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Cycloisomerization of Acetylenic Acids to γ-Alkylidene Lactones using a Palladium(II) Catalyst Supported on Amino-Functionalized Siliceous Mesocellular Foam

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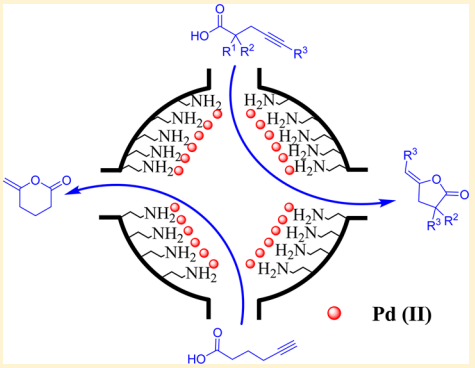
Supporting Information

ABSTRACT: Cycloisomerization of various γ-acetylenic acids to their corresponding γ-alkylidene lactones by the use of a heterogeneous Pd(II) catalyst supported on amino-functionalized siliceous mesocellular foam is described. Substrates containing terminal as well as internal alkynes were cyclized in high to excellent yields within 2−24 h under mild reaction conditions. The protocol exhibited high regio- and stereoselectivity, favoring the *exo*-dig product with high *Z* selectivity. Moreover, the catalyst displayed excellent stability under the employed reaction conditions, as demonstrated by its good recyclability and low leaching.



INTRODUCTION

The transition-metal-catalyzed intramolecular addition of a carboxylic acid to a terminal alkyne is an important transformation in organic synthesis, as it provides access to the γ-alkylidene lactone motif, which is present in a vast number of biologically active natural products.[1−5] To obtain the desired five-membered cyclic lactones arising from *exo*-dig ring closure instead of the isomeric six-membered *endo*-dig products (Figure 1), control of regioselectivity in the cyclization step is required.

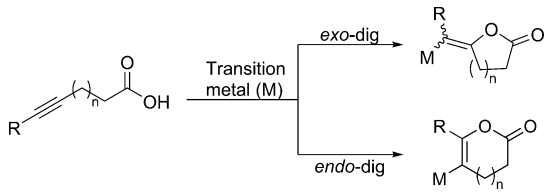


Figure 1. Cycloisomerization occurring in either an *exo*-dig or *endo*-dig manner, both of which are favored according to Baldwin's rules.

Generally, this selectivity can be controlled by the choice of metal catalyst, as well as by careful design of the reaction conditions. Over the past years, numerous protocols based on transition metals such as Rh,[6,7] Hg,[8−11] Ru,[12] Ag,[13−15] Au,[16−19] Cu,[20,21] and Pd[6,14,22−28] have been explored to allow for the synthesis of γ-alkylidene lactones. Unfortunately, most of these protocols require high catalyst loadings, prolonged reaction times, and/or elevated temperatures. In addition, the majority of the reports involve the use of homogeneous catalysis, which is generally associated with difficulties in recycling of the catalyst and additional purification steps to remove trace amounts of metal impurities from the final product. Heterogeneous catalysis, on the other hand, offers a simple solution to these problems and constitutes a green and environmentally benign alternative. To the best of our knowledge, only a handful of examples of heterogeneous protocols for the cycloisomerization of alkynoic acids to the corresponding lactones exist to this date.[24,25,29]

We have recently reported on the preparation of a heterogeneous catalyst based on Pd nanoparticles immobilized on amino-functionalized siliceous mesocellular foam (Pd^0-AmP-MCF).[30,31] Mesocellular foam (MCF) is a mesoporous material that has proven to be an excellent support for both chemical as well as biological catalysts, mainly due to its high surface area, large pore volume, and adjustable pore size.[32−34] Several organic transformations have successfully been accomplished with our novel Pd(0) catalyst, such as aerobic oxidation of primary and secondary alcohols,[31] transfer hydrogenation of alkenes[35] and nitroarenes,[36] racemization and dynamic kinetic resolution of amines,[30] and Suzuki-cross couplings.[35] However, the catalytic activity of the corresponding heterogeneous Pd(II) precatalyst is not as well-explored and has so far only been used together with an amino catalyst for cascade Michael/carbocyclization reactions.[37] Herein, we report on the cycloisomerization of various γ-acetylenic acids to alkylidene lactones catalyzed by Pd^{II}-AmP-MCF.

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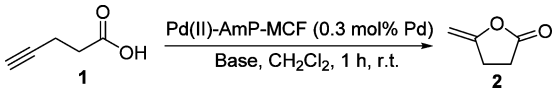
RESULTS AND DISCUSSION

The cycloisomerization of 4-pentynoic acid (**1**) into 5-methylenedihydrofuran-2(3*H*)-one (**2**) was chosen as the model reaction for the screening of reaction conditions, in which the effects of base, solvent, catalyst loading, and reaction temperature were investigated. In order to clearly assess the effect of the change in the different reaction parameters, the reaction time for the screen was chosen to be 1 h. The optimization of the reaction conditions commenced with a screening of a series of bases. Employing Cs_2CO_3 (0.5 equiv) as the base gave a 35% yield of product **2**, while pyridine was shown to be completely incompatible with this protocol (Table 1, entries 1 and 2). The most effective bases proved to be DBU, NaOAc, and Et_3N, all affording yields of ∼50% (Table 1, entries 3−5). Et_3N was chosen for further studies, as it is more cost-effective than DBU. Furthermore, an organic base such as Et_3N is more convenient for recycling studies than the inorganic base NaOAc, as the latter requires additional washing with water between each recycling cycle. The loading of Et_3N was therefore investigated, and it was found that an increase from 0.5 to 1.0 equiv resulted in a decrease of the yield from 47% to 37% (Table 1, entries 5 and 6). The best result was obtained using 0.25 equiv of Et_3N, which afforded 66% yield (Table 1, entry 7). These results suggest that elevated base concentrations have an inhibitory effect on the reaction. However, performing the reaction in the absence of base resulted in negligible amounts of **2** (Table 1, entry 8), confirming that the base is necessary for the formation of the product.

Table 1. Screening the Type of Base and Base Loading for the Cycloisomerization of 1 to 2

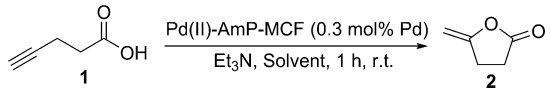


entry	base	loading (equiv)	yield of **2**[a] (%)
1	Cs_2CO_3	0.5	35
2	pyridine	0.5	0
3	DBU	0.5	50
4	NaOAc	0.5	49
5	Et_3N	0.5	47
6	Et_3N	1	37
7	Et_3N	0.25	66
8	Et_3N	0	3

[a]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

An evaluation of the solvent effects showed that coordinating solvents such as THF, EtOH, and CH_3CN reduced the activity of the catalyst, affording only 12%, 16%, and 23% yields of **2** (Table 2, entries 1−3). Less coordinating solvents, such as toluene and CH_2Cl_2, allowed for a more efficient reaction, giving 49% and 66% yields, respectively (Table 2, entries 4 and 5). Finally, the loading of the catalyst was investigated and the use of 0.9 mol % of catalyst afforded the desired product in 93% yield (Table 2, entry 8). However, increasing the reaction time and temperature to 2 h and 40 °C, respectively, afforded an excellent yield of 97% with a low catalyst loading of 0.3 mol % (Table 1, entry 9). In conclusion, the best results were obtained when performing the reaction in CH_2Cl_2 at 40 °C with 0.25 equiv of Et_3N and 0.3 mol % of Pd(II) for 2 h. In a control experiment it was found that the reaction does not proceed in the absence of the Pd(II) catalyst (Table 2, entry 6).

Table 2. Screening of Solvent and Catalyst Loading[a]



entry	solvent	catalyst loading (mol %)	yield[b] (%)
1	EtOH	0.3	12
2	THF	0.3	16
3	CH_3CN	0.3	23
4	toluene	0.3	49
5	CH_2Cl_2	0.3	66
6	CH_2Cl_2	0	0
7	CH_2Cl_2	0.6	76
8	CH_2Cl_2	0.9	93
9[c]	CH_2Cl_2	0.3	97

[a]Conditions: **1** (0.4 mmol), Et_3N (0.25 equiv), Pd^{II}-AmP-MCF (0.3 mol % Pd), solvent (1 mL), room temperature, 1 h. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]Run at 40 °C for 2 h.

The reaction proved to be highly regioselective for all of the 4-acetylenic acids that were investigated, yielding the 5-*exo*-dig lactone. For disubstituted acetylenes the reaction was also highly stereoselective, affording only the *Z* olefinic product. As depicted in Table 3, the catalyst worked well for the cycloisomerization of a variety of acetylenic acids. Both 4-pentynoic acid (**1**) and 2,2-dimethylpent-4-ynoic acid (**3**) were cyclized to afford the corresponding lactones, **2** and **4**, in high yields under the standard conditions (Table 3, entries 1 and 2). Substitution with a longer alkyl chain at the α position reduced the reaction rate, and consequently 2-hexyl-4-pentynoic acid (**5**) required an elevated temperature (50 °C) to give a high yield of **6** (Table 3, entry 3). For the diacid **7**, prolongation of the reaction time to 3 h afforded the corresponding lactone **8** in 97% yield (Table 3, entry 4). The catalyst also proved to be compatible with ester and allylic functionalities, and as a result the acids **9** and **11** were cyclized to the corresponding lactones in high yields (Table 3, entries 5 and 6). Interestingly, internal alkynes could also be cyclized to their corresponding lactones with high *Z* selectivity with this catalytic system, although at an elevated temperature, for a prolonged reaction time, and with a catalyst loading of 0.5 mol %. Alkyne **13** was cyclized in excellent yield within 3 h at 50 °C with 0.5 mol % of Pd (Table 3, entry 7). For alkynes **15** and **17** the reaction time had to be prolonged to 24 h to give comparable yields (Table 3, entries 8 and 9). As is apprent from the results in entries 7−9, the reaction is favored by electron-withdrawing substituents on the phenyl ring, as they increase the electrophilicity of the alkyne moiety. Having a hydroxyl group present on the phenyl ring made the cyclization less efficient, and alkyne **19** was cyclized to afford a 5:1 mixture of the *exo*-dig and *endo*-dig lactone products in 53% yield after 3 h (Table 3, entry 10). Unfortunately, attempts to improve the outcome of the reaction by extending the reaction time proved to be unsuccessful, as a result of the competing decomposition of **20**. The Boc-protected amino acid derivative **21**, on the other hand, could be efficiently cyclized by this catalytic system, affording **22** in high yield within 3 h (Table 3, entry 11). In sharp contrast to the case for 4-pentynoic acid (**1**), the cyclization of 5-hexynoic acid (**23**) required a prolonged reaction time (24 h), higher catalyst loading (0.5 mol %), and

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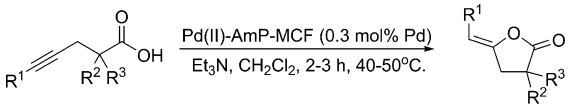
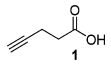
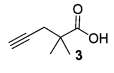
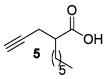
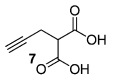
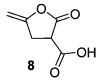
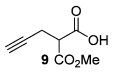
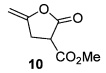
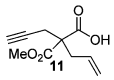
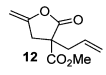
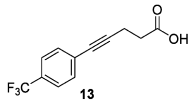
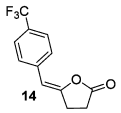
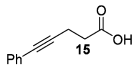
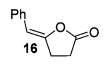
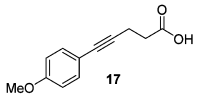
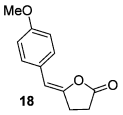
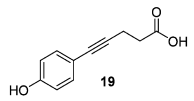
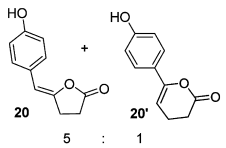
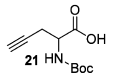
Table 3. Cycloisomerization of Various Acetylenic Acids to Lactones Catalyzed by Pd^{II}-AmP-MCF[a]



Entry	Acetylenic acid	Lactone	Temp (°C)	Time (h)	Yield(%)
1			40	2	77 (97[b])
2			40	2	81 (90[b])
3			50	2	89 (90[b])
4			40	3	54[c] (97[b])
5			40	2	80 (82[b])
6			40	2	93 (96[b])
7			50	3	83[d,e] (99[b])
8			50	24	87[d,e] (88[b])
9[f]			50	24	67[d,e] (73[b])
10			50	3	50[d,e] (53[b])
11			40	3	80 (94[b])
12[f]			50	24	77[d] (78[b])

[a]Reaction conditions: Pd^{II}-AmP-MCF (0.3 mol % Pd), acetylenic acid (0.40 mmol), Et_3N (0.10 mmol), CH_2Cl_2 (1 mL), 40−50 °C, 2−3 h. [b]Determined by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. [c]The product is highly unstable. [d]Run with 0.5 mol % Pd. [e]The double-bond configuration was unambiguously assigned by the ^1H NMR shifts of the vinylic proton and by 1D and 2D NOE experiments. [f]24 h reaction time.

elevated temperature (50 °C) to give comparable yields (Table 3, entry 12), which shows the significant difference in rate between formation of five- and six-membered-ring products. However, the role of the ring size did not affect the *exo*-dig selectivity and **24** was the only product detected by ^1H NMR.

A key aspect of heterogeneous catalysis is the possibility to recycle the catalyst, and therefore we were interested in investigating the recyclability of Pd^{II}-AmP-MCF. In the reaction of 4-pentynoic acid to give lactone **2**, the catalyst was active in five subsequent recycling experiments, although a gradual decrease in activity was observed for each cycle (97%, 91%, 80%, 71%, and 62%, respectively).[38] However, this deactivation was circumvented by carrying out the recycling experiments in the presence of benzoquinone (1 mol %). With this modification, a yield of 97% was repeatedly obtained in four subsequent cycles without any sign of deactivation. This intriguing result demonstrates that the observed deactivation is not a result of catalyst decomposition but is rather caused by reduction of some of the supported Pd(II) species to less active Pd(0). In the presence of benzoquinone the Pd(0) species formed in situ is efficiently reoxidized to active Pd(II), and the recovered heterogeneous catalyst maintains its high catalytic activity and can be reused four times without detectable deactivation. In a control experiment, we found that in the

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presence of benzoquinone also Pd^0-AmP-MCF[30,31] was activated and shown to catalyze the lactonization of 4-pentynoic acid in good yield.

Gratifyingly, analysis of the solid-free filtrates of the reaction solution by ICP-OES showed a very low leaching of only 4 ppm. However, to ensure that the reaction was catalyzed primarily by our heterogeneous Pd(II) catalyst and not by these homogeneous Pd species, the cyclization of acid **1** was performed using corresponding amounts of $Pd(OAc)_2$ (4 ppm). Under the standard conditions a low yield of 18% of **2** was obtained after 2 h of reaction time. Although these results indicate that the homogeneous Pd species participate in the reaction, it is possible to state that it is the heterogeneous Pd(II) catalyst that is responsible for the majority of the product formation.

CONCLUSION

An efficient route for the cycloisomerization of acetylenic acids to their corresponding lactones under relatively mild reaction conditions, using a heterogeneous Pd(II) catalyst, has been developed. The protocol tolerates the presence of different functional groups on both the α and γ positions of the acetylenic acids. Moreover, the reactions were found to be highly regio- and stereoselective, resulting in selective formation of the *exo*-dig products and, for internal alkynes, selective formation of the *Z* configuration product. Several 4-pentynoic acid derivatives were efficiently cyclized in excellent yields within 2−3 h, while internal alkyne substrates as well as 5-hexynoic acid required elevated temperature, higher catalyst loading, and prolonged reaction times for obtaining comparable yields. Furthermore, the heterogeneous Pd(II) catalyst showed high recyclability and a low leaching, making it an attractive option to previously developed homogeneous protocols. The present catalytic system with its mild reaction conditions makes it a promising method for the synthesis of lactones of biological activity.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all materials were obtained from commercial suppliers and used without further purification. THF was purchased as the dry solvent and was column-dried before use. MeOH was purchased as the dry solvent and dried over molecular sieves (4 Å) before use. ^{1}H NMR and ^{13}C NMR were recorded on a 400 MHz instrument. Chemical shifts are reported in ppm, relative to TMS (^{1}H, internal standard, δ(H) 0.00) or solvent residual peaks (^{1}H, δ(H) $CDCl_3$ 7.26; ^{13}C, δ(C) $CDCl_3$ 77.0) with multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, app = apparent), coupling constants (in Hz), and integration. The stereoselectivites of the cyclized products of internal alkynes were determined by ^{1}H NMR shifts of the vinylic proton and by 1D and 2D NOE experiments. The Pd^{II}-AmP-MCF catalyst was characterized for palladium content and leaching by inductively coupled plasma (ICP-OES). Flash chromatography was performed on an automated flash chromatography instrument using silica-based cartridges with UV detection for fraction collection. HRMS data were recorded using TOF ESI detection. Acids **1**, **5**, and **23** are commercially available and were used without further purification. 5-(4-Methoxyphenyl)pent-4-ynoic acid (**17**) was prepared according to a reported procedures.[39] Acids **3**, **7**, **9**, **11**, **13**, **15**, **19**, and **21** were synthesized according to procedures described below.

General Procedure A for Cycloisomerization for Yield Determination by ^{1}H NMR. The pentynoic acid (0.40 mmol), triethylamine (0.10 mmol, 10.1 mg), Pd^{II}-Amp-MCF (0.30−0.50 mol % Pd, 2.56−4.26 mg), and CH_2Cl_2 (1 mL) were placed in a microwave vial, which was sealed and heated in an oil bath at the indicated temperature for an appropriate time. After the reaction was complete, 1,3,5-trimethoxybenzene (67.2 mg, 0.40 mmol) in $CDCl_3$ (1 mL) was added as internal standard, and the reaction vessel was subsequently centrifuged for 10 min. An aliquot of 0.2−0.3 mL was withdrawn, further diluted with $CDCl_3$ (0.3 mL), and analyzed by ^{1}H NMR against the internal standard for yield determination.

General Procedure B for Cycloisomerization. The pentynoic acid (0.80 mmol), triethylamine (0.20 mmol, 20.2 mg), Pd^{II}-Amp-MCF (0.30 mol %, 5.12 mg), and CH_2Cl_2 (2 mL) were placed in a microwave vial, which was sealed and heated in an oil bath at the indicated temperature for an appropriate time. The reaction mixture was subsequently filtered through a short plug of silica gel with pentane/EtOAc (3/2) as the eluent, and the solvents were removed in vacuo to afford the desired product.

*5-Methylenedihydrofuran-2(3H)-one (**2**).*[19] The general procedure B for cycloisomerization was followed, and the reaction mixture was heated at 40 °C for 2 h. Compound **2** was obtained as a colorless oil (60.6 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.77−4.74 (m, 1H), 4.33−4.30 (m, 1H), 2.92−2.84 (m, 2H), 2.71−2.64 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.0, 155.8, 88.9, 28.2, 25.3.

*3,3-Dimethyl-5-methylenedihydrofuran-2(3H)-one (**4**).*[40] The general procedure B for cycloisomerization was followed, and the reaction mixture was heated at 40 °C for 2 h. Compound **4** was obtained as a yellow oil (81.0 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.77−4.74 (m, 1H), 4.34−4.31 (m, 1H), 2.70−2.68 (m, 2H), 1.30 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 180.3, 153.5, 89.5, 41.0, 40.5, 24.8.

*3-Hexyl-5-methylenedihydrofuran-2(3H)-one (**6**).*[41] The general procedure B for cycloisomerization with 0.8 mmol of substrate was followed, and the reaction mixture was heated at 50 °C for 2 h. 3-Hexyl-5-methylenedihydrofuran-2(3*H*)-one was obtained as a colorless oil (130 mg, 89%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.74−4.71 (m, 1H), 4.32−4.28 (m, 1H), 3.04−2.95 (app ddt, *J* = 16.1 Hz, *J* = 9.7 Hz, *J* = 1.6 Hz, 1H), 2.80−2.70 (m, 1H), 2.60−2.51 (ddt, *J* = 16.1 Hz,, *J* = 7.8 Hz, *J* = 2.2 Hz, 1H), 1.93−1.81 (m, 1H), 1.58−1.46 (m, 1H), 1.43−1.22 (m, 8H), 0.91−0.85 (m, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.4, 154.7, 88.8, 40.1, 31.8, 31.7, 31.0, 29.0, 27.1, 22.7, 14.2.

*5-Methylene-2-oxotetrahydrofuran-3-carboxylic Acid (**8**).* 2-(Prop-2-yn-1-yl)malonic acid (113.6 mg, 0.80 mmol), triethylamine (20.2 mg, 0.20 mmol), Pd^{II}-Amp-MCF (5.12 mg, 0.30 mol %), and CH_2Cl_2 (2 mL) were placed in a microwave vial, which was sealed and heated in an oil bath at the 40 °C for 3 h. The reaction mixture was filtered through Celite and eluted with CH_2Cl_2. The solvent was removed to afford a yellow oil (99 mg, 87%).[42] For isolation without triethylamine, the crude yellow oil was dissolved in EtOAc (10 mL) and washed with water (pH 3; 3 × 10 mL). The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford a pale yellow oil (61 mg, 54%) of product. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.88 (m, 1H), 4.48 (m, 1H), 3.82 (m, 1H), 3.34 (m, 1H), 3.17 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.6, 169.6, 152.9, 90.5, 46.2, 29.3. HRMS (ESI): calcd for $C_6H_6O_4Na$ [M + Na^+], 165.0158; found, 165.0166.

*Methyl 5-Methylene-2-oxotetrahydrofuran-3-carboxylate (**10**).*[43] The general procedure B for cycloisomerization was followed, and the reaction mixture was heated at 40 °C for 2 h. Compound **10** was obtained as a yellow oil (99.8 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.83−4.80 (m, 1H), 4.43−4.40 (m, 1H), 3.82 (s, 3H), 3.76 (dd, *J* = 10.4 Hz, *J* = 7.6 Hz, 1H), 3.30 (app ddt, *J* = 16.6 Hz, *J* = 7.6 Hz, *J* = 2.2 Hz, 1H), 3.01 (app ddt, *J* = 16.6 Hz, *J* = 10.4 Hz, *J* = 1.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.6, 167.4, 153.3, 90.0, 53.5, 46.4, 29.5.

*Methyl 3-Allyl-5-methylene-2-oxotetrahydrofuran-3-carboxylate (**12**).*[18] The general procedure B for cycloisomerization was followed and the reaction mixture was heated at 40 °C for 2 h. Compound **12** was obtained as a white solid (146.3 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): 5.75−5.64 (m, 1H), 5.25−5.22 (m, 1H), 5.21−5.17 (m, 1H), 4.82−4.77 (m, 1H), 4.40−4.35 (m, 1H), 3.80 (s, 3H), 3.29 (dt, *J* = 16.7 Hz, *J* = 1.8 Hz, 1H), 2.90 (dt, *J* = 16.7 Hz, *J* = 2.0 Hz, 1H), 2.77

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(dd, J = 14.0 Hz, J = 7.6 Hz, 1H), 2.67 (dd, J = 14.0 Hz, J = 7.1 Hz, 1H).

*(Z)-5-(4-(Trifluoromethyl)benzylidene)dihydrofuran-2(3H)-one (**14**).* 5-(4-(Trifluoromethyl)phenyl)pent-4-ynoic acid (96.8 mg, 0.40 mmol), triethylamine (10.1 mg, 0.10 mmol), Pd^{II}-Amp-MCF (4.26 mg, 0.50 mol % Pd), and CH_2Cl_2 (1 mL) were placed in a microwave vial, which was sealed and heated in an oil bath at 50 °C for 3 h. The crude material was filtered through a plug of silica and the plug eluted with CH_2Cl_2; removal of solvents afforded the pure product as a white solid (79.9 mg, 83%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (app d, J = 8.4 Hz, 2H), 7.56 (app d, J = 8.4 Hz, 2H), 5.60−5.57 (m, 1H), 3.11−3.04 (m, 2H), 2.77−2.71 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.5, 150.3, 137.6, 128.5, 128.5 (q, $^2J_{C-F}$ = 32.3 Hz), 125.5 (q, $^3J_{C-F}$ = 4.5 Hz), 124.4 (q, $^1J_{C-F}$ = 272.7 Hz), 103.9, 26.9, 26.6. HRMS (ESI): calcd for $C_{12}H_9F_3O_2Na$ [M + Na^+], 265.0447; found, 265.0454. A clear cross-peak between the vinylic proton and CH_2 protons was observed in a 2D NOE experiment as well as a clear positive difference peak in 1D NOE for CH_2 protons when the vinylic proton was irradiated at 5.59 ppm.

*(Z)-5-Benzylidenedihydrofuran-2(3H)-one (**16**).*[19] 5-Phenylpent-4-ynoic acid (69.6 mg, 0.40 mmol), triethylamine (10.1 mg, 0.10 mmol), Pd^{II}-Amp-MCF (4.26 mg, 0.50 mol %), and CH_2Cl_2 (1 mL) were placed in a microwave vial, which was sealed and heated in an oil bath at the 50 °C for 3 h. The crude material was filtered through a plug of silica and eluted with pentane/EtOAc (3/2, 3 mL); removal of solvents afforded the pure product as a white solid (60.5 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (app d, J = 7.3 Hz, 2H), 7.32 (app t, J = 7.7 Hz, 2H), 7.23−7.18 8 (m, 1H), 5.56 (t, J = 1.7 Hz, 1H), 3.07−3.01 (m, 2H), 2.75−2.68 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.04, 148.2, 134.0, 128.6, 128.4, 126.9, 105.1, 27.1, 26.5. A clear cross-peak between the vinylic proton and CH_2 protons was observed in a 2D NOE experiment, as well as a clear positive difference peak in 1D NOE for CH_2 protons when the vinylic proton was irradiated at 5.56 ppm. The shift of the vinylic proton was in agreement with literature data.[19]

*(Z)-5-(4-Methoxybenzylidene)dihydrofuran-2(3H)-one (**18**).* 5-(4-Methoxyphenyl)pent-4-ynoic acid (81.6 mg, 0.40 mmol), triethylamine (10.1 mg, 0.10 mmol), Pd^{II}-Amp-MCF (4.26 mg, 0.50 mol %), and CH_2Cl_2 (1 mL) were placed in a microwave vial, which was sealed and heated in an oil bath at 50 °C for 24 h. The crude material was filtered through a plug of silica and diluted with EtOAc (20 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (3 × 20 mL), dried over $MgSO_4$, and filtered, and the solvent was removed to afford the pure product as a white solid (54.6 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51−7.47 (m, 2H), 6.89−6.84 (m, 2H), 5.51−5.48 (m, 1H), 3.81 (s, 3H), 3.05−2.98 (m, 2H), 2.73−2.67 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.2, 158.5, 146.5, 129.7, 126.8, 114.1, 104.6, 55.4, 27.3, 26.4. HRMS (ESI): calcd for $C_{12}H_{12}O_3Na$ [M + Na^+], 227.0679; found, 227.0677. A clear cross-peak between the vinylic proton and CH_2 protons was observed in a 2D NOE experiment, as well as a clear positive difference peak in 1D NOE for CH_2 protons when the vinylic proton was irradiated at 5.49 ppm.

*(Z)-5-(4-Hydroxybenzylidene)dihydrofuran-2(3H)-one (**20**).* 5-(4-Hydroxyphenyl)pent-4-ynoic acid (76.1 mg, 0.40 mmol), triethylamine (10.1 mg, 0.10 mmol), Pd^{II}-Amp-MCF (4.26 mg, 0.50 mol %), and CH_2Cl_2 (1 mL) were placed in a microwave vial, which was sealed and heated in an oil bath at the 50 °C for 3 h. The reaction mixture was filtered through a plug of silica and eluted with pentane/EtOAc (60/40). The organic phase was washed with $NaHCO_3$ (3 × 3 mL), dried over $MgSO_4$, and filtered, and the solvents were removed to afford a 5/1 mixture of *exo*-dig and *endo*-dig isomers **20** and **20′**, respectively, as a white solid (38.2 mg, 50%). **20**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (app d, J = 8.7 Hz, 2H), 6.81 (app d, J = 8.7 Hz, 2H), 5.48 (t, J = 1.7 Hz, 1H), 4.79 (br s, 1H), 3.07−2.97 (m, 2H), 2.75−2.66 (m, 2H). The *endo*-dig isomer **20′** is distinguishable at δ 5.68 (t, J = 4.7 Hz, 1H), 4.93 (br s, 1H), 2.95−2.88 (m, 2H), 2.55−2.48 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 175.2, 154.3, 146.4, 129.8, 115.4, 104.5, 98.3, 27.1, 26.2. HRMS (ESI): calcd for $C_{11}H_9O_3$ [M^-], 189.0557; found, 189.0548. A clear cross-peak between the vinylic proton and CH_2 protons in **20** was observed in a 2D NOE experiment, as well as a clear positive difference peak in 1D NOE for CH_2 protons when the vinylic proton was irradiated at 5.48 ppm.

*tert-Butyl(5-methylene-2-oxotetrahydrofuran-3-yl)carbamate (**22**).*[20] The general procedure B for cycloisomerization was followed, and the reaction mixture was heated at 40 °C for 3 h. Compound **22** was obtained as an off-white solid (136 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.10 (br s, 1H), 4.83−4.79 (m, 1H), 4.42−4.38 (m, 1H), 3.35−3.17 (m, 1H), 2.94−2.79 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1, 152.4, 90.6, 81.2, 50.7, 33.7, 28.4.

*6-Methylenetetrahydro-2H-pyran-2-one (**24**).*[19] The general procedure B for cycloisomerization was followed, and the reaction mixture was heated at 50 °C for 24 h with a catalyst loading of 0.5 mol %. Compound **24** was obtained as a colorless oil (69.1 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): 4.65−4.62 (m, 1H), 4.30−4.27 (m, 1H), 2.62 (t, J = 6.8 Hz, 2H), 2.48 (app d, J = 6.5 Hz, 2H), 1.92−1.83 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.2, 155.4, 93.9, 30.4, 26.9, 18.7.

Recycling Study. A microwave vial was charged with 4-pentynoic acid (39.2 mg, 0.40 mmol), triethylamine (10.1 mg, 0.10 mmol), Pd^{II}-Amp-MCF (2.56 mg, 0.30 mol % Pd), 1,4-benzoquinone (0.5 mg, 1 mol %), 1,3,5-trimethoxybenzene (67.2 mg, 0.40 mmol), and CH_2Cl_2 (1 mL). The microwave vial was sealed and heated for 2 h at 40 °C. The reaction vessel was subsequently centrifuged for 10 min. A 0.2−0.3 mL aliquot was withdrawn, further diluted with $CDCl_3$ (0.3 mL), and analyzed by ^{1}H NMR to determine the ratio of starting material and product. The catalyst was washed twice with CH_2Cl_2 (2 × 3 mL). This procedure was repeated in three subsequent cycles.

Synthesis of Starting Material. *Synthesis of 2,2-Dimethylpent-4-ynoic acid (**3**).* A 2 M solution of LDA in toluene (24 mL, 48 mmol) was added to dry THF (80 mL) at −50 °C and was stirred for 30 min under an argon atmosphere. It was then warmed to −5 °C and was stirred for 10 min, followed by dropwise addition of methyl isobutyrate (4.0 g, 40 mmol). The reaction mixture was cooled to −50 °C, and propargyl bromide (5.7 g, 48 mmol) was added. The reaction mixture was then warmed to room temperature and was stirred for an additional 18 h. The reaction mixture was quenched with saturated aqueous NH_4Cl at 0 °C and extracted with Et_2O (2 × 200 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo to afford crude methyl 2,2-dimethyl-4-pentynoate as an orange oil, which was subsequently hydrolyzed by treatment of 2 M aqueous NaOH (80 mL, H_2O/EtOH (1/1)) at reflux for 3 h. The reaction mixture was then acidified to pH 1 using 1 M aqueous HCl and extracted with Et_2O (3 × 30 mL). The combined ether layers were concentrated in vacuo and extracted with 3 M aqueous NaOH (3 × 30 mL). The combined aqueous layers were acidified to pH 1 using 6 M aqueous HCl and extracted with CH_2Cl_2 (3 × 30 mL). The combined CH_2Cl_2 layers were dried over $MgSO_4$ and filtered, and the solvents were removed in vacuo to afford the pure product as an orange oil (2.3 g, 45%). ^{1}H NMR data were in accordance with those previously reported.[44]

*Synthesis of 2-(Prop-2-yn-1-yl)malonic Acid (**7**).* Sodium (0.48 g, 20.9 mmol) was dissolved in dry MeOH under an inert atmosphere, followed by addition of dimethyl malonate (1.94 g, 14.7 mmol). The reaction mixture was stirred at room temperature for 15 min, after which propargyl bromide (2.18 g, 14.5 mmol) was slowly added. The reaction mixture was then stirred at room temperature for an additional 5 h. The reaction mixture was quenched with 1 M aqueous HCl, concentrated, and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to afford the crude alkylated ester as a colorless oil.

To a solution of NaOH (1.2 g, 29.4 mmol) in H_2O/MeOH (1/7, 80 mL) was added the crude ester, and the reaction mixture was refluxed overnight. After it was warmed to room temperature, the reaction mixture was acidified to pH 1 with 6 M aqueous HCl and extracted with EtOAc (3 × 100 mL). The combined organic layers were extracted with saturated aqueous $NaHCO_3$ (3 × 100 mL) and washed with EtOAc (50 mL). The combined aqueous layers were acidified to pH 1 with 6 M aqueous HCl followed by extraction with EtOAc (3 × 200 mL). The combined organic layers were washed with

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water (100 mL) and brine (100 mL), dried over $MgSO_4$,and filtered, and solvents were removed in vacuo. Purification by column chromatography with a gradient starting at 0% of solvent A and ending at 100% solvent A (solvent A, EtOAc/AcOH (96/4); solvent B, pentane) gave pure 2-(prop-2-yn-1-yl)malonic acid as a white solid (0.57 g, 24%). ^{1}H NMR data were in accordance with those previously reported.[45]

*Synthesis of 2-(Methoxycarbonyl)pent-4-ynoic Acid (**9**).* Sodium (0.48 g, 20.9 mmol) was dissolved in dry MeOH under an inert atmosphere, followed by addition of dimethyl malonate (1.9 g, 14.7 mmol). The reaction mixture was stirred at room temperature for 15 min, after which propargyl bromide (2.2 g, 14.5 mmol) was slowly added. The reaction mixture was then stirred at room temperature for an additional 5 h. The reaction mixture was quenched with 1 M aqueous HCl, concentrated, and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo to afford the crude alkylated ester as a colorless oil.

To a H_2O/MeOH mixture (1/7, 80 mL) was added the crude ester, and the reaction mixture was basified to pH 10 using 6 M aqueous NaOH and refluxed overnight. After it was warmed to room temperature, the reaction mixture was acidified to pH 1 and the product was extracted with EtOAc (3 × 100 mL), dried over $MgSO_4$, and filtered. Purification by column chromatography with a gradient starting at 0% of solvent A and ending at 100% solvent A (solvent A, EtOAc/AcOH (96/4); solvent B, pentane) gave pure 2-(methoxycarbonyl)pent-4-ynoic acid as a white solid (0.77 g, 33%). ^{1}H NMR data were in accordance with those previously reported.[43]

*Synthesis of 2-(Methoxycarbonyl)-2-(prop-2-yn-1-yl)pent-4-enoic Acid (**11**).* To a solution of dimethyl 2-(prop-2-yn-1-yl)malonate (1.0 g, 5.88 mmol) in anhydrous THF (20 mL) under an inert atmosphere was added (153 mg, 6.5 mmol), and the mixture was stirred at room temperature for 5 min, after which allyl bromide (747 mg, 6.2 mmol) was added. The resulting suspension was stirred at room temperature overnight. Subsequently H_2O (20 mL) was added and the reaction mixture was concentrated in vacuo and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$, and filtered, and the solvents were removed in vacuo to afford an oil, which was which was subjected to selective hydrolysis. The crude product was dissolved in MeOH (70 mL) followed by addition of a 0.6 M aqueous solution of NaOH (10 mL), and the mixture was refluxed overnight. The reaction mixture was acidified to pH 2 using 2 M aqueous HCl and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layers were washed with water (50 mL), dried over $MgSO_4$, and filtered, and the solvents were removed in vacuo to afford a colorless oil (800 mg, 68%). ^{1}H NMR data were in accordance with those previously reported.[46]

Synthesis of 5-(4-(Trifluoromethyl)phenyl)pent-4-yn-1-ol. Pd(PPh_3)$_4$ (68.6 mg, 59.4 μmol), CuI (22.8 mg, 0.12 mmol), 4-pentyn-1-ol (500 mg, 5.95 mmol), 1-bromo-4-(trifluoromethyl)-benzene (0.89 g, 3.96 mmol), and Et_3N (0.60 g, 5.95 mmol) were dissolved in MeCN (30 mL) under an inert atmosphere. The resulting suspension was refluxed for 24 h. The resulting solution was filtered through Celite and concentrated in vacuo to give 5-(4-(trifluoromethyl)phenyl)pent-4-yn-1-ol as an orange oil (0.74 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2, 2H), 3.82 (t, J = 6.1 Hz, 2H), 2.56 (t, J = 7.0 Hz, 2H), 1.87 (quin, J = 6.6 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 131.9, 129.5 (q, $^2J_{C-F}$ = 32.7 Hz), 127.7, 125.3 (q, $^3J_{C-F}$ = 3.7 Hz), 124.1 (q, $^1J_{C-F}$ = 272.0 Hz), 92.3, 80.1, 61.7, 31.3, 16.1. HRMS (ESI): calcd for $C_{12}H_{11}F_3ONa$ [M + Na^+], 251.0654; found, 251.0663.

*Synthesis of 5-(4-Ttrifluoromethyl)phenyl)pent-4-ynoic Acid (**13**).* Jones reagent (19.2 mL, 0.5 M CrO_3 in concentrated H_2SO_4/H_2O (2/3)) was added dropwise to a solution of 5-(4-(trifluoromethyl)-phenyl)pent-4-yn-1-ol (1.49 g, 6.4 mmol) in acetone at 0 °C. After it was stirred overnight in an ice bath, the reaction mixture was quenched with *i*-PrOH (5 mL) and concentrated in vacuo. The resulting crude mixture was acidified with 1 M aqueous HCl to pH 1 and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (50 mL) and extracted with saturated aqueous $NaHCO_3$ (3 × 100 mL). The aqueous layer was washed with CH_2Cl_2 (50 mL) and acidified to pH 1 using 1 M aqueous HCl. The product was extracted with CH_2Cl_2 (3 × 200 mL), the extract was dried over $MgSO_4$ and filtered, and the solvents were removed in vacuo. Purification by column chromatography with a gradient starting at 0% of solvent A and ending at 100% solvent A (solvent A, EtOAc/AcOH (96/4); solvent B, pentane) afforded pure 5-(4-(trifluoromethyl)-phenyl)pent-4-ynoic acid (**13**) as a white solid (1.00 g, 64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 8.2 Hz, 2H), 7.48 (d, J = 8.2 Hz, 2H), 2.77 (m, 2H), 2.27 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.0, 132.0, 129.8 (q, $^2J_{C-F}$ = 32.6 Hz), 127.4, 125.3 (q, $^3J_{C-F}$ = 3.7 Hz), 124.35 (q, $^1J_{C-F}$ = 272.5 Hz), 90.4, 80.4, 33.3, 15.2. HRMS (ESI): calcd for $C_{12}H_9F_3O_2Na$ [M + Na^+], 265.0447; found, 265.0457.

Synthesis of 5-Phenylpent-4-yn-1-ol. 4-Pentynol (0.94 g, 10.6 mmol) and Et_3N (3.37 g, 33.3 mmol) were added to a suspension of phenyl iodide (4.56 g, 22.3 mmol), Pd(PPh_3)$_4$ (129 mg, 0.112 mmol), and CuI (42.5 mg, 0.220 mmol) in dry THF (6 mL). The resulting reaction mixture was stirred at room temperature overnight under an inert atmosphere. The reaction mixture was then filtered through silica and purified with a gradient starting at 0% of solvent A and ending at 100% solvent A (solvent A, EtOAc/AcOH (96/4); solvent B, pentane) to afford 5-phenylpent-4-yn-1-ol as a white solid (1.45 g, 78%). ^{1}H NMR data were in accordance with those previously reported.[47]

*Synthesis of 5-Phenylpent-4-ynoic Acid (**15**).* Jones reagent (8.4 mL, 0.5 M CrO_3 in concentrated H_2SO_4/H_2O (2/3)) was added dropwise to a solution of 5-phenylpent-4-yn-1-ol (0.45 g, 2.8 mmol) in acetone at 0 °C. After it was stirred overnight in an ice bath, the reaction mixture was quenched with *i*-PrOH (5 mL) in vacuo. The resulting crude mixture was acidified with 1 M aqueous HCl to pH 1 and extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with water (50 mL) and extracted with saturated aqueous $NaHCO_3$ (3 × 100 mL). The aqueous layer was washed with CH_2Cl_2 (50 mL) and acidified to pH 1 with 1 M aqueous HCl. The product was extracted with CH_2Cl_2 (3 × 200 mL), the extract was dried over $MgSO_4$ and filtered, and the solvents were removed in vacuo. Purification by column chromatography with a gradient starting at 0% of solvent A and ending at 100% solvent A (solvent A, EtOAc/AcOH (96/4), solvent B, pentane) afforded pure 5-phenylpent-4-ynoic acid (**15**) as a white solid (0.29 g, 69%). ^{1}H NMR data were in accordance with those previously reported.[19]

*Synthesis of 5-(4-Hydroxyphenyl)pent-4-ynoic Acid (**19**).* Ethyl-4-pentynoate was prepared following reported procedures.[39] 5-Phenyl-pent-4-ynoic acid was prepared following the reported procedures for the preparation of compound **17** to afford compound **19** as a yellow solid (651 mg, 58%). ^{1}H NMR (500 MHz, MeOD): δ 7.36 (app d, J = 8.3 Hz, 2H), 6.87 (app d, J = 8.3 Hz, 2H), 2.87−2.78 (m, 2H), 2.77−2.71 (m, 2H), 2.69 (m, 1H). ^{13}C NMR (125 MHz, MeOD): δ 175.8, 158.4, 133.9, 116.2, 115.9, 86.7, 82.0, 34.6, 16.0. HRMS (ESI): calcd for $C_{11}H_9O_3$ [M^-], 189.0557; found, 189.0559.

*Synthesis of 2-((tert-Butoxycarbonyl)amino)pent-4-ynoic Acid (**21**).* Boc_2O (216 mg, 0.99 mmol) was added to a suspension of propargyl glycine (100 mg, 0.88 mmol) and K_2CO_3 (137 mg, 0.99 mmol) in THF/H_2O (1/1, 2 mL). The resulting reaction mixture was stirred overnight at room temperature. The reaction mixture was acidified with 1 M aqueous HCl to pH 3 and extracted with EtOAc (3× 10 mL). The combined organic layers were washed with water (pH 3.1 × 10 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo to afford a white solid (154 mg, 70%). ^{1}H NMR data were in accordance with those previously reported.[48]

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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