The Journal of Organic Chemistry

VOLUME 64, NUMBER 21 OCTOBER 15, 1999

Articles

A General and Facile Synthesis of Substituted Furans by Palladium-Catalyzed Cycloisomerization of (*Z*)-2-En-4-yn-1-ols

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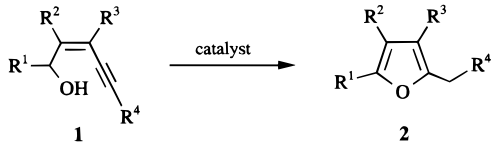
Received May 24, 1999

A general and facile synthesis of furans, based on Pd(II)-catalyzed cycloisomerization of (*Z*)-2-en-4-yn-1-ols, is described. Cycloisomerization reactions are carried out at 25−100 °C in the presence of a very simple catalytic system, consisting of K_2PdI_4, under essentially neutral conditions. This new methodology is very versatile and can be applied to the synthesis of a variety of substituted furans, including particularly fragile, naturally occurring furans such as rosefuran. Efficient synthetic approaches for the regioselective synthesis of suitably substituted (*Z*)-2-en-4-yn-1-ols have been developed.

Introduction

The furan ring is widely distributed as key structural unit in many biologically active molecules, which can find application not only as pharmaceuticals but also as flavoring and fragrance compounds.[1] Furthermore, substituted furans are useful and versatile synthetic intermediates for the preparation of a variety of heterocyclic and acyclic organic compounds.[1b,d,f,2]

The classical synthesis of substituted furans involves the intramolecular dehydration of γ-diketones or the introduction of a substituent into the furan ring, usually through metalation.[1b,f] Recently, several new approaches to the regioselective synthesis of substituted furans starting from acyclic precursors have been developed. Most of these strategies employ suitably functionalized alkyne derivatives as starting materials.[3] A particularly attractive methodology is based on cycloisomerization[4] of the readily available (*Z*)-2-en-4-yn-1-ols **1** (eq 1).



1 **2** (1)

Before our short report,[5] no general method for accomplishing this transformation had been described. The Cu-catalyzed large-scale preparation of 2,3-dimethylfuran starting from (*Z*)-3-methylpent-2-en-4-yn-1-ol was disclosed some years ago.[6a] More recently, cycloisomerization of 2-en-4-yn-1-ols to furans was achieved under strongly

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10.1021/jo990847h CCC: $18.00
Published on Web 09/21/1999

Table 1. Synthesis of Furans 2 by Cycloisomerization of (*Z*)-2-En-4-yn-1-ols 1 in Dry DMA in the Presence of PdI_2 + 2KI, 2.5 mmol of Substrate/mL DMA[a]

entry	enynol **1**	R^1	R^2	R^3	R^4	**1**/PdI_2	*T* (°C)	time (h)	yield of **2**[b] (%)
1[c]	**1a**	H	H	Me	H	500	25 [d]	18	92 (87)
2[c]	**1b**	H	H	Et	H	500	25 [d]	18	94 (89)
3[c]	**1c**	Et	H	Me	H	500	25	20	95 (90)
4[c]	**1d**	Ph	H	Me	H	100	25	18	95
5[c]	**1d**	Ph	H	Me	H	500	45	40	95 (88)
6	**1e**	H	H	Ph	H	100	80	18	30 (23)
7	**1f**	H	H	Me	Bu	100	100	20	90 (81)
8	**1g**	H	H	Me	$Me_2C{=}CH$	100	100	24	85 (77)
9	**1h**	H	H	Me	Ph	300	100	15	82 (76)
10	**1i**	Et	H	Me	Bu	100	100	1	93 (84)
11[c]	**1j**	Ph	H	Me	Bu	100	40	18	55 (49)
12	**1k**	H	H	H	Bu	100	80	22	73 (65)
13	**1l**	H	Et	H	Bu	100	100	2	85
14	**1l**	H	Et	H	Bu	300	100	15	73 (64)
15	**1m**	H	Ph	H	Bu	300	100	1	78 (68)
16	**1m**	H	Ph	H	Bu	100	70	1	90
17	**1n**	Et	Et	H	Bu	200	80	3	80 (72)
18	**1n**	Et	Et	H	Bu	100	40	48	90
19	**1o**	H	Et	Ph	Ph	100	100	45	55 (48)

[a] All reactions were carried out on a 3−10 mmol scale based on enynol **1**. [b] GLC yield (isolated yield) based on **1**. Substrate conversion was practically quantitative in all cases. [c] The reaction was carried out without solvent. [d] The reaction temperature must be controlled with the aid of a water bath owing to the exothermicity of the reaction

basic conditions, i.e., KOBu^t in Bu^{t}OH−THF, in the presence of 18-crown-6.[6b] In a variant of this method, a propynylic −OMOM substituent was used as leaving group.[6c,d] However, these base-promoted reactions were limited to enynols bearing an internal triple bond and were not suitable for the synthesis of base-sensitive furan derivatives or for the synthesis of furans from base-sensitive substrates. For example, the reaction of (*Z*)-3,7-dimethylocta-2,6-dien-4-yn-1-ol **1g** led to the desired furan **2g** (rosefuran, a natural product present in the highly prized oil of rose and many other natural sources) only as a coproduct of a complex mixture.[6e] A methodology based on ruthenium or palladium catalysis has also been described,[6f−i] but even in this case there are important restrictions. The Ru-catalyzed reaction was not suitable for (*Z*)-enynols bearing an internal triple bond, thus limiting the synthetic applicability to 2-methylfurans. On the other hand, the Pd-based catalytic systems [based on $Pd(OAc)_2$ or $Pd(PPh_3)_4$] were only applied to (*Z*)-enynols with R^4 = Ph and did not work with internal enynols bearing a triple bond conjugated with a double bond, such as **1g**.

We now wish to give a full account of the PdI_2-catalyzed cycloisomerization of (*Z*)-2-en-4-yn-1-ols under neutral conditions, which can be applied to variously substituted (*Z*)-enynols, thus allowing a general synthesis of substituted furans in high yields. This new methodology is also valuable for the synthesis of fragile, biologically active furan derivatives such as **2g**.

Results and Discussion

Cycloisomerization reactions of (*Z*)-2-en-4-yn-1-ols **1** to furans **2** were carried out under nitrogen at 25−100 °C in the presence of catalytic amounts of PdI_2 (0.2−1%) in conjunction with 2 equiv of KI. Although the kinetics of enynol conversion was faster in the absence of added solvent, in most cases the use of a dipolar aprotic solvent such as *N*,*N*-dimethylacetamide (DMA) was advantageous to dilute the substrate and/or to curtail substrate or furan decomposition. The use of an excess of iodide ligands was essential for solubilizing PdI_2 in the reaction medium. The most representative results obtained with different (*Z*)-enynols are collected in Table 1.

By analogy to what has been previously reported on the Pd(II)-catalyzed intramolecular nucleophilic attack on carbon−carbon multiple bond,[7] the catalytic process is likely to occur through *anti-exo-dig* intramolecular nucleophilic attack of the hydroxyl group at the triple bond coordinated to Pd(II) followed by protonolysis and isomerization (path a) or vice versa (path b) (Scheme 1; anionic iodide ligands are omitted for simplicity).

The first experiments were carried out using the commercially available (*Z*)-3-methylpent-2-en-4-yn-1-ol **1a**. An exothermic reaction occurred when this enynol was reacted with PdI_2 + 2KI without added solvent, and cooling of the reaction flask with the aid of a water bath was needed in order to control the reaction temperature. GLC and GC−MS analysis of the crude were in agreement with the formation of 2,3-dimethylfuran **2a** in high yield (92% after 18 h with a **1a**: PdI_2 molar ratio = 500, entry 1). The product was easily isolated by transfer distillation in 87% yield. No reaction at all was observed using (*E*)-3-methylpent-2-en-4-yn-1-ol. Accordingly, *E*−*Z* equilibration did not take place with the catalytic system employed, although **1a** is known to be thermodynamically more stable than its *E* isomer.[8] The reaction occurred even using $PdCl_2$ + 2KCl as catalyst; however, both the reaction rate and product yield were lower compared with those obtained using the PdI_2/KI system. In fact, under the same conditions reported above, the use of $PdCl_2$ + 2KCl lead to 69% yield of **2a**

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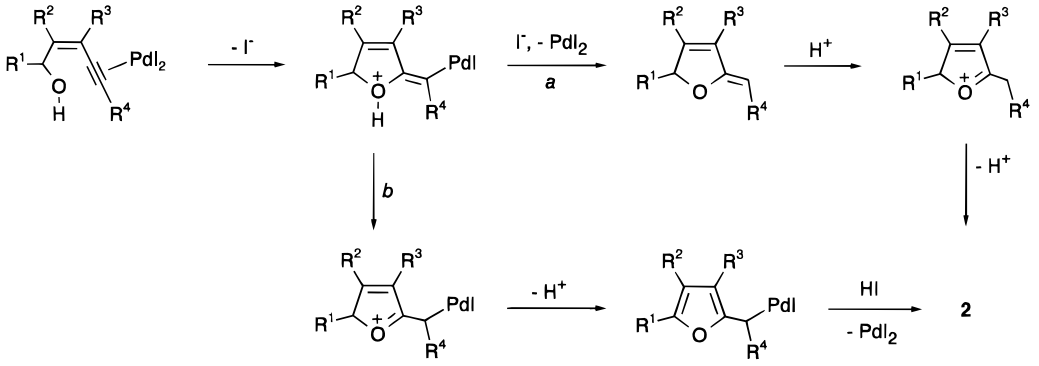
Scheme 1



with a substrate conversion of 85%. The better results obtained using I^- rather than Cl^- as the counterion for Pd(II) can be ascribed to the higher capacity of I^- to act as leaving group as well as to the higher acidity of HI compared with HCl. The first effect clearly favors the cyclization step (which must occur with elimination of X^-), while the latter promotes the protonolysis of the Pd−C bond (Scheme 1).

Other (*Z*)-enynols bearing an alkyl group at C-3 and terminal triple bond reacted in a very similar way with respect to **1a**, as exemplified by (*Z*)-3-ethylpent-2-en-4-yn-1-ol **1b** (entry 2). Additional alkyl substitution at C-1, as in (*Z*)-3-methylhept-3-en-1-yn-5-ol **1c**, did not significantly change the reactivity (entry 3). However, aryl substitution as in (*Z*)-3-methyl-1-phenylpent-2-en-4-yn-1-ol **1d** resulted in a slight decrease of the reaction rate, so either a higher amount of catalyst was needed at 25 °C (entry 4) or the reaction had to be conducted at 45 °C for a longer time (entry 5). Terminal enynols bearing an aryl substituent at C-3 such as (*Z*)-3-phenylpent-2-en-4-yn-1-ol **1e** were much less reactive than analogous substrates substituted with an alkyl group, and the reaction needed to be carried out at 80 °C (entry 6). This is probably due to the fact that an aryl group at C-3 is suitably placed for coordination to palladium, with formation of relatively stable chelate species.[9] Furthermore, the yield of the corresponding furan **2e** was rather low (30% GLC, 23% isolated), probably owing to a competitive decomposition pathway of the starting enynol.

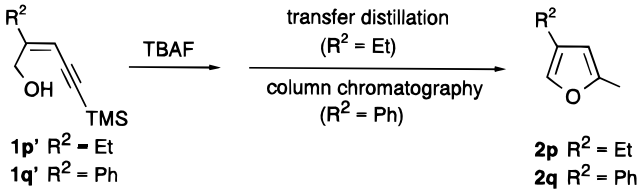
(*Z*)-2-En-4-yn-1-ols substituted at C-3 and with internal triple bond **1f**−**j** were less reactive than the corresponding enynols unsubstituted at C-5, as to be expected in view of the lower coordination ability of the internal triple bond with respect to the terminal one. Cycloisomerizations of these substrates were carried out in dry DMA, which further decreased the reaction rate but ensured better yields of furans as compared with the reactions carried out without added solvent. To achieve acceptable reaction times, the temperature was raised to 100 °C. Alkyl, alkenyl, and aryl substitution at C-5 were all compatible with cyclization conditions, high yield of the corresponding furans being obtained in each case (85−90% GLC, 76−81% isolated, entries 7−9). Substitution at C-5 with a phenyl group as in (*Z*)-3-methyl-5-phenylpent-2-en-4-yn-1-ol **1h** (entry 9) resulted in higher reactivity compared with alkyl or alkenyl substitution (entries 7 and 8, respectively), owing to the higher electrophilic character of the triple bond when conjugated with a phenyl group. Additional substitution at C-1 with an alkyl group, as in (*Z*)-5-methylundec-4-en-6-yn-3-ol **1i**, also led to an increase in reactivity (compare entries 7 and 10). This can be due to the steric effect exerted by the alkyl group, which tends to favor a conformation in which the hydroxyl is closer to the triple bond. However, (*Z*)-3-methyl-1-phenylnon-2-en-4-yn-1-ol **1j** readily underwent decomposition at 100 °C, so the reaction was carried out at 40 °C (without added solvent in order to compensate for the decreasing of the reaction rate at this temperature, entry 11).

(*Z*)-Enynols unsubstituted at C-3 proved to be more reactive with respect to analogous 3-substituted substrates. This is clearly due to the fact that in the absence of a substituent at C-3 the triple bond is less sterically hindered, so coordination to palladium is favored. For example, with 1% PdI_2, (*Z*)-non-2-en-4-yn-1-ol **1k** reacted in 22 h at 80 °C (entry 12) while (*Z*)-3-methylnon-2-en-4-yn-1-ol **1f** required a temperature of 100 °C for 20 h (entry 7). Conversion of **1k** was faster at 100 °C, but the final yield of 2-pentylfuran **2k** was lower compared with the reaction carried out at 80 °C. The reaction of (*Z*)-2-ethylnon-2-en-4-yn-1-ol **1l** at 100 °C with 1% of PdI_2 was complete in 2 h, with 85% GLC yield of furan **2l** (entry 13). The same reaction carried out with a **1l**/PdI_2 molar ratio of 300 required 15 h to obtain **2l** in 73% GLC yield (64% isolated, entry 14). The lower yield obtained with a smaller amount of catalyst is probably due to a decomposition pathway of the substrate, which becomes competitive with the palladium-promoted cyclization. Aryl instead of alkyl substitution at C-2 resulted in higher reactivity. For example, under the same conditions of entry 14, (*Z*)-2-phenylnon-2-en-4-yn-1-ol **1m** reacted in only 1 h instead of 15 h, with a 78% GLC yield of furan **2m** (68% isolated, entry 15). A higher yield (90% GLC) was obtained working at 70 °C with 1% of catalyst (entry 16). As expected, also (*Z*)-4-ethylundec-4-en-6-yn-3-ol **1n**, bearing an additional substituent at C-1, turned out to be more reactive than **1l** and its cycloisomerization with 0.5% of catalyst could be effected in 3 h at 80 °C (entry 17). As usual, a higher yield was obtained at lower temperatures while the reaction rate decreased (entry 18).

The present PdI_2-based methodology worked well also with substrates bearing a substituent on both olefinic carbons. Although the reaction of (*Z*)-3,5-diphenyl-2-ethylpent-2-en-4-yn-1-ol **1o** was rather slow (substrate conversion was not complete before 45 h working at 100

(9) Arene coordination to palladium has been described. For representative examples, see: Davies, J. A. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: Oxford, 1995; Vol. 9, pp 381−382 and references therein.

Scheme 2



°C with 1% of PdI_2), the final yield of the corresponding furan **2o** was still satisfactory (55% GLC, 48% isolated, entry 19).

(*Z*)-Enynols substituted at C-2 and with a terminal triple bond were unstable during the purification procedures (see Experimental Section for details). For example, distillation under reduced pressure of crude (*Z*)-2-ethylpent-2-en-4-yn-1-ol **1p**, obtained by deprotection of the triple bond of (*Z*)-2-ethyl-5-trimethylsilylpent-2-en-4-yn-1-ol **1p′** with TBAF in THF or KF in MeOH, invariably led to partial decomposition, and only small amounts of pure **1p** could be recovered. The desired 4-ethyl-2-methylfuran **2p**, however, was obtained directly by treatment of **1p′** with TBAF without added solvent followed by transfer distillation (94% isolated yield based on **1p′**) (Scheme 2, R^2 = Et). Analogously, column chromatography of the reaction crude deriving from deprotection of the triple bond of (*Z*)-2-phenyl-5-trimethylsilylpent-2-en-4-yn-1-ol **1q′** afforded 2-methyl-4-phenylfuran **2q** (93% isolated yield based on **1q′**) (Scheme 2, R^2 = Ph).

In conclusion, the PdI_2-based methodology here described proved to offer easy access to several types of substituted furans not readily obtainable by other ways.

Experimental Section

General Methods. ^{1}H NMR spectra were run on $CDCl_3$ solutions with Me_4Si as internal standard and recorded at 300 MHz. Chemical shifts and coupling constants (*J*) are given in ppm (δ) and in Hz, respectively. IR spectra were taken on a FT-IR spectrometer. Mass spectra were obtained at 70 eV on a GC−MS apparatus. Microanalyses were performed at our analytical laboratory. DMA was dried over 4 Å molecular sieves and distilled under nitrogen before use. All reactions were carried out under nitrogen and were monitored by TLC on silica gel 60 F_{254} or by GLC using capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase. Column chromatography was performed on silica gel 60 (70−230 mesh). Evaporation refers to the removal of solvent under reduced pressure.

Starting (*Z*)-2-en-4-yn-1-ols **1** and their precursors were prepared as described below. All other materials were commercially available and were used without further purification. Known compounds **1a**,[10] **1c**,[6g] **1d**,[6g] **1g**,[6e] **1h**,[6g] **2a**,[6g] **2b**,[11] **2c**,[6g] **2d**,[6g] **2e**,[12] **2g**,[13] **2h**,[6g] **2k**,[14] **2p**,[15] **2q**,[16] 3-methylpent-4-en-1-yn-3-ol,[17] 3-ethylpent-4-en-1-yn-3-ol,[18] 3-methylnon-1-en-4-yn-3-ol,[18] (*Z*)-3-iodo-3-phenylprop-2-en-1-ol,[19] methyl (*Z*)-non-2-en-4-ynoate,[20] (*Z*)-2-ethyl-3-iodoprop-2-en-1-ol,[21] and (*Z*)-3-iodo-2-phenylprop-2-en-1-ol[21] were characterized by comparison with literature data.

Synthesis of (*Z*)-2-En-4-yn-1-ols. Enynols substituted at C-3 with an alkyl group and bearing either terminal or internal triple bond were prepared by addition of alk-1-ynes to vinyl ketones to give pent-4-en-1-yn-3-ols followed by acid-catalyzed allylic isomerization.[8,22] A mixture of *Z* and *E* isomers was obtained by this method, the more thermodynamically stable *Z* isomer always being the most predominant product.[8] Pure 3-substituted (*Z*)-2-en-4-yn-1-ols were easily isolated by fractional distillation or column chromatography. This method was not suitable for the preparation of enynols substituted at C-3 with an aryl group, since the final yield was very low. An alternative route involved the Pd/Cu-catalyzed coupling [23] between an alk-1-yne and the appropriate (*Z*)-3-aryl-3-iodoprop-2-en-1-ol. As already reported,[5,6e] Pd/Cu-catalyzed coupling between **1a** and 1-bromo-2-methylpropene was the easiest way to prepare **1g**, the precursor of rosefuran **2g**. (*Z*)-Enynols bearing no substituent on the double bond were prepared by reduction of methyl (*Z*)-2-en-4-ynoates, obtained by Pd/Cu-catalyzed coupling between methyl (*Z*)-3-bromoprop-2-enoate and the appropriate alk-1-yne.[24] Coupling between alk-1-ynes and 2-substituted or 2,3-disubstituted (*Z*)-3-iodo-2-en-1-ols allowed a facile preparation of (*Z*)-enynols substituted at C-2 or at C-2 and C-3, respectively. (*Z*)-2-En-4-yn-1-ols with a secondary alcoholic group were easily prepared starting from the corresponding enynols unsubstituted at C-1 through oxidation followed by Grignard reaction.[6g]

Addition of Alk-1-ynes to Vinyl Ketones. The procedures described by Midland[25] and Brandsma[26] were employed to prepare 3-methylpent-4-en-3-ol (74% yield, bp = 63−64 °C/100 mmHg (lit.[17] bp 63.5−64.5 °C/100 mmHg)), 3-ethylpent-4-en-1-yn-3-ol (70%, bp = 68−69 °C/48 mmHg (lit.[18] bp 68.5−69.0 °C/48 mmHg)), 3-methylnon-1-en-4-yn-3-ol (91%, bp = 32 °C/4 × 10^{-2} mmHg, (lit.[18] bp 61.0−61.5/3.5 mmHg)), and 3-methyl-1-phenylpent-4-en-1-yn-3-ol, obtained as a colorless oil (79% yield) by column chromatography (9:1 hexane/AcOEt): IR (neat) 3375, 927 757, 691 cm^{-1}; ^{1}H NMR δ 7.47−7.42 (m, 2 H), 7.34−7.30 (m, 3 H), 6.06 (dd, *J* = 17.1, 10.3, 1 H), 5.60 (dd, *J* = 17.1, 1.0, 1 H), 5.18 (dd, *J* = 10.3, 1.0, 1 H), 1.66 (s, 3 H); MS *m/e* 172 (7, M^+), 171 (27), 157 (100), 129 (80).

Allylic Isomerization of Pent-4-en-1-yn-3-ols. A mixture of the title alcohol (90 mmol) and 10% w/v H_2SO_4 (160 mL) was stirred at 50 °C for 2 h. After cooling, the organic products were extracted with Et_2O and the combined organic layers washed with water, saturated $NaHCO_3$, and water again and then dried over Na_2SO_4. After the solvent was removed by distillation at atmospheric pressure (**1a**, **1b**) or in vacuo (**1f**, **1h**), (*Z*)-2-en-4-yn-1-ols were purified by distillation or column chromatography: **1a** (pale yellow liquid, bp = 75−6 °C/20 mmHg, 81% yield); **1b** (pale yellow liquid, bp = 76−77 °C/13 mmHg, 73%); IR (neat) 3356, 3295, 1013 cm^{-1}; ^{1}H NMR δ 5.95 (t, *J* = 6.7, 1 H), 4.35 (d, *J* = 6.7, 2 H), 3.19 (s, 1 H), 2.18 (q, *J* = 7.5, 2 H), 1.11 (t, *J* = 7.5, 3 H); MS *m/e* 109 (8, $M^+ - 1$), 81 (100); **1f** (pale yellow liquid, bp = 45 °C/2 × 10^{-2} mmHg, 66%); IR (neat) 3385, 2213, 1676 cm^{-1}; ^{1}H NMR δ 5.83−5.76

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(m, 1 H), 4.29 (dq, J = 6.9, 1.1, 2 H), 2.35 (t, J = 6.9, 2 H), 1.87−1.85 (m, 3 H), 1.59−1.36 (m, 4 H), 0.93 (t, J = 7.3, 3 H); MS *m/e* 152 (1, M^+), 109 (100), 95 (44), 81 (65); **1h** (pale yellow oil, hexane/AcOEt from 98:2 to 80:20, 58%).

(*Z*)-3-Phenylpent-2-en-4-yn-1-ol 1e. The method of Marshall[27] and Magriotis[28] applied to 3-phenylprop-2-yn-1-ol[29] was employed to prepare (*Z*)-3-iodo-3-phenylprop-2-en-1-ol. **Coupling Procedure.** To a stirred solution of the vinyl iodide (3.7 g, 14.2 mmol) in Et_2NH (42 mL) were added $Pd(PPh_3)_2Cl_2$ (0.20 g, 0.29 mmol) and CuI (0.29 g, 1.5 mmol). A solution of $Me_3SiC{\equiv}CH$ (2.1 g, 21.5 mmol) in Et_2NH (5.5 mL) was added dropwise, and the resulting mixture was stirred at room temperature for 4 h. After cooling to 0 °C, the mixture was diluted with Et_2O (50 mL) and quenched with 10% HCl. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and a solution of KF (1.2 g, 20.7 mmol) in MeOH (25 mL) was added to the residue. The reaction mixture was allowed to stir at room temperature for 3 h, and then it was diluted with Et_2O (20 mL) and quenched with water (60 mL). The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine (3 × 10 mL), dried (Na_2SO_4), and evaporated. Column chromatography (hexane/AcOEt from 9:1 to 8:2) afforded pure **1e** as a pale yellow oil (1.2 g, 53%): IR (neat) 3328, 3288 cm^{-1}; ^1H NMR δ 7.65−7.58 (m, 2 H), 7.40−7.27 (m, 3 H), 6.63 (t, J = 6.7, 1 H), 4.59 (d, J = 6.7, 2 H), 3.41 (s, 1 H); MS *m/e* 158 (19, M^+), 157 (41), 129 (100), 115 (74).

(*Z*)-Non-2-en-4-yn-1-ol 1k. The method of Marshall[6b] was employed. To a solution of methyl (*Z*)-non-2-en-4-ynoate[24] (4.2 g, 25.1 mmol) in dry ether (270 mL) at −78 °C was added dropwise a 1 M solution of DIBALH in THF (55 mL, 55 mmol). After being stirred at −78 °C for 1 h, the reaction was quenched with water and warmed to room temperature. The reaction mixture was diluted with Et_2O and 10% HCl, and the layers were separated. The organic layer was washed with brine, dried (Na_2SO_4), and evaporated. Column chromatography (hexane/AcOEt from 98:2 to 8:2) afforded pure **1k** as a colorless oil (3.3 g, 95%): IR (neat) 3331, 2215, 1020 cm^{-1}; ^1H NMR δ 6.00 (dt, J = 10.7, 6.3, 1 H), 5.61−5.54 (m, 1 H), 4.38 (dd, J = 6.3, 1.5, 2 H), 2.34 (td, J = 6.8, 2.0, 2 H), 1.58−1.36 (m, 4 H), 0.92 (t, J = 7.3, 3 H); MS *m/e* 138 (1, M^+), 95 (100), 81 (26), 67 (63).

Coupling between Alk-1-ynes and (*Z*)-3-Iodo-2-en-1-ols. The method of Duboudin[21,30] was employed to prepare 2-substituted or 2,3-disubstituted (*Z*)-3-iodo-2-en-1-ols starting from propynyl alcohols. (*Z*)-2-Ethyl-3-iodoprop-2-en-1-ol was obtained in 80% yield (lit.[21] 35%) and (*Z*)-2-phenylprop-2-en-1-ol in 52% yield (lit.[21] 39%); crude (*Z*)-2-ethyl-3-iodo-3-phenylprop-2-en-1-ol was used directly for the next step without further purification. The method of Alami[31] was employed for the coupling. To a cooled (0 °C), stirred mixture of $Pd(PPh_3)_4$ (2.9 g, 2.5 mmol) and CuI (0.95 g, 5 mmol) in pyrrolidine (10 mL) was added a solution of the vinyl iodide (50 mmol) in pyrrolidine (40 mL), followed by stirring for 5 min. A solution of $R^4C{\equiv}CH$ (100 mmol) in pyrrolidine (10 mL) was then added dropwise at 0 °C. After being stirred at 0 °C (R^4 = TMS) or room temperature (R^4 = Bu, Ph) for 2 h (R^2 = Et, R^4 = Bu), 4 h (R^2 = Et, R^4 = TMS; R^2 = Ph, R^4 = Bu; R^2 = Et, R^3 = R^4 = Ph), or 5 h (R^2 = Ph, R^4 = TMS), the reaction mixture was diluted with Et_2O and quenched at 0 °C with 10% HCl. 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 was purified by distillation or column chromatography. **1l** (pale yellow oil, 9:1 hexane/AcOEt, 74%): IR (neat) 3341, 2211, 1023 cm^{-1}; ^1H NMR δ 5.40−5.38 (m, 1 H), 4.35 (s, 2H), 2.34 (td, J = 6.8, 2.0, 2 H), 2.26−2.16 (m, 2 H), 1.59−1.35 (m, 4 H), 1.06 (t, J = 7.3), 0.92 (t, J = 7.1, 3 H); MS *m/e* 166 (7, M^+), 137 (18), 123 (92), 81 (100). **1m** (pale yellow oil, 6:4 hexane/Et_2O, 86%): IR (neat) 3377, 2207, 1026 cm^{-1}; ^1H NMR δ 7.49−7.41 (m, 2 H), 7.37−7.22 (m, 3 H), 5.91 (t, J = 2.1, 1 H), 4.75 (s, 2H), 2.38 (td, J = 7.0, 2.1, 2 H), 1.60−1.35 (m, 4 H), 0.91 (t, J = 7.3, 3 H); MS *m/e* 214 (74, M^+), 171 (96), 157 (70), 141 (72), 128 (100). **1o** (pale yellow oil, hexane/AcOEt from 9:1 to 7:3, 79% based on 3-phenylprop-2-yn-1-ol): IR (neat) 3359, 1489, 1027 cm^{-1}; ^1H NMR δ 7.43−7.27 (m, 10 H), 4.65 (s, 2 H), 2.31 (q, J = 7.3, 2 H), 1.07 (t, J = 7.3, 3 H); MS *m/e* 262 (34, M^+), 233 (100), 215 (51), 205 (70). **1p′** (colorless liquid, bp = 51−52 °C/1 × 10^{-2} mmHg, 88%): IR (neat) 3333, 2133, 1249, 843 cm^{-1}; ^1H NMR δ 5.42 (t, J = 1.9, 1 H), 4.38 (s, 2 H), 2.24 (qd, J = 7.5, 1.9, 2 H), 1.06 (t, J = 7.5), 0.19 (s, 9 H); MS *m/e* 182 (2, M^+), 167 (68), 75 (100), 73 (75). **1q′** (pale yellow oil, 95:5 hexane/AcOEt, 87%): IR (neat) 3380, 2132, 1020, 845 cm^{-1}; ^1H NMR δ 7.51−7.45 (m, 2 H), 7.41−7.29 (m, 3 H), 5.95 (s, 1 H), 4.82 (s, 2 H), 0.24 (s, 9 H); MS *m/e* 230 (31, M^+), 215 (64), 141 (43), 73 (100).

Deprotection of 1p′ and 1q′ with TBAF. To a stirred solution of **1p′** or **1q′** (22.6 mmol) in THF (100 mL) was added tetrabutylammonium fluoride trihydrate (TBAF) (8.7 g, 27.5 mmol), and the mixture was allowed to stir at room temperature for 3 h. The reaction was quenched with water (50 mL), the aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine. After the layers were dried over Na_2SO_4, the solvent was removed by distillation at atmospheric pressure. A mixture of products resulting from decomposition was recovered by distillation of the residue under reduced pressure when R^2 = Et, and only very small amounts (∼0.1 g, 4%) of pure (*Z*)-2-ethylpent-2-en-4-yn-1-ol **1p** could be isolated as a colorless liquid: bp 39−40 °C/1 mmHg; IR (neat) 3354, 3293, 1024 cm^{-1}; ^1H NMR δ 5.39−5.36 (m, 1 H), 4.38 (s, 2 H), 3.10 (d, J = 1.9, 1 H), 2.31−2.21 (m, 2 H), 1.07 (t, J = 7.5, 3 H); MS *m/e* 110 (7, M^+), 95 (11), 81 (100), 77 (22), 53 (94). On the other hand, column chromatography (9:1 hexane/CH_2Cl_2) of the residue obtained with R^2 = Ph afforded directly furan **2q** in 93% yield based on **1q′**. Deprotection of the triple bond of **1p′** (1.0 g, 5.5 mmol) with TBAF (2.05 g, 6.5 mmol) in the absence of added solvent followed by transfer distillation of the reaction crude gave furan **2p** in 94% yield based on **1p′**.

Oxidation with MnO_2 followed by Grignard reaction. Dixneuf's procedure[6g] was employed. Crude aldehydes obtained in the first step were reacted with the Grignard reagent without further purification. Enynols **1c**,**d** were purified as described.[6g] Distillation under reduced pressure (83−84 °C/1 mmHg) afforded pure **1i** as a pale yellow liquid (66% based on **1f**): IR (neat) 3348, 1455 cm^{-1}; ^1H NMR δ 5.57 (dq, J = 8.4, 1.5, 1 H), 4.47 (dt, J = 8.4, 6.6, 1 H), 2.33 (t, J = 6.9, 2 H), 1.83 (d, J = 1.5, 3 H), 1.68−1.35 (m, 6 H), 0.91 (t, J = 7.3, 6 H); MS *m/e* 179 (1, $M^+ - 1$), 151 (31), 95 (100). Pure **1j** (pale yellow oil, 81% based on **1f**) was recovered by column chromatography (9:1 hexane/Et_2O): IR (neat) 3347, 2221, 1006 cm^{-1}; ^1H NMR δ 7.46−7.40 (m, 2 H), 7.39−7.31 (m, 2 H), 7.30−7.22 (m, 1 H), 5.77 (distorted dq, J = 8.7, 1.3, 1 H), 5.72 (distorted d, J = 8.7, 1 H), 2.39 (t, J = 6.9, 2 H), 1.86 (d, J = 1.3, 3 H), 1.63−1.39 (m, 4 H), 0.94 (t, J = 7.2, 3 H); MS *m/e* 228 (3, M^+), 213 (29), 185 (90), 171 (100), 105 (97). (*Z*)-Enynol **1n** was isolated as a pale yellow oil (82% based on **1l**) by column chromatography (9:1 hexane/Et_2O): IR (neat) 3364, 1461 cm^{-1}; ^1H NMR δ 5.32−5.27 (m, 1 H), 4.60 (dd, J = 7.7, 6.4, 1 H), 2.28 (td, J = 6.8, 2.1, 2 H), 2.24−1.92 (m, 2 H), 1.71−1.30 (m, 6 H), 1.00 (t, J = 7.3, 3 H), 0.88 (t, J = 7.3, 3 H), 0.86 (t, J = 7.3, 3 H); MS *m/e* 194 (1, M^+), 165 (25), 151 (30), 109 (100).

General Procedure for Cycloisomerization Reactions. Reactions were carried out on a 3−10 mmol scale based on (*Z*)-enynol **1**. Solvent, substrate: PdI_2 molar ratio, reaction temperature and time, yield of furans **2** are indicated in Table 1. In a typical experiment, PdI_2 and KI (2 mol per mol of palladium) were added to pure **1** or to a solution of **1** in dry DMA

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in a Schlenk flask. The resulting mixture was stirred at the temperature and for the time required to obtain a satisfactory conversion, as shown by GLC and/or TLC analysis (Table 1).

Separation of Products. The crude product derived from reactions carried out without added solvent was purified by transfer distillation (**2a**−**c**) or column chromatography (**2d**, 95:5 hexane/AcOEt; **2j**, 95:5 hexane/Et_2O). The reaction mixtures in DMA were diluted with Et_2O, filtered from the catalyst, washed three times with water, and dried over Na_2SO_4. After the solvent was removed by distillation at atmospheric pressure (**2f**, **2g**, **2i**, **2k**, **2l**) or in vacuo (**2e**, **2h**, **2m**, **2n**, **2o**), products were purified by transfer distillation (**2f**, **2g**, **2i**, **2k**, **2l**) or column chromatography (**2e**, 9:1 hexane/Et_2O; **2h**, 98:2 hexane/AcOEt; **2m**, 9:1 hexane/AcOEt; **2n**, 95:5 hexane/Et_2O; **2o**, hexane/AcOEt from 98:2 to 95:5). 3-Methyl-2-pentylfuran **2f** (colorless oil): IR (neat) 2929, 1512, 727 cm^{-1}; ^1H NMR δ 7.21 (d, J = 1.8, 1 H), 6.15 (d, J = 1.8, 1 H), 2.54 (t, J = 7.4, 2 H), 1.95 (s, 3 H), 1.59 (quint, J = 7.4, 2 H), 1.37−1.21 (m, 4 H), 0.89 (t, J = 6.9, 3 H); MS *m/e* 152 (14, M^+), 95 (100). 5-Ethyl-3-methyl-2-pentylfuran **2i** (colorless oil): IR (neat) 2933, 1577, 1459, 801 cm^{-1}; ^1H NMR δ 5.74 (s, 1 H), 2.56 (q, J = 7.6, 2 H), 2.49 (t, J = 7.4, 2 H), 1.90 (s, 3 H), 1.57 (quint, J = 7.4, 2 H), 1.39−1.24 (m, 4 H), 1.19 (t, J = 7.6, 3 H), 0.89 (t, J = 6.9, 3 H); MS *m/e* 180 (13, M^+), 123 (100). 3-Methyl-2-pentyl-5-phenylfuran **2j** (colorless oil): IR (neat) 2926, 1487, 758, 691 cm^{-1}; ^1H NMR δ 7.63−7.54 (m, 2 H), 7.37−7.26 (m, 2 H), 7.21−7.13 (m, 1 H), 6.43 (s, 1 H), 2.60 (t, J = 7.3, 2 H), 1.98 (s, 3 H), 1.72−1.59 (m, 2 H), 1.40−1.27 (m, 4 H), 0.90 (t, J = 7.1, 3 H); MS *m/e* 228 (17, M^+), 171 (100). 4-Ethyl-2-pentylfuran **2l** (colorless oil): IR (neat) 2929, 1550, 1461, 1123, 805 cm^{-1}; ^1H NMR δ 7.05 (d, J = 1.8, 1 H), 5.88 (d, J = 1.8, 1 H), 2.56 (t, J = 7.4, 2 H), 2.39 (q, J = 7.5, 2 H), 1.68−1.55 (m, 2 H), 1.38−1.26 (m, 4 H), 1.15 (t, J = 7.5, 3 H), 0.89 (t, J = 7.0, 3 H); MS *m/e* 166 (17, M^+), 109 (100). 2-Pentyl-4-phenylfuran **2m** (pale yellow oil): IR (neat) 2929, 1451, 1131, 927, 746, 693 cm^{-1}; ^1H NMR δ 7.59 (d, J = 1.1, 1 H), 7.56−7.17 (m, 5 H), 6.31 (d, J = 1.1, 1 H), 2.64 (t, J = 7.6, 2 H), 1.75−1.62 (m, 2 H), 1.43−1.31 (m, 4 H), 0.95−0.88 (m, 3 H); MS 214 (63, M^+), 157 (100), 128 (69). 2,3-Diethyl-5-pentylfuran **2n** (colorless oil): IR (neat) 2934, 1460 cm^{-1}; ^1H NMR δ 5.75 (s, 1 H), 2.50 (q, J = 7.6, 2 H), 2.49 (t, J = 7.5, 2 H), 2.27 (q, J = 7.6, 2 H), 1.62−1.50 (m, 2 H), 1.34−1.26 (m, 4 H), 1.13 (t, J = 7.6, 3 H), 1.07 (t, J = 7.6, 3 H), 0.89−0.83 (m, 3 H); MS *m/e* = 194 (18, M^+), 179 (24), 137 (100). 2-Benzyl-4-ethyl-3-phenylfuran **2o** (colorless oil): IR (neat) 2965, 1494, 1453, 765, 727, 699 cm^{-1}; ^1H NMR δ 7.43−7.14 (m, 11 H), 3.94 (s, 2 H), 2.41 (qd, J = 7.5, 1.2, 2 H), 1.08 (t, J = 7.5, 3 H); MS *m/e* 262 (100, M^+), 261 (70), 233 (19), 205 (23).

Acknowledgment. Financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (MURST) is gratefully acknowledged.

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

JO990847H