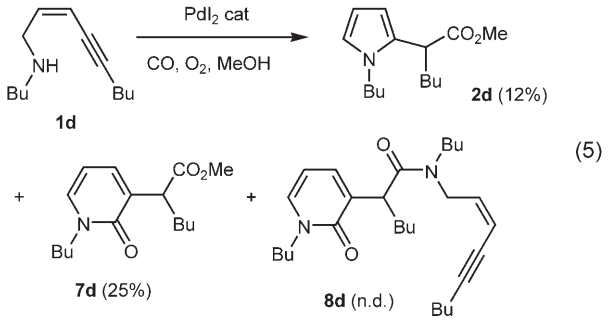
Scheme 5.

1a (Table 2, entry 9), these substrates led to the corresponding pyrrole-2-acetic esters **2b** and **c** in satisfactory yields [75–70% by GLC, 65–61% isolated, Eq. (3) and Table 2, entries 10 and 11]. In the case of (*Z*)-butyl-[2-ethyl-5-(trimethylsilanyl)pent-2-en-4-ynyl]amine **1b**, the trimethylsilanyl group was lost in the course of the process, as we already observed in the oxidative carbonylation of (*Z*)-(5-trimethylsilanyl)-2-en-4-yn-1-ols.[5] This reactivity allows the preparation of α-unsubstituted pyrrole-2-acetic esters, which cannot be obtained starting from (*Z*)-(2-en-4-ynyl)-amines bearing a terminal triple bond due to their instability and their spontaneous tendency to cycloisomerize to give the corresponding pyrroles.[8] The promoting effect by CO_2 was confirmed by the results obtained by carrying out the reaction in the absence of CO_2: the yields of carbonylated products were lower with respect to those obtained under the standard conditions, and cycloisomerization products **3b** and **c** were obtained in higher yields (entries 12 and 13).

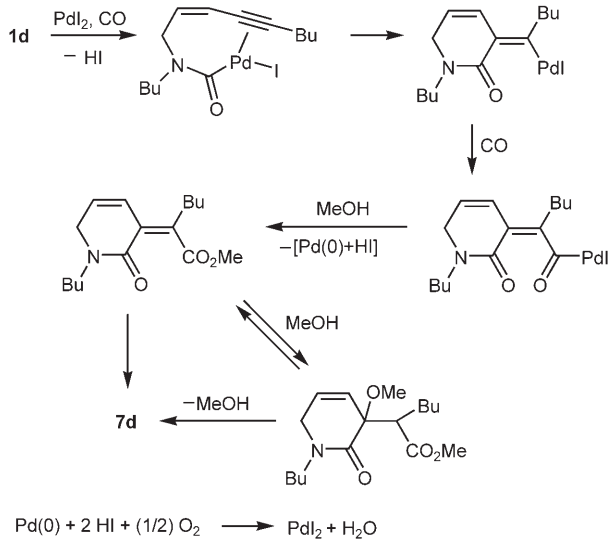


3a: R = R^2 = Bu, R^1 = Et
3b: R = Bu, R^1 = Et, R^2 = H
3c: R = R^2 = Bu, R^1 = Ph

Very interestingly, the reaction of a secondary (*Z*)-(2-en-4-ynyl)amine bearing no substituents at C-2 and C-3, such as butyl(non-2-en-4-ynyl)amine **1d**, carried out under the same conditions of entries 9–11 for 4 h, led to a mixture of products, including the expected pyrrole-2-acetic ester **2d** (12% isolated yield) together with (pyridine-2-one)-3-acetic ester **7d** (25% isolated yield) and a heavier product, whose mass spectrum was compatible with the (pyridine-2-one)-3-acetic amide structure **8d** [Eq.(5), n.d. = not determined].[13]



Formation of product **7d** follows a cyclocarbonylation-alkoxycarbonylation pathway, similar to that already observed in the case of other functionalized alkynes (Scheme 6).[1–4] The key intermediate is a carbamoylpalladium species,[14] stabilized by triple bond coordination. Intramolecular triple bond insertion then occurs, followed by CO insertion and nucleophilic displacement by MeOH, with elimination of Pd(0) and HI and formation of a 3,6-dihydro-1*H*-pyridin-2-one intermediate. This compound eventually isomerizes to give the final product, probably *via* MeOH addition to the double bond followed by MeOH elimination (Scheme 6). Palladium(0) is then reoxidized according to the usual mechanism (Scheme 3). Formation of (pyridine-2-one)-3-acetic amide **8d** occurs through a mechanism similar to that showed in Scheme 6, with the substrate replacing MeOH in the nucleophilic displacement step.

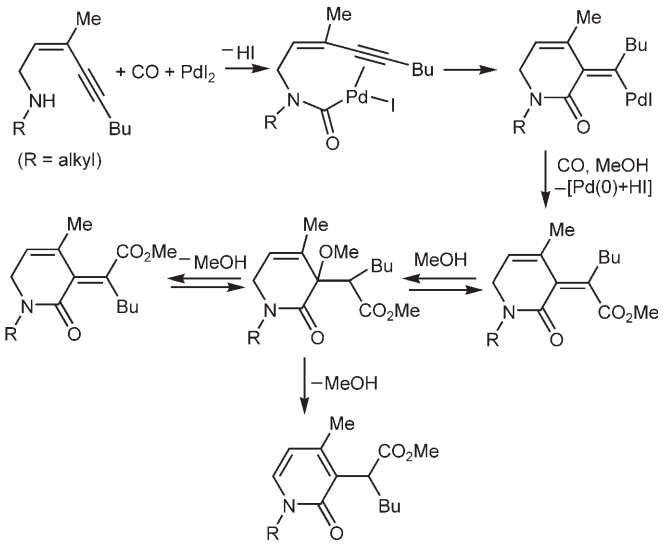


Scheme 6.

Thus, two competitive oxidative carbonylation mechanisms are in principle possible with enynamines, that is, the cyclization-alkoxycarbonylation mechanism (Scheme 1) and the cyclocarbonylation-alkoxycarbonylation mechanism (Scheme 6). As we have seen, both these mechanisms are followed in the case of a 2,3-unsusbtituted enynamine, such as **1d**, while only the first mechanism was followed by 2-substituted enynamines **1a–c**. The selectivity observed with these latter substrates can be ascribed to a "steric assistance" effect,[15] ensuing from the decrease of steric repulsion between the substituent at C-2 and the CH_2NHR or $CH_2NRCO_2^-$ moiety going through the transition state leading to the 5-membered intermediate. Such a steric assistance effect clearly favors an initial 5-*exo-dig* cyclization, as shown in Scheme 4.

The results obtained so far prompted us to test the reactivity of enynamines unsubstituted at C-2 and substituted at C-3, such as benzyl-(3-methylnon-2-en-4-ynyl)amine **1e** or butyl-(3-methylnon-2-en-4-ynyl)-amine **1f**. In fact, with these substrates, the above-mentioned steric assistance effect could not be at work, while the steric effect exerted by the substituent at C-3 was actually expected to *hinder* the cyclization-alkoxycarbonylation mechanism. In fact, as we have seen (Scheme 1), this mechanism involves an anti *exo-dig* attack of the amino group to the triple bond coordinated to Pd(II), with the metal center on the opposite site with respect to the nucleophilic group and therefore close to the substituent at C-3. On the other hand, the cyclocarbonylation-alkoxycarbonylation mechanism could still be at work, since in this case the triple bond coordination to Pd(II) occurs on the opposite site with respect to the C-3 substituent (Scheme 7).

Indeed, when the reaction of **1e** was carried out under the conditions optimized for 2-susbtituted enynamines **1a–c** (entries 9-11), GLC-MS analysis showed the formation of (pyridine-2-one)-3-acetic ester **7e** (32% GLC yield, 22% isolated), together with a larger amount of a heavier product, whose mass spectrum was compatible with the (pyridine-2-one)-3-acetic amide structure **8e** [Eq. (6) and Table 3, entry 14].[16]



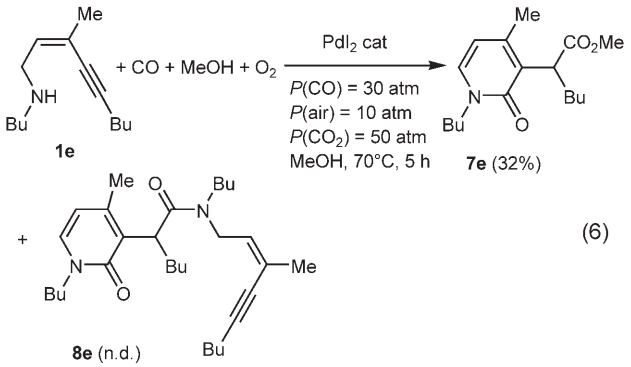
Scheme 7.

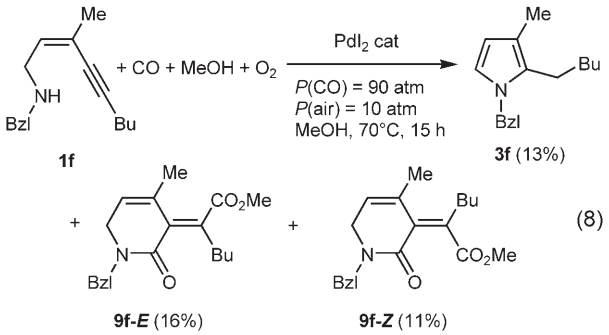
A slightly lower selectivity was obtained by decreasing the amount of KI (entry 15) or by increasing the substrate concentration (entry 16), while the same reaction carried out in the absence of CO_2 led to a significant reduction of both the substrate conversion (58%) and product yield (7%, entry 17). This clearly means that CO_2 acts as a promoter even in the oxidative carbonylation of 3-susbtituted enynamines leading to (pyridine-2-one)-3-acetic derivatives. This is conceivable, since also in this case CO_2 may act by

Table 3. Reactions of butyl-(3-methylnon-2-en-4-ynyl)amine **1e** with CO and O_2 in MeOH at 70°C in the presence of PdI_2-KI catalytic system.[a]

Entry	PdI_2:KI:**1e** Molar Ratio	Concentration of **1e**[b]	Conversion of **1e** [%][c]	Yield of **7e** [%][d]
14	1:200:100	0.05	100	32 (22)
15	1:100:100	0.05	100	28
16	1:200:100	0.22	100	15
17[e]	1:200:100	0.05	58	7
18[f,g]	1:50:100	0.22	55	

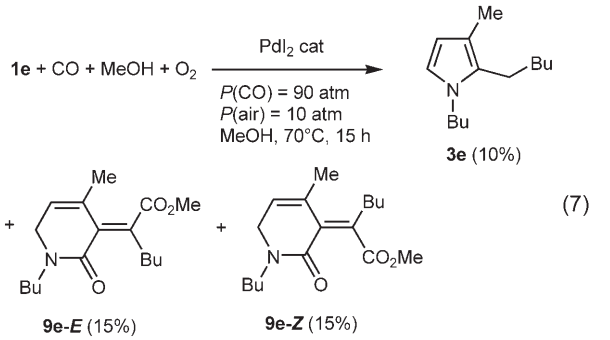
[a] Unless otherwise noted, all reactions were carried out in MeOH at 70°C under 90 atm (at 25°C) of a 3:1:5 mixture of CO:air:CO_2 for 5 h (1–2 mmol scale based on **1e**).
[b] Mmol of **1e**/mL of MeOH.
[c] Based on starting **1e**, by GLC.
[d] GLC yield (isolated yield) based on **1e**.
[e] The reaction was carried out under 40 atm (at 25°C) of a 3:1 mixture of CO:air.
[f] The reaction was carried out under 100 atm (at 25°C) of a 9:1 mixture of CO:air for 15 h.
[g] The reaction led to the formation of 1-butyl-3-methyl-2-pentyl-1*H*-pyrrole **3e** (10% GLC yield, 8% isolated) and 2-(1-butyl-4-methyl-2-oxo-1,6-dihydro-2*H*-pyridin-3-ylidene)hexanoic acid methyl ester **9e** (30% GLC yield, 21% isolated).





"buffering" the substrate basicity, thus allowing a higher concentration of HI, necessary for Pd(0) reoxidation.

Interestingly, when **1e** was allowed to react under conditions similar to those employed in the analogous carbonylation of the corresponding 3-methylnon-2-en-4-yn-1-ol (70 °C for 15 h in MeOH as the solvent, substrate concentration = 0.22 mmol mL^{-1} of MeOH, under 100 atm of a 9:1 mixture of CO-air, 1 mol % of PdI_2 along with 50 equivs. of KI), it was possible to obtain and isolate the 3,6-dihydro-1*H*-pyridin-2-one intermediate **9e** as a *ca.* 1:1 *E*:*Z* mixture [total GLC yield: 30 %, isolated 21 %, at 55 % substrate conversion, entry 18 and Eq. (7)].



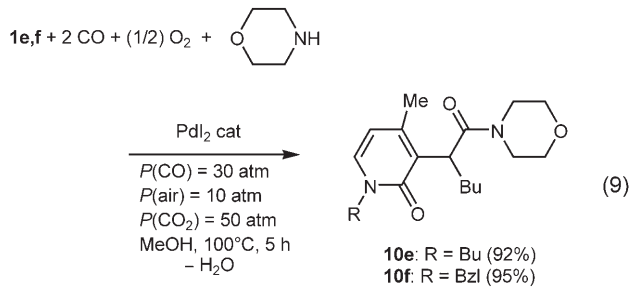
Similar results were obtained using enynamine **1f**, which, under the same conditions of entry 18, afforded a mixture of 3,6-dihydro-1*H*-pyridin-2-one derivatives **9f-*E*** and **9f-*Z*** in 27 % GLC yield (20 % isolated) at 55 % substrate conversion [Eq. (8)].[17]

The formation of (pyridine-2-one)-3-acetic amide **8e** suggested the possibility to selectively synthesize other amide derivatives by carrying out the reaction in the presence of a suitable excess of a nucleophilic amine. Indeed, when the same reaction of entry 14 was carried out in the presence of morpholine (3 equivs. with respect to **1e**), 1-butyl-4-methyl-3-[1-(morpholine-4-carbonyl)pentyl]-1*H*-pyridin-2-one **10e** was obtained as the sole product in 22 % GLC yield at 27 % substrate conversion (Table 4, entry 19). Substrate conversion reached 100 % at 100 °C, giving **10e** in 92 % GLC yield [77 % isolated, Eq. (9) and entry 21].

Table 4. Reactions of butyl-(3-methylnon-2-en-4-ynyl)amine **1e** with CO, O_2 and morpholine in the presence of PdI_2-KI catalytic system.[a]

Entry	Solvent	T [°C]	Conversion of **1e** [%][b]	Yield of **10e** [%][c]
19	MeOH	70	27	22
20	MeOH	80	45	38
21	MeOH	100	100	92 (77)
22	DMA	80	50	38
23	DMA	100	100	81 (73)

[a] All reactions were carried out using a PdI_2:KI:**1e**:morpholine molar ratio of 1:200:100:300 under 90 atm (at 25 °C) of a 3:1:5 mixture of CO:air:CO_2 for 5 h (1–2 mmol scale based on **1e**, 0.05 mmol of **1e**/mL of solvent).
[b] Based on starting **1e**, by GLC.
[c] GLC yield (isolated yield) based on **1e**.



In these reactions, morpholine was partially converted into morpholin-4-yl-oxoacetic acid methyl ester, whose formation somewhat complicated the purification procedure of **10e** (see Experimental Section for details). We therefore also carried out the reaction in a non-nucleophilic solvent such as *N*,*N*-dimethylacetamide (DMA, entries 22 and 23). Working at 80 °C for 5 h, substrate conversion and GLC yield of

10e were 50% and 38%, respectively (entry 22), while at 100°C the conversion of **1e** was quantitative and the GLC yield of **10e** reached 81% (73% isolated, entry 23).

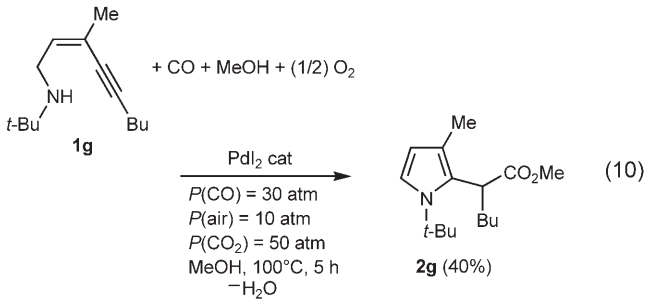
Enynamine **1f** could also be selectively converted into the corresponding amide **10f** working in the presence of a nucleophilic amine such as morpholine. In DMA as the solvent under the same conditions of entry 23, the yield of **10f** was moderate (46%, by GLC, Table 5, entry 24), while in MeOH, under the same conditions of entry 21, the GLC yield of **10f** was as high as 95% [86% isolated, Eq. (9) and entry 25]. It is worth noting that the GLC yield of **10f** dropped to 52% working in MeOH in the absence of CO_2 (entry 26).

Table 5. Reactions benzyl-(3-methylnon-2-en-4-ynyl)amine **1f** with CO, O_2 and morpholine in the presence of PdI_2-KI catalytic system.[a]

Entry	Solvent	T [°C]	Conversion of **1f** [%][b]	Yield of **10f** [%][c]
24	DMA	100	94	46
25	MeOH	100	100	95 (86)
26[d]	MeOH	100	100	52

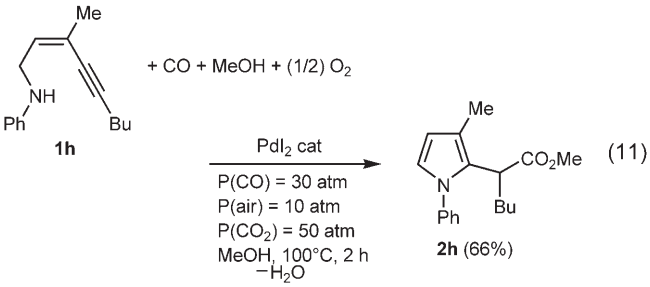
[a] Unless otherwise noted, all reactions were carried out at 100°C using a PdI_2:KI:**1f**:morpholine molar ratio of 1:200:100:300 under 90 atm (at 25°C) of a 3:1:5 mixture of CO:air:CO_2 for 5 h (1–2 mmol scale based on **1f**, 0.05 mmol of **1f**/mL of solvent).
[b] Based on starting **1f**, by GLC.
[c] GLC yield (isolated yield) based on **1f**.
[d] The reaction was carried out under 40 atm (at 25°C) of a 3:1 mixture of CO:air.

Very interestingly, we have found that it is also possible to direct the oxidative carbonylation of 3-substitued enynamines towards the formation of pyrrole-2-acetic derivatives, by placing a bulky alkyl group or a phenyl group on the nitrogen atom, as in the case of (*Z*)-*tert*-butyl-(3-methylnon-2-en-4-ynyl)amine **1g** and (*Z*)-(3-methylnon-2-en-4-ynyl)phenylamine **1h**, respectively. In these cases, in fact, formation of the carbamoylpalladium species (which, as we have seen, is the key intermediate in the cyclocarbonylation-carbonylation mechanism, Scheme 7), is hindered for steric reasons, so the cyclization-carbonylation mechanism (Scheme 1) becomes the favored reaction pathway. Under the same conditions of entry 14, but at 100°C rather than 70°C, conversion of **1g** was 48% after 5 h, with a 40% GLC yield of 2-(1-*tert*-butyl-3-methyl-1*H*-pyrrol-2-yl)hexanoic acid methyl ester **2g** [32% isolated, Eq. (10)]. The substrate conversion was slightly higher when the reaction was carried out for longer times or when the **1g**:PdI_2 molar ratio was decreased, but the yield of **2g** did not improve significantly.

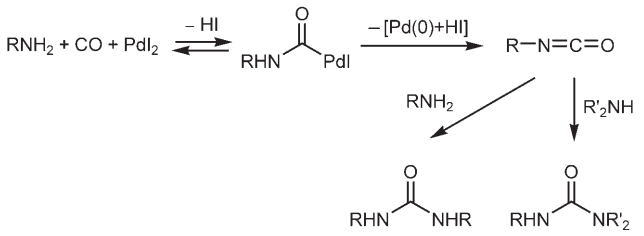


Enynamine **1h** turned out to be more reactive than **1g**. Under the same conditions as above, substrate conversion was quantitative after 2 h, with selective formation of the corresponding pyrrole-2-acetic ester **2h** in good yield [66% by GLC, 58% isolated, Eq. (11)].

As expected in view of the reactivity of a primary amino group under oxidative carbonylation conditions in the presence of the PdI_2-KI catalytic system,[18] an enynamine bearing a primary amino group afforded urea derivatives rather than cyclization products. In fact, under our conditions, primary amines are easily converted into ureas through the formation of an isocyanate as intermediate (Scheme 8).[18]

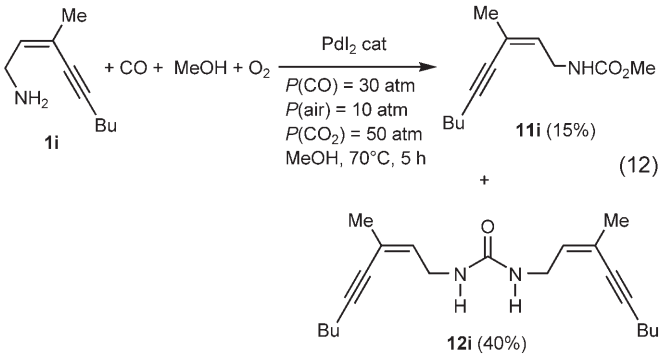


Thus, the reaction of (*Z*)-3-methylnon-2-en-4-ynylamine **1i**, carried out in MeOH for 5 h under the same conditions of entry 14, afforded the methyl carbamate **11i** in 15% isolated yield together with the symmetrical urea **12i** as the main reaction product



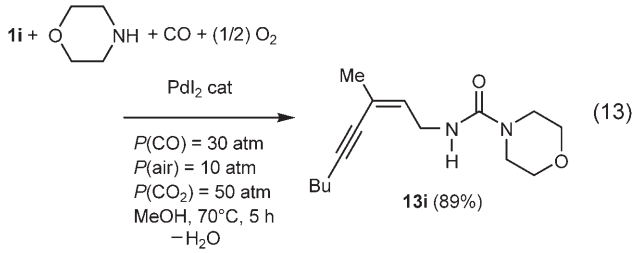
Scheme 8.

[40% isolated yield, Eq. (12)] at total substrate conversion.



(12)

When the same reaction was carried out in the presence of an excess of morpholine (morpholine:**1i** = 3:1), the mixed urea **13i** was selectively formed in 89% GLC yield [81% isolated, Eq. (13)]. The CO_2



(13)

effect was at work even in this case: indeed, in the absence of CO_2, the substrate conversion was 53% with a yield of **13i** of 29%.

Conclusions

In conclusion, we have shown that the PdI_2/KI-catalyzed oxidative carbonylation of readily available (*Z*)-(2-en-4-ynyl)amines **1** is a powerful methodology for the one-step synthesis of important carbonyl derivatives such as pyrrole-2-acetic esters, (pyridine-2-one)-3-acetic amides, or urea derivatives under relatively mild conditions. We have found that several mechanistic pathways may be at work, and that it is possible to direct the catalytic process towards a particular route by suitably changing the substitution pattern of the substrate and the nature of the external nucleophile. We have also demonstrated that CO_2 may act as an effective and peculiar promoter in these reactions, owing to its capability to "buffer" the basicity of the amino group of the substrate without hampering its nucleophilicity.

Experimental Section

General Remarks

Melting points were determined with a Reichert Thermovar apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX Avance 300 spectrometer at 300 MHz and 75 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken with a Perkin–Elmer Paragon 1000 PC FT-IR spectrometer. Mass spectra were obtained using a Shimadzu QP-2010 GC-MS apparatus at 70 eV ionization voltage. Microanalyses were carried out with a Carlo Erba Elemental Analyzer Mod. 1106. All reactions were analyzed by TLC on silica gel 60 F_{254} and by GLC using a Shimadzu GC-2010 gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase (HP-5). Column chromatography was performed on silica gel 60 (Merck, 70–230 mesh) or neutral alumina. Evaporation refers to the removal of solvent under reduced pressure.

Substrates were prepared, purified and characterized as described in the Supporting Information. The procedures for the oxidation of **3a** with molecular oxygen to give 1,5-dihydropyrrol-2-ones **4a** or **5a**,[10] and the characterization data for all products can also be found in the Supporting Information.

Typical Procedure for Oxidative Methoxycarbonylation of 2-Substituted Enynamimes 1a–c and Separation of Products [Eq. (3) and Table 2, entries 9–11]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (3.7 mg, 1.03×10^{-2} mmol), KI (341.9 mg, 2.06 mmol) and a solution of **1a–c** (1.03 mmol) in MeOH (20.5 mL). The autoclave was pressurized at room temperature with stirring with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 70 °C with stirring for 5 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the products purified by column chromatography (SiO_2): **2a** (hexane-AcOEt from 98:2 to 95:5, pale yellow oil, 182.5 mg, 63% based on **1a**); **2b** (hexane-AcOEt, 95:5, pale yellow oil, yield: 150.2 mg, 65% based on **1b**); **2c** (hexane-AcOEt, 99:1, yellow oil, yield: 205.3 mg, 61% based on **1c**).

Oxidative Methoxycarbonylation of Butyl(non-2-en-4-ynyl)amine 1d and Separation of Products [Eq. (5)]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (3.0 mg, 8.33×10^{-3} mmol), KI (277.8 mg, 1.67 mmol) and a solution of **1d** (159.9 mg, 0.83 mmol) in MeOH (16.6 mL). The autoclave was pressurized at room temperature with stirring with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 70 °C with stirring for 4 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the products purified by column chromatography (SiO_2), using hexane-AcOEt, from 7:3 to 6:4, as

the eluent, to afford **2d** (yellow oil, yield: 25.0 mg, 12%) followed by **7d** (yellow oil, yield: 58.0 mg, 25%) and unidentified decomposition products.

Oxidative Methoxycarbonylation of Butyl-(3-methylnon-2-en-4-ynyl)amine 1e at 30 atm of CO and Separation of Products [Eq. (6) and Table 3, entry 14]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (3.0 mg, 8.33×10^{-3} mmol), KI (277.8 mg, 1.67 mmol) and a solution of **1e** (173.0 mg, 0.83 mmol) in MeOH (16.6 mL). The autoclave was pressurized at room temperature with stirring with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 70°C with stirring for 5 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the products purified by column chromatography (SiO_2), using hexane-AcOEt, 8:2, as the eluent, to afford **7e** (colorless oil, yield: 54.0 mg, 22%) followed by unidentified decomposition products.

Oxidative Methoxycarbonylation of Butyl-(3-methylnon-2-en-4-ynyl)amine 1e at 90 atm of CO and Separation of Products [Eq. (7) and Table 3, entry 18]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (10.5 mg, 2.92×10^{-2} mmol), KI (242.0 mg, 1.46 mmol) and a solution of **1e** (644.7 mg, 3.11 mmol) in MeOH (14.0 mL). The autoclave was pressurized at room temperature with stirring with CO (90 atm) and air (up to 100 atm of total pressure), and then heated at 70°C with stirring for 15 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the products purified by column chromatography (SiO_2), using hexane-AcOEt, 9:1, as the eluent, to afford **3e** (colorless oil, yield: 51.2 mg, 8%) followed by a mixture of **9e-*E*** and **9e-*Z*** (yellow oil; total yield: 192.0 mg, 21%).

Oxidative Methoxycarbonylation of Benzyl-(3-methylnon-2-en-4-ynyl)amine 1f at 90 atm of CO and Separation of Products [Eq. (8)]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (10.0 mg, 2.78×10^{-2} mmol), KI (230.0 mg, 1.39 mmol) and a solution of **1f** (674.0 mg, 2.79 mmol) in MeOH (12.7 mL). The autoclave was pressurized at room temperature with stirring with CO (90 atm) and air (up to 100 atm of total pressure), and then heated at 70°C with stirring for 15 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the products purified by column chromatography (SiO_2), using hexane-AcOEt, from 9:1 to 8:2, as the eluent, to afford **3f** (colorless oil, yield: 71.5 mg, 10%) followed by a mixture of **9f-*E*** and **9f-*Z*** (yellow oil; total yield: 183.0 mg, 20%).

Oxidative Aminocarbonylation of Butyl-(3-methylnon-2-en-4-ynyl)amine 1e in MeOH and Separation of Products [Eq. (9) and Table 4, entry 21]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (3.0 mg, 8.33×10^{-3} mmol), KI (277.8 mg, 1.67 mmol) and a solution of **1e** (173.0 mg, 0.83 mmol) and morpholine (220.0 mg, 2.53 mmol) in MeOH (16.6 mL). The autoclave was pressurized at room temperature with stirring with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 100°C with stirring for 5 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the product purified by column chromatography (SiO_2), using hexane-acetone, from 9:1 to 8:2, as the eluent, to afford **10e** as a pale yellow solid, which was somewhat impure with morpholin-4-yl-oxoacetic acid methyl ester. Further purification by preparative TLC (hexane-acetone, 9:1) afforded pure **10e** as a pale yellow solid, mp 81–83°C (yield: 223.0 mg, 77%).

Oxidative Aminocarbonylation of Butyl-(3-methylnon-2-en-4-ynyl)amine 1e in DMA and Separation of Products (Table 4, entry 23).

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (3.0 mg, 8.33×10^{-3} mmol), KI (277.8 mg, 1.67 mmol) and a solution of **1e** (173.0 mg, 0.83 mmol) and morpholine (220.0 mg, 2.53 mmol) in DMA (16.6 mL). The autoclave was pressurized at room temperature with stirring with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 100°C with stirring for 5 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the product purified by column chromatography (SiO_2), using hexane-acetone, from 9:1 to 8:2, as the eluent, to afford pure **10e** as a pale yellow solid, mp 81–83°C (yield: 212.0 mg, 73%).

Oxidative Aminocarbonylation of Benzyl-(3-methylnon-2-en-4-ynyl)amine 1f in MeOH and Separation of Products [Eq. (9) and Table 5, entry 25]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (3.0 mg, 8.33×10^{-3} mmol), KI (277.8 mg, 1.67 mmol) and a solution of **1f** (200.0 mg, 0.83 mmol) and morpholine (220.0 mg, 2.53 mmol) in MeOH (16.6 mL). The autoclave was pressurized at room temperature with stirring with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 100°C with stirring for 5 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the product purified by column chromatography (SiO_2), using hexane-AcOEt, 8:2, to give pure **10f** as a colorless solid, mp 77–78°C (yield: 272.7 mg, 86%).

Oxidative Methoxycarbonylation of *tert*-Butyl-(3-methylnon-2-en-4-ynyl)amine 1g and Separation of Products [Eq. (10)]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (3.0 mg, 8.33×10^{-3} mmol), KI (277.8 mg, 1.67 mmol) and a solution of **1g** (177.2 mg, 0.85 mmol) in MeOH (17.0 mL). The autoclave was pressurized at room temperature with stirring with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 100°C with stirring for 5 h. After cooling, the autoclave was degassed, the solvent evaporated under

reduced pressure, and the product purified by column chromatography (SiO_2), using hexane-AcOEt, from 95:5 to 9:1, as the eluent, to afford **2g** as a yellow oil (yield: 73.1 mg, 32%).

Oxidative Methoxycarbonylation of Phenyl-(3-methylnon-2-en-4-ynyl)amine 1 h and Separation of Products [Eq. (11)]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (3.0 mg, 8.33×10^{-3} mmol), KI (277.8 mg, 1.67 mmol) and a solution of **1h** (191.0 mg, 0.84 mmol) in MeOH (16.8 mL). The autoclave was pressurized at room temperature with stirring with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 100 °C with stirring for 2 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the product purified by column chromatography (SiO_2), using hexane-AcOEt, from 100:0 to 95:5, as the eluent, to afford **2h** as a yellow oil (yield: 140.0 mg, 58%).

Oxidative Carbonylation of (3-methylnon-2-en-4-ynyl)amine 1i in the Absence of Morpholine and Separation of Products [Eq. (12)]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39×10^{-2} mmol), KI (462.0 mg, 2.78 mmol) and a solution of **1i** (210.0 mg, 1.39 mmol) in MeOH (27.8 mL). The autoclave was pressurized at room temperature with stirring with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 70 °C with stirring for 5 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the products purified by column chromatography (SiO_2), using hexane-AcOEt, from 9:1 to 8:2, as the eluent, to afford **11i** (yellow oil, yield: 44.1 mg, 15%) followed by **12i** (colorless solid, mp 83–84 °C, yield: 92.1 mg, 40%).

Oxidative Carbonylation of (3-methylnon-2-en-4-ynyl)amine 1i in the Presence of Morpholine and Separation of Products [Eq. (13)]

A 250-mL stainless steel autoclave was charged in the presence of air with PdI_2 (5.0 mg, 1.39×10^{-2} mmol), KI (462.0 mg, 2.78 mmol) and a solution of **1i** (210.0 mg, 1.39 mmol) and morpholine (365.0 mg, 4.19 mmol) in MeOH (27.8 mL). The autoclave was pressurized at room temperature with stirring with CO_2 (50 atm), CO (up to 80 atm) and air (up to 90 atm of total pressure), and then heated at 70 °C with stirring for 5 h. After cooling, the autoclave was degassed, the solvent evaporated under reduced pressure, and the product purified by column chromatography (SiO_2), using hexane-AcOEt, from 8:2 to 6:4, as the eluent, to afford **13i** as a pale yellow solid, mp 59–60 °C (yield: 298.5 mg, 81%).

References

[1] For excellent recent reviews, see: a) S. A. Vizer, K. B. Yerzhanov, A. A. A. Al Quntar, V. M. Dembitsky, *Tetrahedron* **2004**, *60*, 5499–5538; b) G. Zeni, R. C. Larock, *Chem. Rev.* **2004**, *104*, 2285–2309; c) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127–2198.

[2] B. Gabriele, G. Salerno, M. Costa, *Synlett* **2004**, 2468–2483.

[3] B. Gabriele, G. Salerno, M. Costa, G. P. Chiusoli, *Curr. Org. Chem.* **2004**, *8*, 919–946.

[4] B. Gabriele, G. Salerno, M. Costa, G. P. Chiusoli, *J. Organomet. Chem.* **2003**, *687*, 219–228.

[5] B. Gabriele, G. Salerno, F. De Pascali, M. Costa, G. P. Chiusoli, *J. Org. Chem.* **1999**, *64*, 7693–7699.

[6] B. Gabriele, G. Salerno, A. Fazio, F. B. Campana, *Chem. Commun.* **2002**, 1408–1409.

[7] Several derivatives of these classes of carbonyl compounds have shown interesting pharmacological activity. For representative examples, see: a) J. R. Carson, S. Wong, *J. Med. Chem.* **1973**, *16*, 172–174; b) J. R. Carson, (McNeil Laboratories, Inc.), Ger. Offen. 2,339,140, **1974**; *Chem. Abstr.* **1974**, *80*, P133244f; c) J. R. Carson, (McNeil Laboratories, Inc.), US Patent 4,048,191 A, **1975**; *Chem. Abstr.* **1976**, *85*, P108517t; d) M. W. Whitehouse, K. D. Rainsford, *J. Pharm. Pharmacol.* **1980**, *32*, 795–796; e) L. J. Powers, S. W. Fogt, Z. S. Ariyan, D. J. Rippin, R. D. Heilman, R. J. Matthews, *J. Med. Chem.* **1981**, *24*, 604–609; f) J. F. Pritchard, R. K. Desiraju, *J. Pharm. Sci.* **1982**, *71*, 964–965; g) R. Zurita, (Laboratorios Rubio S. A.), Spanish Patent 502650, **1982**; *Chem. Abstr.* **1982**, *97*, P162811v; h) J. B. Doherty, M. N. Chang, C. P. Dorn, Jr., (Merck and Co., Inc.), European Patent 72013, **1983**; *Chem. Abstr.* **1983**, *99*, P22311y; i) J. B. Doherthy, M. N. Chang, C. P. Dorn, US Patent 4,434,175, **1984**; *Chem. Abstr.* **1984**, *100*, P191732f; j) G. A. Youngdale, T. F. Oglia, *J. Med. Chem.* **1985**, *28*, 1790–1796; k) J. M. Muchowski, E. Galeazzi, R. Greenhouse, A. Guzmán, V. Peréz, N. Ackerman, S. A. Ballaron, J. R. Rovito, A. J. Tomolosis, J. M. Young, W. H. Rooks, II, *J. Med. Chem.* **1989**, *32*, 1202–1207; l) M. Lehr, *Eur. J. Med. Chem. Chim. Ther.* **1997**, *32*, 805–814; m) M. Lehr, *J. Med. Chem.* **1997**, *40*, 3381–3392; n) C. Dendrinou-Samara, G. Tsotsou, L. V. Ekateriniadou, A. H. Kortsaris, C. P. Reptopoulou, A. Terzis, D. A. Kyriakidis, D. P. Kessissoglou, *J. Inorg. Biochem.* **1998**, *71*, 171–179; o) S. Sortino, J. C. Scaiano, G. De Guidi, S. Monti, *Photochem. Photobiol.* **1999**, *70*, 549–556; p) O. A. Attanasi, S. M. Colombani, L. De Crescentini, R. Giorgi, S. Monti, A. Perrone, F. R. Perrulli, A. R. Renzetti, S. Santeusanio, *Farmaco*, **1999**, *54*, 64–76; q) S. D. Larsen, M. A. Connell, M. M. Cudahy, B. R. Evans, P. D. May, M. D. Meglasson, T. J. O'Sullivan, H. J. Schostarez, J. C. Sih, F. C. Stevens, S. P. Tanis, C. M. Tegley, J. A. Tucker, V. A. Vaillancourt, T. J. Vidmar, W. Watt, J. H. Yu, *J. Med. Chem.* **2001**, *44*, 1217–1230; r) C. Anagnostou, I. Nicolaou, V. J. Demopoulos, *Pharmazie* **2002**, *57*, 435–437.

[8] The spontaneous or metal-catalyzed cycloisomerization of (*Z*)-(2-en-4-ynyl)amines was reported to be a general methodology for the synthesis of substituted pyr-

roles: B. Gabriele, G. Salerno, A. Fazio *J. Org. Chem.* **2003**, *68*, 7853–7861.
[9] The oxidation of the pyrrole ring is a well-known reaction. For general references, see: a) R. A. Jones, in: *Comprehensive Heterocyclic Chemistry*, Vol. 4, (Eds.: A. R. Katritzky, C. W. Rees, C. W. Bird, G. W. H. Cheeseman), Pergamon, Oxford, 1984, pp. 246–254; b) A. R. Katritzky, A. F. Pozharskii, *Handbook of Heterocyclic Chemistry*, 2nd edn., Pergamon, Oxford, **2000**, p. 318.
[10] That compounds **4a** and **5a** could derive from a subsequent oxidation of **3a** was confirmed by reacting pure **3a** under the same conditions as above, but in the absence of CO and with a **3a**/KI/PdI_2 molar ratio of 500:50:1, either in anhydrous MeOH or in aqueous dioxane as the solvent, to give **4a** or **5a** in 45% or 27% isolated yield, respectively. See Supporting Information for details.
[11] The formation of unidentified heavy products accounted for substrate conversion (100%).
[12] B. Gabriele, M. Costa, G. Salerno, G. P. Chiusoli, *J. Chem. Soc., Perkin Trans. 1* **1994**, 83–87.
[13] In particular, the mass spectrum of **8d** showed the molecular ion ($M^+ = 440$) with a relative intensity of 8% with respect to the base peak ($m/z = 248$), corresponding to the ion ensuing from the cleavage of the amide bond. Unfortunately, all the attempts to separate **8d** in the pure state were unsuccessful, since this compound invariably underwent decomposition during the purification procedure (see Experimental Section for details).
[14] Carbamoylpalladium complexes, stabilized by appropriate ligands, were reported in the literature. See, for example: M. Aresta, P. Giannoccaro, I. Tommasi, A. Dibenedetto, A. M. M. Lanfredi, F. Ugozzoli, *Organometallics* **2000**, *19*, 3879–3889 and references cited therein.
[15] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, John Wiley & Sons, New York, 1994, pp. 720–721.
[16] In particular, the mass spectrum showed the molecular ion ($M^+ = 468$) with a relative intensity of 7% with respect to the base peak ($m/z = 262$), corresponding to the ion ensuing from the cleavage of the amide bond. Unfortunately, all the attempts to separate **8e** at the pure state were unsuccessful, since this compound invariably underwent decomposition during the purification procedure (see Experimental Section for details).
[17] The analysis of the NOESY spectrum of the mixture of **9f-*E*** and **9f-*Z*** allowed the assignments of the signals to each single diastereoisomer. In particular, the NOESY spectrum (in $CDCl_3$ at 25 °C) for the more abundant isomer showed a distinct interaction between the protons of the CO_2Me group and the protons of the methyl group at C-4, thus indicating *E* stereochemistry for this isomer. From the ^1H NMR integration data (either in $CDCl_3$ or in DMSO-d_6), it was therefore possible to calculate the *E*:*Z* ratio, which turned out to be *ca.* 3:2. The interconversion between the two diastereoisomers at 120 °C turned out to be fast with respect to the NMR timescale, since a single ^1H NMR spectrum (in DMSO-d_6), corresponding to an averaged situation, was observed at that temperature (see Supporting Information for details).
[18] B. Gabriele, G. Salerno, R. Mancuso, M. Costa, *J. Org. Chem.* **2004**, *69*, 4741–4750.

