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Article

Extrapolation of the gold-catalyzed cycloisomerization to the palladium-catalyzed cross-coupling/cycloisomerization of acetylenic alcohols for the synthesis of polysubstituted furans: Scope and application to tandem processes

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ABSTRACT

This paper describes the development of an integrated approach for the preparation of diverse furan derivatives from acetylenic alcohols by gold and palladium catalyzed π -activation chemistry. Notably, this new method was found to be amenable to cyclooctyl-containing substrates, which represents a significant extension to this methodology compared with our previous reports. Furthermore, this newly developed method allowed for the direct construction of cyclooctyl furans from their synthetic precursors under Sonogashira conditions. Experimental results revealed that palladium played two major functions in these reactions, including (1) an essential catalyst in the cross-coupling reaction of the substrates; and (2) facilitating the cyclization of the acetylenic alcohol intermediates through a typical π -activation process. The scope of this chemistry was highlighted by the one-pot synthesis of 3-iodofuran, which provided an opportunity for further functionalization (via coupling methods). Finally, the AuBr_3 protocol was also elaborated to domino cyclization/C–H activation reactions, as well as the cyclization of acyclic precursors. Taken together, the results of this study demonstrate that gold and palladium catalysts can be used to complement each other in cyclization reactions.

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1. Introduction

Homogeneous gold catalysts continue to attract increasing levels of interest in organic chemistry because of the efficiency, mild nature and unique properties [1–15]. Our collective understanding of gold catalysis has been facilitated by the theories of frontier molecular orbitals [16], relativistic effects [17,18] and π -acidity [19]. The unusual reactivity of gold catalysts, namely the activation of C–C triple bonds, has led to the development of a wide range of powerful methods for the effi-

cient construction of diverse structural frameworks and molecular architectures [20,21]. The strong σ -donor and weak π -acceptor properties of alkynes render gold-complexed alkynes electrophilic and therefore opens the door for the discovery of new reactions [22,23]. In contrast to the vast majority of transition metal-catalyzed processes, the high oxidation potential of Au(I) to Au(III) allows most Au(I)-catalyzed reactions to proceed without the requirement for an inert atmosphere. We have initiated a program to exploit the unique reactivity of alkyne precursors towards gold catalysis for the synthesis of

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carbo- and heterocyclic compounds [24–30]. Furans fused to cycloalkyl ring systems (e.g., cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl rings) have found numerous applications in a variety of different areas ranging from natural products to medicinal chemistry [31–38]. Consequently, contemporary synthetic chemistry has witnessed the development of a plethora of highly efficient synthetic strategies for the construction of these sub-structures [39–56]. However, despite significant advances in this area, there are still some challenging substrates for this reaction, including cyclooctyl derivatives. As part of our ongoing interest in the development of transition-metal catalysts for the synthesis of carbo- and heterocyclic systems [24–30,57–63], we recently reported the gold-catalyzed preparation of fused-furans containing five, six and seven member rings [24]. In a continuation of this work, it was envisaged that furans fused to an eight member ring could also be prepared in a similar manner. During our study towards the preparation of the requisite synthons, we found that the exposure of 2-bromocyclooct-2-enol to terminal acetylenes under Sonogashira conditions led to a sequential cross-coupling/cycloisomerization process, which resulted in the formation of the fused furans. In other words, this process provided direct access to the desired cyclooctyl furans through a “gold-free” protocol. In this paper, we provide a detailed account of our work, including the synthetic elaboration of commercially available starting materials to give complex cyclooctyl furans, as well as the exploitation of tandem processes and the synthetic potential of these fused furan systems.

2. Experimental

2.1. Materials, methods and instruments

All of the commercially available solvents and reagents were used as supplied without further purification. Solutions in organic solvents were dried over anhydrous Na_2SO_4 . Solvents were evaporated under reduced pressure. Melting points (MP) were obtained using open capillaries and have been reported as the uncorrected values. Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR spectrophotometer (Hopkinton, MA, USA). The IR spectra were recorded as KBr pellets for solid compounds and neat sample for liquid compounds. ^1H and ^{13}C NMR spectra were recorded on a JEOL spectrometer (Peabody, MA, USA) at 500 and 125 MHz, respectively. The samples for NMR spectroscopy were prepared in $\text{DMSO}-d_6$ and CDCl_3 . The chemical shifts (δ) for the ^1H NMR spectra have been reported relative to tetramethylsilane (TMS, $\delta = 0.00$), which was used as an internal reference standard, and expressed in parts per million (ppm). The number of protons (n) for a given resonance has been indicated as $n\text{H}$ and the spin multiplicities have been given as follows: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets) and m (multiplet). The coupling constants (J) have been given in hertz. GC-MS spectra were recorded on a Perkin-Elmer system. Elemental analyses were recorded on a Thermo Finnigan FLASH EA 1112CHN analyzer (Niulab Equipments, Mumbai, India). All of the compounds analyzed in

the current study gave C, H and N results that were within $\pm 0.5\%$ of the theoretical values. Purifications by column chromatography were conducted over silica gel (100–200 mesh, SRL, Mumbai, India) using a mixture of petroleum ether and ethyl acetate (EtOAc) as the eluent. Analytical thin-layer chromatography (TLC) was performed on pre-coated plastic sheets of silica gel G/UV-254 of 0.2 mm in thickness (Macherey-Nagel, Düren, Germany) using analytical grade solvents. The TLC plates were visualized with iodine spray (10% w/w I_2 in silica gel), UV light ($\lambda = 254$ and 365 nm) and alkaline KMnO_4 solution.

2.2. General procedure for the synthesis of the 2-alkynyl-cycloalk-2-enols (**5a–5l**)

Dry triethylamine (5 mL) was added to a mixture of iodo compound **3** (1.0 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (5 mol%) and CuI (5 mol%) in an oven-dried flask under N_2 , and the resulting suspension was magnetically stirred for 5 min. Terminal alkyne **4** (1.2 mmol) was then added to the reaction in a drop-wise manner, and the resulting mixture was stirred at room temperature until TLC analysis showed the disappearance of the 2-iodo-cycloalk-2-enol starting material (~ 6 h). The reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (4×15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure to give the crude product as a residue. The residue was subsequently purified by column chromatography over silica gel eluting with a 9:1 (v/v) mixture of EtOAc and petroleum ether to afford the pure product (**5a–5l**).

2-(Phenylethynyl)-cyclohept-2-enol (**5a**). Brown oil; IR (CH_2Cl_2): 3395, 2923, 2354, 1595, 1438, 752 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 1.67–1.71 (m, 4H), 1.93–1.97 (m, 2H), 2.13–2.20 (m, 1H), 2.30–2.40 (m, 2H), 6.43 (t, 1H, $J = 6.8$ Hz), 7.29–7.30 (m, 4H), 7.42–7.44 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 25.7, 27.2, 28.6, 35.1, 71.3, 87.6, 91.2, 123.1, 128.3, 128.4, 131.2, 131.5, 138.9. GC-MS: $m/z = 212$. Anal. Calcd. for $\text{C}_{15}\text{H}_{16}\text{O}$: C, 84.87%; H, 7.60%. Found: C, 84.80%; H, 7.64%.

2-(4-Pentylphenylethynyl)-cyclohept-2-enol (**5b**). Brown oil; IR (CH_2Cl_2): 3435, 2927, 1679, 1595, 1438, 838 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 0.87 (t, 3H, $J = 6.9$ Hz), 1.28–1.32 (m, 5H), 1.51–1.68 (m, 5H), 1.93–1.95 (m, 2H), 2.15–2.18 (m, 2H), 2.25–2.30 (m, 1H), 2.58 (t, 2H, $J = 8.4$ Hz), 4.43 (brs, 1H), 6.40 (t, 1H, $J = 6.1$ Hz), 7.10 (d, 2H, $J = 7.6$ Hz), 7.34 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 14.1, 22.6, 26.0, 27.3, 28.5, 31.0, 31.5, 35.1, 35.9, 71.3, 86.8, 91.6, 120.1, 123.2, 128.6, 131.4, 138.4, 143.5. GC-MS: $m/z = 282$. Anal. Calcd. for $\text{C}_{20}\text{H}_{26}\text{O}$: C, 85.06%; H, 9.28%. Found: C, 84.98%; H, 9.30%.

2-Thiophen-2-ylethynyl-cyclohept-2-enol (**5c**). Brown oil; IR (CH_2Cl_2): 3421, 2925, 2842, 1654, 1444, 1079, 850, 698 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 1.35–1.40 (m, 1H), 1.58–1.72 (m, 3H), 1.77–1.83 (m, 1H), 1.90–1.98 (m, 2H), 2.28–2.40 (m, 2H), 4.43 (brs, 1H), 6.41 (t, 1H, $J = 1.5$ Hz), 6.94 (t, 1H, $J = 5.3$ Hz), 7.16 (d, 1H, $J = 3.8$ Hz), 7.23 (d, 1H, $J = 5.3$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 25.7, 27.1, 28.6, 35.0, 71.4, 84.0, 91.6, 123.2, 127.1, 127.2, 131.0, 131.8, 139.4. GC-MS: $m/z = 218$. Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{OS}$: C, 71.52%; H, 6.46%. Found: C,

71.40%; H, 6.50%.

2-Hex-1-ynyl-cyclohept-2-enol (**5d**). Colorless oil; IR (CH_2Cl_2): 3368, 2928, 2851, 1707, 1447, 1065, 909, 732 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 0.96 (t, 3H, $J = 6.8$ Hz), 1.28–1.34 (m, 6H), 1.36–1.48 (m, 4H), 1.97–2.10 (m, 4H), 2.50 (m, 1H), 4.17 (brs, 1H), 6.07 (t, 1H, $J = 3.8$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 13.5, 18.3, 19.1, 22.5, 24.7, 25.8, 29.8, 30.1, 69.4, 80.0, 92.0, 130.2, 137.5. GC-MS: $m/z = 192$. Anal. Calcd. for $\text{C}_{13}\text{H}_{20}\text{O}$: C, 81.20%; H, 10.48%. Found: C, 81.31%; H, 10.54%.

2-(1-Hydroxy-cyclohexylethynyl)-cyclohept-2-enol (**5e**). Colorless oil; IR (CH_2Cl_2): 3500, 3450, 2930, 1640, 1435, 1199, 799 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 1.12–1.18 (m, 4H), 1.35–1.51 (m, 6H), 1.59–1.65 (m, 4H), 1.69–1.77 (m, 4H), 1.91–1.99 (m, 1H), 3.30 (brs, 1H), 4.20 (brs, 1H), 6.16 (t, 1H, $J = 3.9$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 14.1, 18.2, 22.6, 24.6, 25.2, 25.6, 30.5, 39.0, 67.3, 69.4, 75.1, 82.9, 93.0, 124.4, 139.0. GC-MS: $m/z = 234$. Anal. Calcd. for $\text{C}_{15}\text{H}_{22}\text{O}_2$: C, 76.88%; H, 9.46%. Found: C, 77.00%; H, 9.44%.

2-(Phenylethynyl)-cyclohex-2-enol (**5f**). Brown oil; IR (CH_2Cl_2): 3383, 2928, 1592, 1053, 755 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 1.60–1.62 (m, 1H), 1.75–1.78 (m, 3H), 1.87–1.90 (m, 1H), 2.12–2.21 (m, 2H), 4.26 (brs, 1H), 6.30 (t, 1H, $J = 4.6$ Hz), 7.28–7.29 (m, 3H), 7.43–7.44 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 18.1, 26.0, 30.6, 66.9, 88.4, 89.3, 123.2, 124.2, 128.2, 128.3, 131.6, 137.8. GC-MS: $m/z = 198$. Anal. Calcd. for $\text{C}_{14}\text{H}_{14}\text{O}$: C, 84.81%; H, 7.12%. Found: C, 84.91%; H, 7.09%.

2-(4-Pentylphenylethynyl)-cyclohex-2-enol (**5g**). Brown oil; IR (CH_2Cl_2): 3400, 2928, 2363, 1509, 1461, 1047, 980 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 0.87 (t, 3H, $J = 6.9$ Hz), 1.25–1.32 (m, 4H), 1.57–1.60 (m, 3H), 1.74–1.76 (m, 2H), 1.88–1.90 (m, 1H), 2.11–2.22 (m, 3H), 2.57 (t, 2H, $J = 7.6$ Hz), 4.22 (brs, 1H), 6.28 (t, 1H, $J = 4.6$ Hz), 7.11 (d, 2H, $J = 8.4$ Hz), 7.34 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 14.1, 18.2, 22.6, 26.0, 30.6, 31.0, 31.5, 35.9, 67.0, 87.5, 89.6, 120.2, 124.4, 128.5, 131.5, 137.3, 143.4. GC-MS: $m/z = 268$. Anal. Calcd. for $\text{C}_{19}\text{H}_{24}\text{O}$: C, 85.03%; H, 9.01%. Found: C, 85.18%; H, 8.96%.

2-Pyridin-2-ylethynyl-cyclohex-2-enol (**5h**). Yellow oil; IR (CH_2Cl_2): 3450, 3398, 2929, 2369, 1500, 1450, 1055, 977 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 1.58–1.60 (m, 1H), 1.75–1.77 (m, 2H), 1.86–1.88 (m, 1H), 2.12–2.18 (m, 2H), 2.21–2.24 (m, 1H), 4.31 (brs, 1H), 6.41 (t, 1H, $J = 4.6$ Hz), 7.17 (t, 1H, $J = 7.6$ Hz), 7.39 (d, 1H, $J = 6.8$ Hz), 7.61 (t, 1H, $J = 7.6$ Hz), 8.53 (d, 1H, $J = 5.3$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 18.1, 26.2, 30.7, 66.5, 88.3, 89.1, 122.6, 124.1, 127.0, 136.2, 139.6, 143.4, 149.8. GC-MS: $m/z = 199$. Anal. Calcd. for $\text{C}_{13}\text{H}_{13}\text{NO}$: C, 78.36%; H, 6.58%; N, 7.03%. Found: C, 78.47%; H, 6.56%; N, 7.00%.

2-Hex-1-ynyl-cyclohex-2-enol (**5i**). Colorless oil; IR (CH_2Cl_2): 3430, 2930, 1501, 1455, 990, 803 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 0.96 (t, 3H, $J = 6.8$ Hz), 1.32–1.44 (m, 4H), 1.60–1.79 (m, 4H), 1.90–2.15 (m, 5H), 4.09 (brs, 1H), 5.91 (t, 1H, $J = 4.3$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 13.6, 19.2, 21.5, 25.0, 28.4, 31.2, 36.8, 69.9, 78.7, 90.3, 132.3, 137.8. GC-MS: $m/z = 178$. Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{O}$: C, 80.85%; H, 10.18%. Found: C, 80.99%; H, 10.12%.

2-(1-Hydroxy-cyclohexylethynyl)-cyclohex-2-enol (**5j**). Colorless oil; IR (CH_2Cl_2): 3505, 3451, 2929, 1513, 1219, 782 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 1.18–1.23 (m, 2H), 1.43–1.59 (m,

6H), 1.63–1.73 (m, 3H), 1.79–1.91 (m, 3H), 2.00–2.05 (m, 1H), 2.08–2.15 (m, 1H), 2.80–2.99 (m, 1H), 3.35 (brs, 1H), 4.14 (brs, 1H), 6.15 (t, 1H, $J = 3.8$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 18.3, 23.5, 25.2, 25.7, 25.8, 30.7, 40.0, 68.9, 83.3, 92.9, 123.9, 129.9. GC-MS: $m/z = 220$. Anal. Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_2$: C, 76.33%; H, 9.15%. Found: C, 76.44%; H, 9.12%.

2-(Phenylethynyl)-cyclopent-2-enol (**5k**). Brown oil; IR (CH_2Cl_2): 3368, 2924, 2363, 1485, 1309, 1048, 756 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 1.82–1.84 (m, 1H), 2.14 (s, 1H), 2.34–2.37 (m, 2H), 2.58–2.60 (m, 1H), 4.87 (brs, 1H), 6.29 (t, 1H, $J = 3.05$ Hz), 7.29–7.31 (m, 2H), 7.45–7.46 (m, 3H). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 31.0, 32.9, 77.1, 84.7, 92.1, 123.1, 128.2, 128.4 (2C), 131.7, 140.5. GC-MS: $m/z = 184$. Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{O}$: C, 84.75%; H, 6.57%. Found: C, 84.80%; H, 6.55%.

2-(4-Pentylphenylethynyl)-cyclopent-2-enol (**5l**). Brown oil; IR (CH_2Cl_2): 3377, 2914, 2363, 1491, 1313, 1041, 759 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 0.87 (t, 3H, $J = 6.9$ Hz), 1.27–1.34 (m, 4H), 1.58–1.63 (m, 2H), 1.80–1.84 (m, 1H), 2.03 (s, 1H), 2.33–2.37 (m, 2H), 2.56–2.62 (m, 3H), 4.86 (s, 1H), 6.26 (s, 1H), 7.11 (d, 2H, $J = 7.6$ Hz), 7.36 (d, 2H, $J = 8.4$ Hz). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 14.1, 22.6, 30.9, 31.0, 31.5, 32.9, 35.9, 79.1, 83.9, 92.5, 120.2, 128.4, 128.5, 131.6, 139.9, 143.5. GC-MS: $m/z = 254$. Anal. Calcd. for $\text{C}_{18}\text{H}_{22}\text{O}$: C, 84.99%; H, 8.72%. Found: C, 84.85%; H, 8.78%.

Experimental procedure for the synthesis of compound (**5m**). A mixture of compound **3a** (205 mg, 1 mmol), phenylethynylcopper(I) (164 mg, 1 mmol) and dry Et_3N (5 mL) was heated at 80 °C under an atmosphere of N_2 for 6 h. The mixture was then poured into ice-cold water (25 mL) and extracted with Et_2O (3×10 mL). The combined organic extracts were washed sequentially with 2M HCl (5 mL), 5% NaHCO_3 (5 mL) and water (10 mL), and then dried over anhydrous MgSO_4 . The solvent was removed under reduced pressure to afford the crude product, which was purified by column chromatography over silica gel eluting with a 1:4 (v/v) mixture of EtOAc and petroleum ether to afford the pure product **5m** as a light yellow solid. IR (KBr): 3390, 2921, 2352, 1595, 1431, 748 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 1.62–1.77 (m, 6H), 1.99–2.08 (m, 2H), 2.17–2.23 (m, 1H), 2.34–2.43 (m, 2H), 6.45 (t, 1H, $J = 6.9$ Hz), 7.32–7.40 (m, 4H), 7.48–7.52 (m, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 24.3, 25.9, 27.5, 28.9, 35.4, 71.7, 87.9, 91.6, 123.6, 128.5, 128.9, 131.7, 131.9, 140.4. GC-MS: $m/z = 226$. Anal. Calcd. for $\text{C}_{16}\text{H}_{18}\text{O}$: C, 84.80%; H, 8.02%. Found: C, 84.95%; H, 7.96%.

2.3. General procedure for the synthesis of fused furans (**6a–6l** and **6q**)

AuBr_3 (5 mol%) was added a stirred solution of 2-acetylenic alcohol **5** (1.0 mmol) in dichloroethane (1 mL) under N_2 , and the resulting mixture was stirred at the specified temperature and the specified time (see Table 2 and Schemes 2 and 7). Upon completion of the reaction, as indicated by TLC, the reaction mixture was quenched with 10 mL of water and extracted with dichloromethane (3×5 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure to afford the crude product, which was

purified by column chromatography over silica gel (100–200 mesh) eluting with a mixture of cyclohexane and EtOAc to afford pure product (**6a**–**6l** and **6q**).

2-Phenyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan (**6a**). Colorless oil; IR (CH₂Cl₂): 2924, 2851, 1676, 1450, 803 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.75–1.82 (m, 6H), 2.53 (t, 2H, *J* = 5.3 Hz), 2.86 (t, 2H, *J* = 6.1 Hz), 6.45 (s, 1H), 7.21 (t, 1H, *J* = 7.6 Hz), 7.36 (t, 2H, *J* = 8.4 Hz), 7.63 (d, 2H, *J* = 7.6 Hz). ¹³C NMR (125 MHz, CDCl₃): δ_C 26.3, 26.7, 28.8, 29.1, 30.9, 108.8, 123.0, 123.2, 126.5, 128.6, 131.4, 149.8, 153.4. GC-MS: *m/z* = 212. Anal. Calcd. for C₁₅H₁₆O: C, 84.87%; H, 7.60%. Found: C, 85.00%; H, 7.55%.

2-(4-Pentylphenyl)-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan (**6b**). Colorless liquid; IR (CH₂Cl₂): 2926, 2851, 1676, 1450, 803 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 0.90 (t, 3H, *J* = 6.9 Hz), 1.33–1.36 (m, 5H), 1.62 (t, 2H, *J* = 7.6 Hz), 1.72–1.79 (m, 5H), 2.51 (t, 2H, *J* = 6.1 Hz), 2.59 (t, 2H, *J* = 7.6 Hz), 2.83 (t, 2H, *J* = 6.1 Hz), 6.37 (s, 1H), 7.15 (d, 2H, *J* = 8.4 Hz), 7.51 (d, 2H, *J* = 7.6 Hz). ¹³C NMR (125 MHz, CDCl₃): δ_C 14.1, 22.6, 26.3, 26.7, 28.8, 29.1, 30.9, 31.2, 31.6, 35.7, 108.0, 122.8, 123.2, 128.6, 128.9, 141.3, 150.1, 152.9. GC-MS: *m/z* = 282. Anal. Calcd. for C₂₀H₂₆O: C, 85.06%; H, 9.28%. Found: C, 85.00%; H, 9.30%.

2-Thiophen-2-yl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan (**6c**). Brown oil; IR (CH₂Cl₂): 2921, 2847, 1663, 1573, 1443, 1218, 1080, 840, 691 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.72–1.73 (m, 4H), 1.77–1.79 (m, 2H), 2.49 (t, 2H, *J* = 6.1 Hz), 2.81 (t, 2H, *J* = 6.1 Hz), 6.29 (s, 1H), 7.00 (dd, 1H, *J*₁ = 3.8 Hz, *J*₂ = 3.8 Hz), 7.14–7.15 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ_C 26.2, 26.6, 28.7, 29.0, 30.8, 108.8, 121.3, 122.9, 123.1, 127.6, 134.5, 145.5, 153.0. GC-MS: *m/z* = 218. Anal. Calcd. for C₁₃H₁₄OS: C, 71.52%; H, 6.46%. Found: C, 71.58%; H, 6.45%.

2-Butyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan (**6d**). Colorless liquid; IR (CH₂Cl₂): 2919, 2850, 1660, 1565, 1435, 1211, 1075, 850 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 0.95 (t, 3H, *J* = 6.8 Hz), 1.27–1.34 (m, 4H), 1.55–1.65 (m, 6H), 2.31–2.55 (m, 6H), 6.03 (s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ_C 14.0, 20.2, 20.3, 24.4, 29.9, 30.1, 31.2, 32.6, 32.8, 106.4, 112.8, 149.8, 152.0. GC-MS: *m/z* = 192. Anal. Calcd. for C₁₃H₂₀O: C, 81.20%; H, 10.48%. Found: C, 81.30%; H, 10.44%.

1-(5,6,7,8-Tetrahydro-4*H*-cyclohepta[*b*]furan-2-yl)-cyclohexanol (**6e**). Colorless liquid; IR (CH₂Cl₂): 3477, 2940, 2935, 1652, 1439, 1231, 799, 702 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.19–1.26 (m, 2H), 1.55–1.63 (m, 6H), 1.72–1.79 (m, 4H), 1.75–1.81 (m, 4H), 1.92–2.15 (m, 4H), 3.99 (brs, 1H), 6.49 (s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ_C 16.9, 17.3, 18.5, 18.9, 19.9, 20.1, 22.8, 31.2, 35.3, 105.9, 117.8, 140.7, 151.0. GC-MS: *m/z* = 234. Anal. Calcd. for C₁₅H₂₂O₂: C, 76.88%; H, 9.46%. Found: C, 77.01%; H, 9.44%.

2-Phenyl-4,5,6,7-tetrahydro-benzofuran (**6f**). Colorless liquid; IR (CH₂Cl₂): 2934, 2851, 1669, 1447, 1247, 760, 690 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.75–1.78 (m, 2H), 1.84–1.89 (m, 2H), 2.46 (t, 2H, *J* = 6.1 Hz), 2.67 (t, 2H, *J* = 6.1 Hz), 6.47 (s, 1H), 7.20 (t, 1H, *J* = 7.6 Hz), 7.35 (t, 2H, *J* = 7.6 Hz), 7.62 (d, 2H, *J* = 6.9 Hz). ¹³C NMR (125 MHz, CDCl₃): δ_C 22.2, 23.1, 23.2, 23.4, 106.1, 119.0, 123.3, 126.6, 128.6, 131.5, 150.9. GC-MS: *m/z* = 198. Anal. Calcd. for C₁₄H₁₄O: C, 84.81%; H, 7.12%. Found: C, 84.75%; H, 7.15%.

2-(4-Pentylphenyl)-4,5,6,7-tetrahydro-benzofuran (**6g**). Colorless liquid; IR (CH₂Cl₂): 2928, 2851, 2354, 1495, 1452, 909, 838 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 0.92 (t, 3H, *J* = 6.8 Hz), 1.30–1.36 (m, 5H), 1.64–1.66 (m, 3H), 1.80–1.88 (m, 2H), 1.99–2.28 (m, 2H), 2.59–2.77 (m, 4H), 6.35 (s, 1H), 7.18 (d, 1H, *J* = 8.4 Hz), 7.25 (d, 1H, *J* = 7.6 Hz), 7.52–7.57 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ_C 14.2, 22.1, 22.9, 23.1, 23.5, 30.7, 31.2, 31.6, 35.8, 105.2, 118.8, 123.3, 126.6, 141.5, 147.7, 150.1, 152.1. GC-MS: *m/z* = 268. Anal. Calcd. for C₁₉H₂₄O: C, 85.03%; H, 9.01%. Found: C, 84.98%; H, 9.03%.

2-(4,5,6,7-Tetrahydro-benzofuran-2-yl)-pyridine (**6h**). Yellow oil; IR (CH₂Cl₂): 3400, 2930, 2850, 1680, 1450, 823 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.65–1.74 (m, 3H), 2.21–2.24 (m, 2H), 2.38–2.40 (m, 1H), 2.44 (t, 1H, *J* = 7.6 Hz), 2.66 (t, 1H, *J* = 6.1 Hz), 6.36 (s, 1H), 7.14–7.17 (m, 1H), 7.56 (t, 1H, *J* = 7.6 Hz), 7.63–7.65 (m, 1H), 8.57 (d, 1H, *J* = 3.8 Hz). ¹³C NMR (125 MHz, CDCl₃): δ_C 19.7, 24.6, 27.7, 29.7, 82.9, 104.2, 113.7, 120.1, 123.0, 136.4, 143.2, 149.6, 160.1. GC-MS: *m/z* = 199. Anal. Calcd. for C₁₃H₁₃NO: C, 78.36%; H, 6.58%; N, 7.03%. Found: C, 78.25%; H, 6.60%; N, 7.07%.

2-Butyl-4,5,6,7-tetrahydrobenzofuran (**6i**). Colorless oil; IR (CH₂Cl₂): 2935, 2853, 1675, 1447, 799, 763 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 0.93 (t, 3H, *J* = 6.9 Hz), 1.33–1.69 (m, 8H), 2.35–2.60 (m, 6H), 6.01 (s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ_C 13.4, 20.9, 21.2, 29.5, 31.1, 32.3, 35.4, 36.0, 106.3, 112.6, 149.5, 151.1. GC-MS: *m/z* = 178. Anal. Calcd. for C₁₂H₁₈O: C, 80.85%; H, 10.18%. Found: C, 80.74%; H, 10.22%.

1-(4,5,6,7-Tetrahydro-benzofuran-2-yl)-cyclohexanol (**6j**). Colorless oil; IR (CH₂Cl₂): 3480, 2935, 2929, 1669, 1447, 1250, 800, 713 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.20–1.25 (m, 2H), 1.49–1.61 (m, 6H), 1.65–1.69 (m, 4H), 1.72–1.75 (m, 2H), 1.89–2.10 (m, 4H), 3.95 (brs, 1H), 6.51 (s, 1H). ¹³C NMR (125 MHz, CDCl₃): δ_C 17.2, 17.4, 18.0, 18.2, 19.0, 20.1, 22.6, 35.7, 105.2, 118.0, 141.9, 151.2. GC-MS: *m/z* = 220. Anal. Calcd. for C₁₄H₂₀O₂: C, 76.33%; H, 9.15%. Found: C, 76.25%; H, 9.17%.

2-Phenyl-5,6-dihydro-4*H*-cyclopenta[*b*]furan (**6k**). Colorless oil; IR (CH₂Cl₂): 2935, 2859, 1681, 1453, 810 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.79–1.83 (m, 2H), 1.95 (t, 2H, *J* = 6.3 Hz), 2.56 (t, 2H, *J* = 6.2 Hz), 6.50 (s, 1H), 7.15 (t, 1H, *J* = 7.6 Hz), 7.34 (t, 2H, *J* = 8.4 Hz), 7.63 (d, 2H, *J* = 7.6 Hz). ¹³C NMR (125 MHz, CDCl₃): δ_C 23.5, 23.7, 24.2, 105.1, 118.0, 122.3, 125.5, 127.6, 130.5, 150.7, 151.9. GC-MS: *m/z* = 184. Anal. Calcd. for C₁₃H₁₂O: C, 84.75%; H, 6.57%. Found: C, 84.86%; H, 6.54%.

2-(4-Pentylphenyl)-5,6-dihydro-4*H*-cyclopenta[*b*]furan (**6l**). Colorless oil; IR (CH₂Cl₂): 2931, 2856, 1680, 1455, 892, 800 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 0.94 (t, 3H, *J* = 6.8 Hz), 1.36–1.41 (m, 5H), 1.68–1.71 (m, 3H), 1.76–1.80 (m, 2H), 1.93 (t, 2H, *J* = 6.2 Hz), 2.56 (t, 2H, *J* = 6.3 Hz), 6.43 (s, 1H), 7.22 (d, 2H, *J* = 7.6 Hz), 7.34 (d, 2H, *J* = 7.6 Hz). ¹³C NMR (125 MHz, CDCl₃): δ_C 14.3, 22.0, 22.8, 23.0, 30.6, 31.1, 31.6, 35.8, 104.9, 117.9, 123.4, 123.8, 128.7, 148.0, 150.0, 152.0. GC-MS: *m/z* = 254. Anal. Calcd. for C₁₈H₂₂O: C, 84.99%; H, 8.72%. Found: C, 85.10%; H, 8.67%.

2,3-Dimethylfuran (**6q**). Colorless liquid; IR (neat): 3150, 3115, 1501, 1164, 1075, 801 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.91 (s, 3H), 2.29 (s, 3H), 6.19 (d, 1H, *J* = 6.0 Hz), 7.41 (d, 1H, *J* = 6.0 Hz). ¹³C NMR (125 MHz, CDCl₃): δ_C 9.3, 11.0, 113.3, 114.5,

140.5, 147.9. GC-MS: m/z = 96. Anal. Calcd. for C_6H_8O : C, 74.97%; H, 8.39%. Found: C, 75.15%; H, 8.26%.

2.4. General procedure for the synthesis of the cycloocta[b]furans (**6m–6o**)

Dry triethylamine (5 mL) was added to a mixture of 2-bromo-cyclooct-2-enol **3d** (1.0 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol%) and CuI (5 mol%) in an oven-dried flask under N_2 , and the resulting suspension was stirred for 5 min. Terminal alkyne **4** (1.2 mmol) was then added to the reaction in a dropwise manner, and the resulting mixture was stirred at room temperature until it reached completion, indicated by the disappearance of 2-bromo-cyclooct-2-enol by TLC (~6 h). The reaction was diluted with water (50 mL) and extracted with ethyl acetate (4×15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated under reduced pressure to give the crude product. The crude was then purified by column chromatography over silica gel eluting with a 1:9 (v/v) mixture of EtOAc and petroleum ether to afford the pure product (**6m–6o**). Compound **6m** was synthesized in the way using the catalyst and conditions depicted in Scheme 3.

2-Phenyl-4,5,6,7,8,9-hexahydrocycloocta[b]furan (**6m**). Colorless oil; IR (CH_2Cl_2): 3081, 3055, 2927, 2844, 1625, 1606, 1541, 1485, 1455, 1351, 895, 797 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ_H 1.49–1.55 (m, 4H), 1.65–1.70 (m, 2H), 1.75–1.80 (m, 2H), 2.55 (t, 2H, J = 6.2 Hz), 2.85 (t, 2H, J = 6.2 Hz), 6.41 (s, 1H), 7.15–7.20 (m, 1H), 7.30–7.35 (m, 2H), 7.60–7.64 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.8, 25.3, 26.1, 27.4, 28.9, 108.1, 120.5, 123.1, 126.4, 128.5, 131.3, 150.5, 151.7. GC-MS: m/z = 226. Anal. Calcd. for $C_{16}H_{18}O$: C, 84.91%; H, 8.02%. Found: C, 85.11%; H, 7.98%.

2-Pentyl-4,5,6,7,8,9-hexahydrocycloocta[b]furan (**6n**). Colorless oil; IR (CH_2Cl_2): 2927, 2860, 1733, 1520, 1455, 1345, 1257, 1165, 1090, 1010, 930, 850 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ_H 0.89 (t, 3H, J = 6.4 Hz), 1.30–1.35 (m, 4H), 1.44–1.68 (m, 10H), 2.44–2.55 (m, 4H), 2.70 (m, 2H), 5.69 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 14.1, 22.3, 23.8, 25.3, 26.0, 26.1, 27.5, 28.0, 28.1, 28.9, 31.5, 107.5, 118.5, 149.5, 152.9. GC-MS: m/z = 220. Anal. Calcd. for $C_{15}H_{24}O$: C, 81.76%; H, 10.98%. Found: C, 81.91%; H, 10.92%.

2-(3-(Benzyloxy)propyl)-4,5,6,7,8,9-hexahydrocycloocta[b]furan (**6o**). Colorless oil; IR (CH_2Cl_2): 2925, 2853, 1572, 1495, 1476, 1450, 1410, 1361, 1305, 1280, 1250, 1210, 1145, 1100, 1074, 1025, 983, 960, 905, 881, 858, 800 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ_H 1.35–1.70 (m, 8H), 1.85 (q, 2H, J = 6.7 Hz), 2.39 (t, 2H, J = 6.3 Hz), 2.55–2.65 (m, 6H), 3.45 (t, 2H, J = 6.7 Hz), 5.65 (s, 1H), 7.20–7.29 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 23.7, 24.6, 25.3, 25.8, 26.0, 27.3, 28.2, 28.7, 69.4, 73.0, 108.0, 118.6, 127.5, 127.6, 127.7, 128.4, 128.5, 138.5, 149.7, 152.0. GC-MS: m/z = 321. Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.50%; H, 8.78%. Found: C, 80.21%; H, 8.85%.

2.5. Experimental procedure for the preparation of 3-iodo-2-phenyl-4,5,6,7,8,9-hexahydrocycloocta[b]furan **8a**

Dry triethylamine (50 mL) was added to a mixture of

2-bromo-cyclooct-2-enol **3d** (10.0 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol%), and CuI (5 mol%) in an oven-dried flask under N_2 , and the resulting suspension was stirred for 5 min. Phenylacetylene **4a** (1.2 eq.) was then added to the reaction in a dropwise manner, and the resulting mixture was stirred at room temperature for 6 h. Molecular iodine (1.0 eq.) was then added to the reaction, and the resulting mixture was stirred for further 2 h. The mixture was then quenched with a saturated solution of sodium thiosulfate and extracted with EtOAc (3×50 mL). The combined organic extracts were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography over silica gel (100–200 mesh) eluting cyclohexane/EtOAc to afford pure **8a** as a colorless liquid. IR (neat): 3084, 3059, 2929, 2851, 1635, 1610, 1549, 1489, 1449 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ_H 1.65–1.79 (m, 4H); 1.81–1.92 (m, 4H); 2.37 (t, 2H, J = 6.1 Hz); 2.72 (t, 2H, J = 6.2 Hz); 7.34 (t, 1H, J = 7.6 Hz); 7.48 (t, 2H, J = 7.6 Hz); 8.02 (d, 2H, J = 7.6 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 20.7, 21.9, 22.9, 23.4, 23.6, 66.9, 123.7, 126.5, 128.0, 128.9, 129.0, 131.2, 150.1, 151.5. GC-MS: m/z = 352. Anal. Calcd. for $C_{16}H_{17}IO$: C, 54.56%; H, 4.86%. Found: C, 53.91%; H, 4.95%.

2.6. Experimental procedure for the Negishi coupling of **8a**

A solution of organozinc reagent **7a** (1.05 eq.) in THF was added to a stirred solution of **8a** (1.0 mmol) and $Pd(Ph_3P)_4$ (10 mol%) in dry dioxane at 0 °C, and the resulting mixture was stirred at 25 °C for 30 min. The reaction was quenched with 0.5 mol/L HCl and extracted with Et₂O. The combined organic extracts were then washed sequentially with saturated $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4 . The solvent was then removed under reduced pressure to give the crude product, which was purified by column chromatography over silica gel (100–200 mesh) eluting with a mixture of hexane and EtOAc to give the pure product **9a** as a colorless solid. MP 72–74 °C; IR (KBr): 3069, 3025, 2935, 1519, 1489, 1449, 1375, 781 cm^{-1} . 1H NMR (500 MHz, $CDCl_3$): δ_H 1.34–1.45 (m, 4H), 1.67–1.77 (m, 4H), 2.36 (s, 3H), 2.47 (t, 2H, J = 7.6 Hz), 2.89 (t, 2H, J = 8.1 Hz), 6.95–7.04 (m, 2H), 7.12 (t, 1H, J = 7.6 Hz), 7.29–7.40 (m, 4H), 7.51–7.67 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 21.5, 22.9, 24.1, 25.5, 27.0, 30.5, 57.4, 115.1, 116.5, 119.5, 120.2, 124.1, 127.9, 129.8, 130.4, 132.5, 131.9, 146.7, 150.9, 160.1. GC-MS: m/z = 316. Anal. Calcd. for $C_{23}H_{24}O$: C, 87.30%; H, 7.64%. Found: C, 88.11%; H, 7.55%.

2.7. Experimental procedure for the Sonogashira coupling of **8a**

Dry triethylamine (5 mL) was added to a mixture of compound **8a** (1.0 mmol), $Pd(PPh_3)_2Cl_2$ (5 mol%) and CuI (5 mol%) were placed in an oven-dried flask under N_2 , and the resulting suspension was stirred for 5 min. Phenylacetylene **4a** (1.1 eq.) was added to the reaction in a dropwise manner, and the resulting mixture was stirred at room temperature for 3 h. The reaction was diluted with water (50 mL) and extracted with ethyl acetate (4×15 mL). The combined organic extracts were dried over anhydrous sodium sulfate and concentrated to dry-

ness to give the crude product, which was purified by column chromatography over silica gel eluting with a mixture of EtOAc and petroleum ether to afford the pure product **10a** as a yellow solid. MP 110–112 °C; IR (KBr): 3060, 3018, 2939, 2855, 2219, 1642, 1608, 1556, 1499, 1351 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.66–1.79 (m, 4H), 1.85–1.93 (m, 4H), 2.55 (t, 2H, *J* = 6.7 Hz), 2.69 (t, 2H, *J* = 6.4 Hz), 7.29 (t, 1H, *J* = 7.6 Hz), 7.35–7.41 (m, 5H), 7.51–7.55 (m, 2H), 8.05 (d, 2H, *J* = 8.1 Hz). ¹³C NMR (125 MHz, CDCl₃): δ_C 20.7, 21.0, 21.3, 22.8, 23.1, 23.4, 84.1, 97.5, 105.2, 123.6, 124.5, 124.9, 127.9, 128.4, 128.8, 129.6, 131.5, 132.2, 151.1, 153.4. GC-MS: *m/z* = 326. Anal. Calcd. for C₂₄H₂₂O: C, 88.31%; H, 6.79%. Found: C, 88.91%; H, 6.65%.

2.8. Experimental procedure for the Suzuki coupling of **8a**

To a stirred solution of iodofuran **8a** (1.0 mmol) in dimethoxyethane at room temperature was added phenylboronic acid **11a** (1.0 eq.), Pd(PPh₃)₄ (10 mol%) and Cs₂CO₃ (1.0 eq.), and the resulting mixture was stirred at 60 °C for 1 h. The mixture was cooled to room temperature and filtered through a sintered crucible. The filtrate was collected and concentrated to dryness under reduced pressure to give the crude product, which was purified by column chromatography over silica gel eluting with a mixture of EtOAc and petroleum ether to afford the pure product **12a** as a colorless solid. MP 88–90 °C; IR (KBr): 3068, 3025, 2932, 1515, 1475, 1381, 763 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.65–1.78 (m, 4H), 1.83–1.92 (m, 4H), 2.39 (t, 2H, *J* = 6.7 Hz), 2.75 (t, 2H, *J* = 6.6 Hz), 6.78–6.89 (m, 2H), 7.17–7.35 (m, 5H), 7.44–7.55 (m, 3H). ¹³C NMR (125 MHz, CDCl₃): δ_C 20.9, 21.3, 22.7, 22.9, 23.1, 23.4, 55.7, 114.1, 114.2, 119.8, 122.1, 125.6, 126.5, 126.6, 127.4, 128.5, 130.8, 131.9, 146.8, 150.5, 158.9. GC-MS: *m/z* = 302. Anal. Calcd. for C₂₂H₂₂O: C, 87.38%; H, 7.33%. Found: C, 86.97%; H, 7.45%.

2.9. Experimental procedure for the Stille coupling of **8a**

To a stirred solution of iodofuran **8a** (1.0 mmol) in dry THF (10 mL) at room temperature was added Pd(PPh₃)₄ (10 mol%), LiCl (3.0 eq.) and tributyl(vinyl)tin (2.0 eq.), and the resulting mixture was stirred at room temperature for 12 h. The mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure to give a residue, which was purified by column chromatography over silica gel (100–200 mesh) eluting with a mixture of hexane and EtOAc to afford **14a** as a colorless liquid. IR (neat): 3091, 3061, 3035, 2935, 2849, 1631, 1614, 1591, 1471, 1455, 1425, 1345, 781 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.65–1.79 (m, 4H), 1.85–1.94 (m, 4H), 2.55–2.67 (m, 4H), 5.35 (dd, 1H, *J*₁ = 12.2 Hz; *J*₂ = 2.1 Hz), 5.47 (dd, 1H, *J*₁ = 18.4 Hz; *J*₂ = 12.2 Hz), 6.91 (dd, 1H, *J*₁ = 18.2 Hz, *J*₂ = 12.2 Hz), 7.29–7.34 (m, 1H), 7.40–7.45 (m, 2H), 7.67 (t, 2H, *J* = 7.6 Hz). ¹³C NMR (125 MHz, CDCl₃): δ_C 21.5, 22.6, 22.9, 23.4, 115.2, 118.3, 127.1, 128.8, 129.6, 130.1, 130.3, 131.9, 149.5, 150.6. GC-MS: *m/z* = 252. Anal. Calcd. for C₁₈H₂₀O: C, 85.67%; H, 7.99%. Found: C, 86.07%; H, 7.87%.

2.10. Experimental procedure for the Heck coupling of **8a**

To a stirred solution of iodofuran **8a** (1.0 mmol) in DMAc (1.5 mL) at room temperature was added ethylacrylate (1.1 eq.), Pd(OAc)₂ (5 mol%), *n*Bu₃P (25 mol%) and pyridine (3.0 eq.), and the resulting mixture was stirred at 50 °C for 1 h. The mixture was then diluted with brine (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with brine (20 mL) and dried over anhydrous MgSO₄. The solvent was then removed under reduced pressure to give a residue, which was purified by column chromatography over silica gel eluting with a mixture of hexane and EtOAc to give **16a** as a pale yellow liquid. IR (neat): 3095, 3061, 2941, 2841, 1717, 1635, 1621, 1542, 1480, 1455, 1425, 1341, 781 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.29 (t, 3H, *J* = 7.6 Hz), 1.66–1.78 (m, 4H), 1.81–1.92 (m, 4H), 2.67–2.75 (m, 4H), 3.96 (q, 2H, *J* = 7.6 Hz), 6.52 (d, 1H, *J* = 16.4 Hz), 7.30 (t, 1H, *J* = 7.6 Hz), 7.45 (t, 2H, *J* = 7.6 Hz), 7.65 (t, 2H, *J* = 7.6 Hz), 7.95 (d, 1H, *J* = 16.4 Hz). ¹³C NMR (125 MHz, CDCl₃): δ_C 13.8, 21.8, 22.4, 22.7, 23.0, 23.3, 51.5, 61.7, 117.1, 117.5, 117.9, 127.2, 128.0, 128.6, 130.8, 137.5, 151.8, 153.8, 167.1. GC-MS: *m/z* = 324. Anal. Calcd. for C₂₁H₂₄O₃: C, 77.75%; H, 7.46%. Found: C, 77.57%; H, 7.53%.

2.11. Experimental procedure for the one-pot synthesis of compound **18a**

AuBr₃ (5 mol%) was added to a solution of compound **6f** (1.0 mmol) in dichloroethane (1 mL) under N₂ at room temperature, and the resulting mixture was heated at 70 °C for 30 min. Butenone **17a** (1.2 eq.) was then added to the reaction, and the resulting mixture was stirred for 20 min. Upon completion of the reaction, as indicated by TLC, the reaction mixture was quenched with water (10 mL) and extracted with dichloromethane (3 × 5 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography over silica gel (100–200 mesh) eluting with a mixture of cyclohexane and EtOAc to afford pure product **18a** as a yellow liquid. IR (neat): 3098, 3055, 2946, 1685, 1586, 1355 cm⁻¹. ¹H NMR (500 MHz, CDCl₃): δ_H 1.78–1.85 (m, 2H), 1.88–1.95 (m, 2H), 2.19 (s, 3H), 2.45 (t, 2H, *J* = 6.9 Hz), 2.61 (t, 2H, *J* = 6.7 Hz), 2.81 (t, 2H, *J* = 3.4 Hz), 2.95 (t, 2H, *J* = 2.8 Hz), 7.29 (t, 1H, *J* = 7.6 Hz), 7.45 (t, 2H, *J* = 7.6 Hz), 7.66–7.77 (m, 2H). ¹³C NMR (125 MHz, CDCl₃): δ_C 19.5, 20.5, 21.4, 22.9, 23.6, 30.1, 44.2, 118.2, 119.1, 120.1, 121.1, 123.5, 124.3, 128.5, 150.3, 151.4, 208.8. GC-MS: *m/z* = 268. Anal. Calcd. for C₁₈H₂₀O₂: C, 80.56%; H, 7.51%. Found: C, 81.07%; H, 7.39%.

2.12. Experimental procedure for the one-pot synthesis of compound **19a**

To a mixture of AuBr₃ (5 mol%) and AgSbF₆ (5 mol%) in dry dichloroethane (1 mL) under N₂ was added a solution of compound **6f** (1.0 mmol) in dichloroethane (1 mL), and the resulting mixture was heated at 70 °C for 30 min. Phenylacetylene **4a** (1.2 eq.) was added to the reaction, and the resulting mixture was stirred for 3 h. The reaction was then cooled to room temperature and quenched with water (10 mL). The resulting mixture was extracted with dichloromethane (3 × 5 mL) and the combined organic layers were dried over anhydrous

Na_2SO_4 . The solvent was then removed under reduced pressure to afford the crude product, which was purified by column chromatography over silica gel (100–200 mesh) eluting with a mixture of cyclohexane and EtOAc to afford pure product **19a** as colorless liquid. IR (neat): 3095, 3054, 2941, 1685, 1609, 1450, 1355, 898, 747 cm^{-1} . ^1H NMR (500 MHz, CDCl_3): δ_{H} 1.77–1.85 (m, 2H), 1.89–1.96 (m, 2H), 2.65 (t, 2H, $J = 6.4$ Hz), 2.78 (t, 2H, $J = 6.6$ Hz), 5.41 (d, 1H, $J = 2.3$ Hz), 5.67 (d, 1H, $J = 2.0$ Hz), 7.15–7.29 (m, 4H), 7.35–7.48 (m, 5H), 7.49–7.54 (m, 1H). ^{13}C NMR (125 MHz, CDCl_3): δ_{C} 19.5, 22.5, 23.4, 23.9, 105.5, 120.1, 121.2, 124.4, 127.5, 127.9, 128.1, 128.3, 128.6, 129.3, 141.2, 145.8, 150.4, 150.6. GC-MS: $m/z = 300$. Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{O}$: C, 87.96%; H, 6.71%. Found: C, 88.17%; H, 6.63%.

3. Results and discussion

We previously reported a convenient method for the synthesis of fused furans via AuBr_3 -catalyzed cycloisomerization of 2-alkynyl-cycloalk-2-enols (Scheme 1) [24]. The requisite 2-alkynyl-cycloalk-2-enols were synthesized via the α -iodination of the corresponding cycloalken-2-ones **1** with $\text{I}_2/\text{pyridine}$, which afforded the 2-iodocycloalk-2-enones **2** [64–66]. Subsequent 1,2-reduction of these 2-iodocycloalk-2-enones **2** with a stoichiometric mixture of NaBH_4 and $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ gave the 2-iodoenols **3** [67,68]. These iodoenols were then treated with a variety of terminal alkynes **4** under Sonogashira conditions [69,70] to give the hitherto unknown 2-alkynyl-cycloalk-2-enols **5** in excellent yields. A wide range of coupling products were successfully synthesized under these conditions, including those bearing aliphatic, aromatic and heteroaromatic substituents, with yields ranging from good to excellent (Table 1).

The results of a series of optimization studies revealed that all of the substrates underwent the desired cycloisomerization reaction in the presence of 5 mol% AuBr_3 in 1,2-dichloroethane (Table 2). As shown in Table 2, the yields of the fused furans varied from good to excellent depending on the nature of the substituent attached to the alkyne moiety and the reaction temperature. Furthermore, the results indicated that the efficiency of the cyclization was dependent on the nature and the size of the ring attached to the alkyne moiety for substrates **5a–5l**. For example, substrates bearing a cycloheptyl ring, the

Scheme 1. AuBr_3 -catalyzed synthesis of furans **6a–6l**.

Table 1

Synthesis of acetylenic alcohols.

Entry	<i>n</i>	R 4	5 ^a	Yield ^b (%)
1	3	phenylacetylene (4a)	5a	90
2	3	1-ethynyl-4-pentylbenzene (4b)	5b	92
3	3	2-ethynylthiophene (4c)	5c	88
4	3	1-hexyne (4d)	5d	89
5	3	1-ethynylcyclohexanol (4e)	5e	77
6	2	phenylacetylene (4a)	5f	91
7	2	1-ethynyl-4-pentylbenzene (4b)	5g	94
8	2	2-ethynylpyridine (4f)	5h	79
9	2	1-hexyne (4g)	5i	89
10	2	1-ethynylcyclohexanol (4e)	5j	79
11	1	phenylacetylene (4a)	5k	80
12	1	1-ethynyl-4-pentylbenzene (4b)	5l	81

^a All of the products were characterized by IR, ^1H NMR, ^{13}C NMR and GC-MS analyses.

^b Isolated yield after column chromatography.

reaction proceeds smoothly over a short reaction time, even at room temperature (Table 2, entries 1–5). Substrates bearing a cyclohexyl ring also reacted rapidly to produce the desired products in good yields when the reaction was carried out for 30 min at 70 °C (Table 2, entries 6–10). However, substrates with a cyclopentyl ring reacted slowly to give low yields of the desired products, even when the reaction time was extended to 45 min (Table 2, entries 11 and 12). These observations can be rationalized in terms of the greater degree of strain associated with the resulting cyclopenta[*b*]furan products compared with the cyclohexa[*b*]furan and cyclohepta[*b*]furan products. The results of these experiments also revealed that the nature of the substituent on the alkyne of the 2-alkynylcycloalk-2-enol substrate did not play a significant role in determining the success of the cyclization, because aliphatic, aromatic and heteroaromatic groups were well tolerated at this position to give almost identical yields of the products. The formation of the products was confirmed by the appearance of a singlet peak in their ^1H NMR spectra in CDCl_3 with a δ_{H} value in the range of 6.20–6.30 ppm, which was attributed to the C3-H of the furan ring. Moreover, the ^{13}C NMR spectra of these products all contained a peak with a δ_{C} value in the range of 104–109 ppm, which con-

Table 2

Synthesis of furans **6a–6l**.

Entry	5	6 ^a	Yield ^b (%)
1	5a	6a	90
2	5b	6b	91
3	5c	6c	89
4	5d	6d	95
5	5e	6e	79
6	5f	6f	86
7	5g	6g	88
8	5h	6h	70
9	5i	6i	92
10	5j	6j	83
11	5k	6k	60
12	5l	6l	66

^a All of these products were characterized by IR, ^1H NMR, ^{13}C NMR and GC-MS analyses.

^b Isolated yield after column chromatography.

firmed the presence of the C3 carbon of the furan ring.

In light of their biological significance and their prevalence as the core substructures in numerous crenulide diterpenoid natural products, we became interested in extending the scope of our study to cyclooctyl-fused furan ring systems [71,72]. Using the optimized reaction conditions, we initially explored the general scope of our methodology by investigating the synthesis of a series of cyclooctyl furans (Scheme 2). According to the literature, the precursors for this cyclization reaction could be synthesized from commercially available cycloheptene (**1d**) [73,74]. Thus, the cyclopropanation of **1d** with CHBr_3 afforded cycloadduct **2d**, which underwent a ring expansion reaction with AgClO_4 in aqueous acetone to furnish the 2-bromoenoal **3d** [75]. Surprisingly, the subsequent alkynylation of **3d** under the standard Sonogashira conditions did not lead to the expected alkynylated product **5**. In contrast to other ring systems ($n = 1, 2, 3$), we found that the eight-membered ring **3d** reacted rapidly under the Sonogashira condition to afford the cyclized product **6** directly without the isolation of the cross-coupled intermediate **5**.

At this stage in the study, the identity of the catalytic species involved in this one-pot operation was unknown. As well as playing an important role in oxidative addition reactions [76,77], palladium salts can catalyze the intramolecular cyclization reactions of alkynes bearing a hydroxyl tether [78–81]. Prompted by this literature survey, we assumed that palladium was the catalyst involved in this tandem process. To test this hypothesis, we investigated the synthesis and isolation of alkyne **5m**, which was readily prepared by the Castro-Stephens

coupling of 2-bromoenoal **3d** with phenylethynylcopper(I) [82] (Scheme 3). This reaction led to the stable alkyne **5m** in excellent yield without the formation of any of the corresponding cyclized product **6m**, which suggested that Et_3N and CuBr (formed as by-product) were not acting as catalysts for the cyclization. We subsequently investigated the cyclization of **5m** using 5 mol% $\text{PdCl}_2(\text{Ph}_3\text{P})_2$ and found that the reaction proceeded smoothly to afford the cyclization product **6m** in excellent yield. PdCl_2 also gave the cyclized product **6m** in excellent yield, which indicated that this reaction did not require a neutral phosphine ligand. These two test reactions clearly indicated that Pd(II) was the active catalytic species involved in this transformation. Notably, the reaction of **5m** with CuI (co-catalyst in the Sonogashira reaction) under the same conditions led to only trace quantities of the cyclization product **6m** with 80% of starting material being recovered unchanged. This result therefore precluded the participation of CuI in the cyclization reaction. Finally, the reaction of **5m** with a catalytic amount of AuBr_3 also afforded a clean conversion to product **6m**, which suggested that our gold-based methodology was indeed applicable to cyclooctyl systems.

Based on these results, we proposed a mechanism for the formation of fused furans, which is shown in Scheme 4. Thus, the initial coordination of the soft Lewis acidic metal $[\text{M}]$ to alkyne **5** would lead to π -complex **5I**. The increased electrophilicity of the alkyne would allow for the nucleophilic attack of the adjoining hydroxyl group to give the cyclized intermediate **5II**. The subsequent proto-deauration of **5II** would result in the formation of **5III**, which would undergo an isomerization

Scheme 2. Synthesis of cyclooctylfurans **6m–6o**.

Scheme 3. Cyclization of **5m** by several transition metal catalysts.

Scheme 4. Tentative mechanism for the formation of furans 6.

reaction to produce the fused furan **6**.

At this stage in the study, we decided to delineate the scope of our chemistry through a series of synthetic elaborations. Keeping in mind the versatility of the iodide functionality in organometallic transformations, we attempted the one-pot synthesis of 3-iodofuran **8a** (Scheme 5). Pleasingly, this sequential process provided the desired iodide **8a** in 84% yield. The subsequent Negishi coupling reaction of compound **8a** with the arylzinc reagent **7a** in the presence of 10 mol% $\text{Pd}(\text{Ph}_3\text{P})_4$ allowed for the introduction of an aryl group, with the tetra-substituted furan product **9a** being isolated in 79% yield [83,84]. Furthermore, the Sonogashira reaction of **8a** with phenylacetylene (**4a**) provided the functionalized alkyne **10a** in 88% yield [69]. The Suzuki-Miyaura coupling reaction of **8a** with phenylboronic acid **11a** afforded the 2,3-diphenyl substituted furan **12a** in 90% yield [85]. Lastly, compound **8a** also underwent Stille and Heck coupling reactions with

tributyl(vinyl)tin (**13a**) and ethylacrylate (**15a**), respectively, to give the corresponding 3-vinyl derivatives **14a** and **16a** in moderate to good yields [86,87].

Having demonstrated the catalytic application of this newly developed palladium-catalyzed tandem process, we turned our attention back towards the possibility of using AuBr_3 to facilitate other interesting one-pot procedures with particular emphasis on Michael- [88] and Friedel-Crafts-type reactions [89] (Scheme 6). For example, the cyclization of substrate **5f** under the optimized conditions followed by the *in situ* addition of methyl vinyl ketone **17a** resulted in the formation of the Michael adduct **18a** in 80% yield. Furthermore, the tandem Friedel-Crafts alkenylation of **5f** with phenylacetylene (**4a**) in the presence of a silver co-catalyst resulted in product **19a** bearing a C=C bond, albeit in a low yield of 22%. It is noteworthy, however, that this reaction proceeded regioselectively, with the addition only occurring at the internal

Scheme 5. Pd-catalyzed organometallic transformations of **8a**.

Scheme 6. AuBr₃-catalyzed sequential processes. Scheme 7. AuBr₃ catalyzed cyclization of acyclic substrates.

carbon of alkyne **4a**, as indicated by NMR analysis of the crude mixture. This observation was consistent with those of previous studies, in that the Au π -acid drove the addition of an arene/heteroarene to the internal carbon of the terminal acetylene [89].

Finally, we were intrigued by the prospect of applying this methodology to acyclic acetylenic alcohols for the synthesis of non-fused furan rings (see Scheme 7). The requisite (*Z*)-iodoallylic alcohol **3e** was prepared by the reaction of commercially available butyn-1-ol (**20a**) with Red-Al [NaAlH₂(OCH₂CH₂OMe)₂], followed by quenching of the resulting carbanion with I₂ [90]. Subsequent Sonogashira coupling of **3e** with ethynyltrimethylsilane **4h** gave alkyne **5p** [91]. Disappointingly, the reaction of silylated alkyne **5p** under our validated conditions did not provide the expected product **6p**, even under reflux conditions. This result was attributed to the reduced aurphilicity of alkyne **5p** as a result of the deactivating effect of the silyl group. However, substrate **5q** bearing an unsubstituted terminal alkyne underwent a 5-*exo-dig* cyclization exclusively to give furan **6q** as the only product. The regioselectivity of this reaction was attributed to the greater electrophilicity of the remote sp-hybridized carbon of the alkyne.

4. Conclusions

The use of AuBr₃ as a catalyst allowed for the smooth and effective cycloisomerization of 2-alkynylcycloalk-2-enols to give the corresponding cycloalkyl-fused furans. A detailed study of this methodology as a synthetic strategy for the formation of a diverse range of furan derivatives has also been provided in terms of its scope and limitations towards ring-free substrates. We also observed the *in situ* cross-coupling/cycloisomerization of α -bromocyclooct-2-enols with terminal alkynes under Sonogashira conditions and showed that Pd(II)

was the active catalytic species involved in this process. This methodology was also applied to a series of tandem processes, which provided access to a wide range of functionalized furan molecules. Given that most of these substrates are commercially available or synthetically accessible this new method could be used for the synthesis of furan-based libraries for detailed SAR studies in medicinal chemistry. Further studies towards identifying new applications for this process to generate furan-based chemical libraries of potential pharmacological interest are currently underway.

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Graphical Abstract

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Extrapolation of the gold-catalyzed cycloisomerization to the palladium-catalyzed cross-coupling/cycloisomerization of acetylenic alcohols for the synthesis of polysubstituted furans: Scope and application to tandem processes

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Furan derivatives have been efficiently synthesized from acetylenic alcohols using a combination of gold and palladium catalysis. The utility of this protocol has been highlighted by performing several tandem and one-pot reactions.

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金催化的环化反应与钯催化的炔醇偶联/环化反应相结合用于合成多取代呋喃衍生物：串联反应的应用范围

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摘要: 开发了一种由金和钯催化 π -活化炔醇合成呋喃衍生物的集成方法。该合成策略是最显著的特点适用于带环辛基的底物, 其适用范围比之前报道的有很大扩展。在Sonogashira反应条件下, 由相应底物可直接得到环辛基呋喃。Pd在这些反应中起到2个重要作用: 底物发生偶联反应的关键催化剂; 通过 π -活化促进炔醇中间体成环反应。该方法在一步合成3-碘呋喃反应中作用很突出, 使通过偶联法进一步官能团化成为可能。我们还将AuBr₃用于多米诺成环/C–H键活化反应和无环前体的成环反应。本文结果表明, 在该类成环反应中金和钯催化剂相辅相成。

关键词: 呋喃衍生物; 环化反应; 金催化; 钯催化; 一锅法; 串联反应

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