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Note

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Synthesis of 3-Aryl-2-pyrones by Palladium-catalyzed Cross-coupling of Aryl Iodides with Cyclic Vinyldiazo Ester

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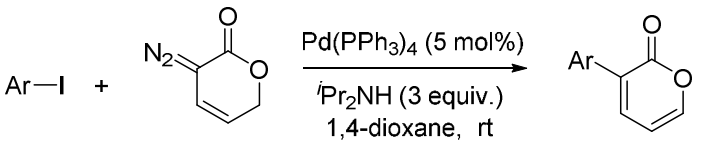


ABSTRACT: A palladium-catalyzed cross-coupling reaction of aryl iodides with cyclic vinyldiazo ester was developed. The reaction provides various 3-aryl-2-pyrones in good yields with high functional group tolerance. The synthetic application of the resulting 3-aryl-2-pyrones as the diene component in a Diels–Alder reaction was also described.

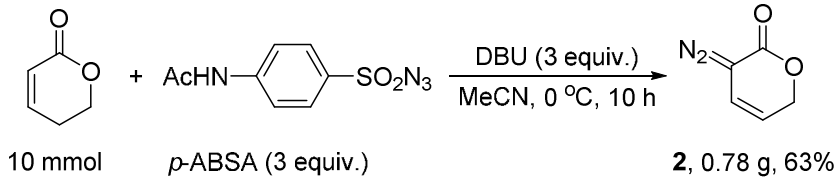
2-Pyrone is an important class of lactones present in many natural products and pharmaceuticals.[1] Compounds with different substitutions on the 2-pyrone skeleton possess a wide range of biological activities, such as anti-HIV,[2] antimicrobial,[3] anti-inflammatory,[4] anticancer,[5] and antifungal.[6] Owing to its unique unsaturated six-membered lactone structure, 2-pyrone has been commonly utilized as a diene component in Diels–Alder reactions,[7] and as an attractive building block for the synthesis of heterocycles.[8] Consequently, the synthesis of various substituted 2-pyrones has been widely covered in the literature and inspired significantly different

strategies.[9] In particular, 3-substituted 2-pyrones without any additional activating functional groups are typical substrates for exploring photochemical isomerization of 2-pyrones.[10] To our surprise, the current methods for substituted 2-pyrones synthesis can hardly be suitable to access such simple derivatives.[11] Although the direct coupling of organometallic reagents with halogenated 2-pyrones has been developed for their synthesis,[12] the prefunctionalized 3-halo-2-pyrone has to been prepared from commercially available dihydropyran-2-one by three steps with low yield and poor regionselectivity.[13] Therefore, the development of novel approaches for the efficient synthesis of 3-substituted 2-pyrones is still highly desirable.

Palladium-catalyzed cross-coupling reaction involving diazo compounds as the nucleophilic partner has been demonstrated to be a highly valuable tool for C-C bond formation.[14] The characteristic step for this new type of reaction is the migratory insertion of Pd carbene species, which has been found to be quite general in terms of various migratory groups.[14b] With regard to the synthesis of conjugated dienes by this transformation, Wang and co-workers reported a Pd-catalyzed cross-coupling of diazo compounds with allyl halides, in which the allyl migratory insertion of Pd carbene is involved.[15] Barluenga and Valdés developed an elegant migratory insertion/palladatropic rearrangement/*β*-hydride elimination cascade to produce dienes.[16] Migration insertion was also employed for the generation of transient cyclopropyl carbinyl palladium species, leading to 1,3-butadiene products through a sequential β-carbon elimination/ β-hydride elimination process.[17] Using this strategy, our group recently disclosed a regioselective ring-enlargement of strained bicyclic

cyclopropane derivatives to access benzoxepines.[18] Despite these progresses, the conversion of vinyldiazo compounds into conjugated dienes is notably absent from the literature.[19] Herein, we reported a Pd-catalyzed cross-coupling reaction of aryl iodides and cyclic vinyldiazo esters, which affords various 3-aryl-2-prones in good yields. Moreover, an oxidative coupling of terminal alkynes with cyclic vinyldiazo esters for the synthesis of 3-alkynyl-2-prones was also demonstrated, albeit with low efficiency.

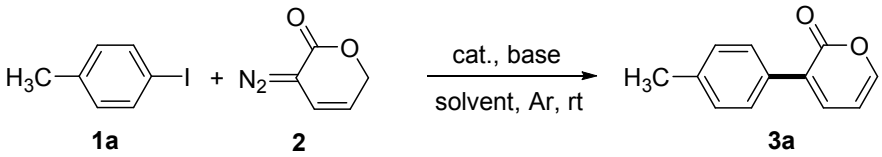
Scheme 1. Synthesis of vinyldiazo ester 2



Initially, vinyldiazo ester **2** was prepared in 63% yield on 0.78 g scale by the treatment of commercially available 3,5-dihydropyran-2-one with *p*-ABSA in the presence of DBU (scheme 1).[20] Then its coupling with 4-iodotoluene **1a** was investigated. When the reaction was carried out in the presence of $Pd_2(dba)_3$/Xphos, which is a general catalytic system for Pd-catalyzed cross-coupling reactions of diazo compounds, product **3a** was detected in 10% yield (table 1, entry 1). Switching the ligand from Xphos to tri(2-furyl)phosphine in 1,4-dioxane at room temperature led to **3a** in 22% yield (table 1, entry 2). However, the combination of $Pd_2(dba)_3$ with strong electron-rich ligand such as PCy_3 or $P(^tBu)_3 \cdot HBF_4$ was ineffective (table 1, entries 3 and 4). $Pd(PPh_3)_2Cl_2$ was effective catalyst for the reaction, providing 2-pyrone **3a** in the yield of 35% (table 1, entry 5). Pleasingly, we found that the yield

was further increased to 90% when 5 mol% of $Pd(PPh_3)_4$ was employed (table 1, entry 6). Reducing the catalytic loading to 2.5% started to have a negative impact on the reactivity, resulting in an incomplete reaction (table 1, entry 7). The yield of **3a** decreased sharply when the reaction was carried out at higher temperature (table 1, entries 8 and 9), which might be attributed to the fast decomposition of vinyldiazo ester **2**.

Table 1. Cross-coupling reaction of 4-iodotoluene 1a and vinyldiazo ester 2 catalyzed by various palladium catalyst[a]



1a **2** **3a**

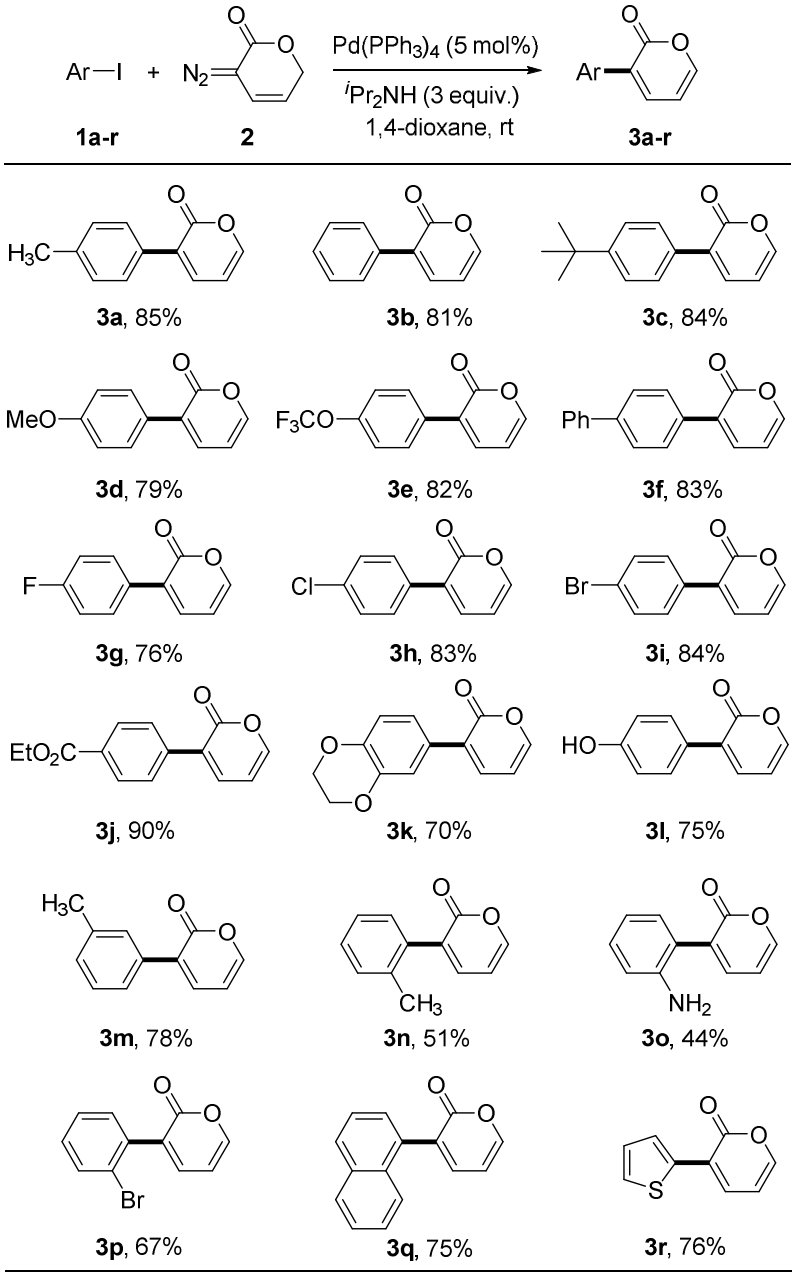
entry	cat. (mol%)/ligand (mol%)	T/°C	yield (%)[b]
1	$Pd_2(dba)_3$ (2.5)/Xphos (10)	25	10
2	$Pd_2(dba)_3$ (2.5)/P(2-furyl)$_3$ (10)	25	22
3	$Pd_2(dba)_3$ (2.5)/PCy_3 (10)	25	trace
4	$Pd_2(dba)_3$ (2.5)/P(^{t}Bu)$_3$·HBF_4 (10)	25	trace
5	$Pd(PPh_3)_2Cl_2$ (5)	25	35
6	$Pd(PPh_3)_4$ (5)	25	90
7	$Pd(PPh_3)_4$ (2.5)	25	65
8	$Pd(PPh_3)_4$ (5)	40	67
9	$Pd(PPh_3)_4$ (5)	80	31

[a] Reaction conditions: 4-iodotoluene **1a** (0.2 mmol), vinyldiazo ester **2** (1.3 equiv.), ^{i}Pr$_2$NH (3 equiv.) and catalyst in dry 1,4-dioxane (2 mL) under argon for 24 h. [b] Yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard.

The optimized conditions were then applied to the cross-coupling of vinyldiazo ester **2** with a series of aryl iodides. As shown in scheme 2, a number of functional groups, including methyl (**3a**, **3m**, **3n**), *tert*-butyl (**3c**), methoxy (**3d**), trifluoromethoxy (**3e**), dioxyethylene (**3k**), ether (**3j**), F (**3g**), Cl (**3h**), Br (**3i**, **3p**), phenyl (**3f**), free amino (**3o**) and hydroxyl (**3l**), on the aryl moiety were tolerated well under the standard conditions. The electronic properties of the substituents on the *para*-position do not affect the efficacy of the reaction, for instance, both 4-iodoanisole and ethyl 4-iodobenzoate underwent the coupling with vinyldiazo ester **2** smoothly, affording the corresponding 2-pyrones **3d** and **3j** in the yields of 79% and 90% respectively. Good yield was also achieved from the cross-coupling of *meta*-iodotoluene with vinyldiazo ester **2**. Substrates bearing methyl, free amino, and bormo group on the *ortho*-position were effective, albeit generating the corresponding products **3n-p** with moderately high yields. It is noteworthy that a bromo substituent on the aromatic ring, which usually undergoes oxidative addition with Pd(0) catalyst, could survive under the standard conditions. The preservation of the bromo group in 2-pyrones **3i** and **3p** might be attributed to the lower reactivity of bromobenzene, as well as the low temperature of this reaction. It is also worth mentioning that 4-iodophenol and 2-iodoaniline could be employed to react with vinyldiazo ester **2** directly without the need of functional group protection. The reaction is not limited to aryl iodides, as exemplified by the use of 1-iodonaphthalene to generate 3-naphthyl-2-pyrone **3q**. We were pleased to find that 2-iodothiophene was also suitable for the reaction, providing the desire product **3r** in 76% yield. However, the

coupling partner under present reaction conditions is limited to aryl iodides. When aryl bromides or aryl triflates were employed, no coupling product was detected and both starting materials remained unchanged.[21]

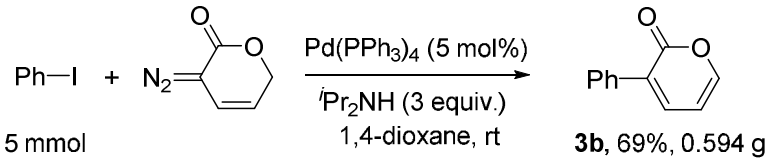
Scheme 2. Pd-catalyzed cross-coupling of vinyldiazo ester with aryl iodides[a]



[a] The reaction was carried out using aryl iodide **1** (0.2 mmol), vinyl diazo ester **2** (0.26 mmol), and $^{i}Pr_2NH$ (3 equiv.) in the presence of $Pd(PPh_3)_4$ (5 mol%) in 2 mL of dry 1,4-dioxane under argon at room temperature. [b] Isolated yield.

To demonstrate the practical usefulness of this reaction, the Pd-catalyzed cross-coupling reaction of iodobenzene and vinyldiazo ester **2** has been carried out on 5 mmol scale. As shown in scheme 3, 0.594 g of desired 3-phenyl-2-pyrone **3b** was obtained in slightly diminished yield (69%) after 48 hours of reaction at room temperature.

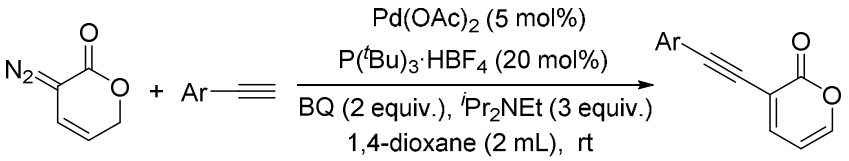
Scheme 3. Gram-Scale Reaction



In 2011, Wang and co-workers developed a palladium-catalyzed oxidative cross-coupling of terminal alkynes and diazo compounds for the synthesis of conjugated enynes.[22] However, vinyl diazo compounds have never been examined as the substrates for this reaction. We thus sought to further investigate the formation of 3-alkynyl-2-pyrones by a similar Pd-catalyzed oxidative coupling of terminal alkynes and vinyldiazo ester **2**. Our initial efforts to realize the transformation commenced with the reaction of **2** with phenylacetylene using the optimized conditions in Wang's report, and the desired 3-phenylethynyl-2-pyrone **4a** was isolated in 20% yield. To improve the efficiency of the reaction, the effects of various ligands, bases, oxidants and solvents were evaluated (see Table S1 in the Supporting Information). The yield of **4a** was increased to 39% with 1,4-dioxane as the solvent in the presence of $Pd(OAc)_2$, $P(^tBu)_3$, BQ, and $^{i-}Pr_2NEt$. Unfortunately, the effort to further improve the

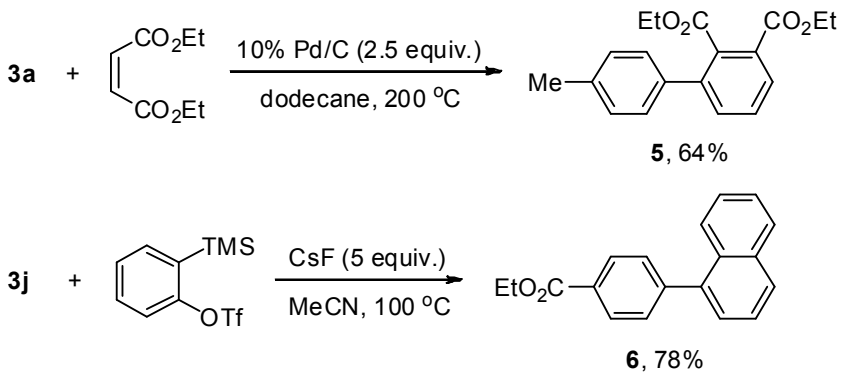
yield was unsuccessful. Different from Wang's reaction that was carried out at 80 °C, we found room temperature favored the formation of **4a**, owing to the lower stability of vinyl diazo ester **2**. Next, other terminal alkynes including 4-chlorophenylacetylene and 4-ethynylanisole were examined, and their oxidative coupling with vinyldiazo ester **2** gave the corresponding 3-alkynyl-2-pyrones **4b** and **4c** in the yields of 37% and 32%, respectively (scheme 4).

Scheme 4. Pd-catalyzed oxidative coupling of terminal alkynes with vinyldiazo ester 1.



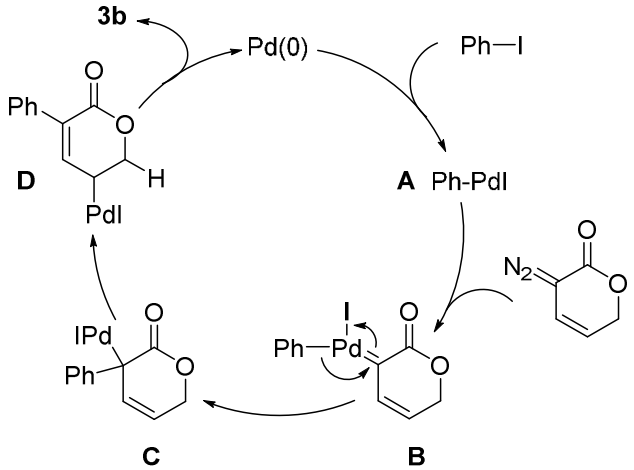
To demonstrate the synthetic application of 3-substituted 2-pyrones obtained by present method, **3a** was employed as the diene component in a Diels–Alder reaction with diethyl maleate in the presence of 10% Pd/C. We were pleased to find that the reaction gave the desired biphenyl **5** in 64% yield. The D-A reaction of **3j** with benzyne also occurred smoothly, providing naphthalene **6** in the yield of 78% (scheme 5).

Scheme 5. Synthetic applications of 3-aryl-2-pyrones.



A plausible mechanism for this palladium-catalyzed cross-coupling of aryl iodides and vinyldiazo ester is shown in scheme 6. The oxidative addition of Pd(0) to iodobenzene affords Pd(II) intermediate **A**, which would react with vinyldiazo ester to give the palladium–carbene intermediate **B**. Migratory insertion of the phenyl group into the carbenic carbon leads to η^1-allylpalladium complex **C**.[14] Palladatropic rearrangement of **C** to η^3-allylpalladium intermeidated **D** followed by β-hydride elimination regenerate the Pd(0) catalyst and give the 3-phenyl-2-pyrone product.[16]

Scheme 6. A plausible mechanism



In conclusion, we have developed an efficient synthetic method for the synthesis of 3-aryl-2-pyrones *via* Pd-catalyzed cross-coupling reactions of aryl iodides and vinyl diazo ester. A wide range of functional groups were found that are able to tolerate the reaction conditions. The synthetic applications of resulting 3-aryl-2-pyrones, as a diene component in the Diels–Alder reactions, were demonstrated. Moreover, the conversion of vinyl diazo ester to 3-alkynyl-2-pyrones by a palladium-catalyzed oxidative coupling with terminal alkynes was also investigated. Because vinyl diazo ester can be easily prepared from commercially available 3,5-dihydropyran-2-one in only one simple step, the present protocol provides a valuable synthetic route to 3-substituted 2-pyrones, suppressing the stoichiometric organometallic reagents that used in previous methods.

EXPERIMENTAL SECTION

General: Except for the synthesis of the starting materials, all reactions were performed under argon atmosphere in a 10 mL microwave tube. 1,4-Dioxane was dried over CaH_2 before use. For chromatography, 200-300 mesh silica gel was employed. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ on 400 MHz nuclear magnetic resonance spectrometer. Chemical shifts (δ) were given in ppm, referenced to the residual proton resonance of $CDCl_3$ (7.26), to the carbon resonance of $CDCl_3$ (77.16). HRMS spectra were recorded on an electrospray ionization quadrupole time-of-flight (ESI-Q-TOF) mass spectrometer. IR spectra are reported in wave numbers, cm^{-1}. Melting points were measured with a heating speed of 4 °C/min.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

General procedure for Pd-catalyzed cross-coupling reaction of aryl iodides and vinyl diazo ester. A 10 mL microwave tube was charged with $Pd(PPh_3)_4$ (5 mol%), aryl iodides (0.2 mmol) and vinyl diazo ester **2** (0.26 mmol) under argon atmosphere. Then 2 mL of 1, 4-dioxane and $^{i}Pr_2NH$ (3 equiv., 0.6 mmol) were added *via* syringe, and the resulting solution was stirred at room temperature. After the reaction was completed as monitored by TLC, the mixture was filtered through a short path of silica gel, eluting with ethyl acetate. The volatile compounds were removed in *vacuo* and the residue was purified by column chromatography to give the coupling products.

3-(p-tolyl)-2H-pyran-2-one (3a). [12a] White solid (85%, 32 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 116–117 ^{o}C; IR (KBr, cm^{-1}) 3091, 2942, 1709, 1626, 1554, 1312, 1114, 824, 788, 551; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.9 Hz, 2H), 7.47 (d, J = 3.6 Hz, 1H), 7.40 (d, J = 6.6 Hz, 1H), 7.22 (d, J = 7.8 Hz, 2H), 6.31 (t, J = 5.8 Hz, 1H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 150.5, 138.7, 138.7, 131.8, 129.2, 128.5, 128.1, 106.8, 21.3; EI-MS (*m/z*, relative intensity): 186 (M^+, 75), 171 (17), 158 (30), 129 (100), 115 (80), 91 (7).

3-phenyl-2H-pyran-2-one (3b). [12a] White solid (81%, 28 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 104–105 ^{o}C; IR (KBr, cm^{-1}) 3089, 2932, 1709, 1694, 1552, 1316, 1113, 783, 696, 550; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 7.4 Hz, 2H), 7.53 – 7.47 (m, 1H), 7.47 – 7.33 (m, 4H), 6.34 (t, J = 5.8 Hz, 1H); ^{13}C NMR

(101 MHz, $CDCl_3$) δ 161.6, 150.9, 139.4, 134.7, 128.8, 128.7, 128.5, 128.3, 106.8; EI-MS (*m/z*, relative intensity): 172 (M^+, 34), 144 (30), 115 (100), 89 (23), 77 (2).

3-(4-(tert-butyl)phenyl)-2H-pyran-2-one (3c). White solid (84%, 38 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 102–103 ^oC; IR (KBr, cm^{-1}) 3088, 2966, 1700, 1624, 1556, 1342, 1111, 967, 783, 735, 568; ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.0 Hz, 2H), 7.50 – 7.40 (m, 4H),, 6.33 (t, J = 5.8 Hz, 1H), 1.34 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.7, 151.9, 150.5, 138.8, 131.8, 128.6, 127.9, 125.5, 106.9, 34.7, 31.3; HRMS (ESI) calcd. for $C_{15}H_{17}O_2$ [$(M + H)^+$] 229.1223, found: 229.1222.

3-(4-methoxyphenyl)-2H-pyran-2-one (3d). [12a] White solid (79%, 32 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 94–95 ^oC; IR (KBr, cm^{-1}) 3095, 2964, 1706, 1625, 1557, 1513, 1299, 1034, 834, 777, 553; ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.3 Hz, 2H), 7.46 (d, J = 4.4 Hz, 1H), 7.37 (d, J = 6.6 Hz, 1H), 6.93 (d, J = 8.3 Hz, 2H), 6.31 (t, J = 5.8 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 160.1, 150.2, 138.0, 129.5, 128.2, 127.1, 113.9, 106.9, 55.4; EI-MS (*m/z*, relative intensity): 202 (M^+, 100), 174 (13), 159 (74), 145 (25), 131 (65), 102 (43), 51 (20).

3-(4-(trifluoromethoxy)phenyl)-2H-pyran-2-one (3e). Pale yellow solid (86%, 44 mg, eluent: petroleum ether/ethyl acetate = 5/1), mp 76–77 ^oC; IR (KBr, cm^{-1}) 3088, 2927, 1694, 1626, 1557, 1506, 1258, 1161, 849, 792, 558; ^1H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 2H), 7.53 (dd, J = 5.1, 2.1 Hz, 1H), 7.45 (dd, J = 6.7, 2.1 Hz, 1H), 7.28 – 7.23 (m, 2H), 6.36 (dd, J = 6.7, 5.1 Hz, 1H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -57.77; ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 151.3, 149.5, 139.7, 133.3, 129.9,

127.4, 120.9, 110.6 (q, J_{C-F} = 257.6 Hz), 106.8; HRMS (ESI) calcd. for $C_{12}H_8O_3F_3$ [$(M + H)^+$] 257.0420, found: 257.0418.

3-([1,1'-biphenyl]-4-yl)-2H-pyran-2-one (3f). White solid (83%, 41 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 153–154 °C; IR (KBr, cm^{-1}) 3091, 2923, 1695, 1626, 1552, 1405, 1344, 1094, 843, 780, 527; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.0 Hz, 2H), 7.64 (dd, J = 10.9, 8.5 Hz, 4H), 7.55 – 7.41 (m, 4H), 7.37 (t, J = 7.2 Hz, 1H), 6.35 (t, J = 5.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 150.8, 141.6, 140.5, 139.1, 133.6, 128.9, 128.7, 128.2, 127.7, 127.2, 127.2, 106.9; HRMS (ESI) calcd. for $C_{17}H_{13}O_2$ [$(M + H)^+$] 249.0910, found: 249.0908.

3-(4-fluorophenyl)-2H-pyran-2-one (3g). Pale yellow solid (76%, 29 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 123–124 °C; IR (KBr, cm^{-1}) 3109, 3090, 1709, 1624, 1557, 1510, 1304, 1232, 845, 792, 553; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 7.9, 5.7 Hz, 2H), 7.50 (d, J = 4.9 Hz, 1H), 7.41 (d, J = 6.6 Hz, 1H), 7.09 (t, J = 8.5 Hz, 2H), 6.34 (t, J = 5.8 Hz, 1H); ^{19}F NMR (377 MHz, $CDCl_3$) δ -112.61 (s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.3, 161.7 (d, J_{C-F} = 26.3 Hz), 150.9, 139.2, 130.7 (d, J_{C-F} = 3.2 Hz), 130.2 (d, J_{C-F} = 8.2 Hz), 127.7, 115.5 (d, J_{C-F} = 21.6 Hz), 106.8; HRMS (ESI) calcd. for $C_{11}H_8O_2F$ [$(M + H)^+$] 191.0503, found: 191.0502.

3-(4-chlorophenyl)-2H-pyran-2-one (3h). White solid (83%, 34 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 117–118 °C; IR (KBr, cm^{-1}) 3110, 3090, 1694, 1625, 1554, 1339, 1231, 1096, 837, 790, 550; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, J = 8.4 Hz, 2H), 7.51 (dd, J = 4.9, 1.5 Hz, 1H), 7.43 (dd, J = 6.7, 1.3 Hz, 1H), 7.37 (d, J = 8.4 Hz, 2H), 6.38 – 6.30 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3,

151.2, 139.4, 134.8, 133.1, 129.6, 128.7, 127.5, 106.8; HRMS (ESI) calcd. for $C_{11}H_8O_2Cl$ [$(M + H)^+$] 207.0207, found: 207.0206.

3-(4-bromophenyl)-2H-pyran-2-one (3i).[12a] White solid (84%, 42 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 114–115 ^oC; IR (KBr, cm^{-1}) 3089, 1705, 1625, 1553, 1489, 1338, 1230, 1114, 1090, 830, 776, 550; ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 4H), 7.50 (dd, J = 5.1, 2.0 Hz, 1H), 7.43 (dd, J = 6.7, 2.1 Hz, 1H), 6.33 (d, J = 6.7, 5.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 161.2, 151.2, 139.4, 133.5, 131.6, 129.8, 127.4, 123.0, 106.8; EI-MS (*m/z*, relative intensity): 250 (M^+, 28), 224 (15), 193 (28), 171 (69), 115 (100), 51 (9).

3-ethyl 4-(2-oxo-2H-pyran-3-yl)benzoate (3j). Pale yellow solid (90%, 44 mg, eluent: petroleum ether/ethyl acetate = 5/1), mp 72–73 ^oC; IR (KBr, cm^{-1}) 3104, 2983, 1718, 1626, 1555, 1341, 1273, 1110, 1022, 784, 549; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 8.4 Hz, 2H), 7.73 (d, J = 8.4 Hz, 2H), 7.58 – 7.47 (m, 2H), 6.37 (dd, J = 6.6, 5.2 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 161.1, 151.7, 140.2, 139.0, 130.6, 129.7, 128.2, 127.7, 106.8, 61.2, 14.4; HRMS (ESI) calcd. for $C_{14}H_{13}O_4$ [$(M + H)^+$] 245.0808, found: 245.0805.

3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)-2H-pyran-2-one (3k). White solid (70%, 32 mg, eluent: petroleum ether/ethyl acetate = 5/1), mp 147–148 ^oC; IR (KBr, cm^{-1}) 3089, 2938, 2887, 1709, 1624, 1556, 1501, 1315, 1282, 1063, 885, 781, 700, 564; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46 (dd, J = 5.1, 2.0 Hz, 1H), 7.36 (dd, J = 6.7, 2.0 Hz, 1H), 7.22 (d, J = 2.2 Hz, 1H), 7.14 (dd, J = 8.4, 2.2 Hz, 1H), 6.88 (d, J = 8.5 Hz, 1H), 6.30 (dd, J = 6.7, 5.1 Hz, 1H), 4.28 – 4.24 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

161.6, 150.3, 144.3, 143.4, 138.3, 128.0, 128.0, 121.6, 117.3, 117.3, 106.8, 64.6, 64.4; HRMS (ESI) calcd. for $C_{13}H_{11}O_4$ [$(M + H)^+$] 231.0652, found: 231.0648.

3-(4-hydroxyphenyl)-2H-pyran-2-one (3l). Pale yellow solid (75%, 28 mg, eluent: petroleum ether/ethyl acetate = 3/1), mp 134–135 ^oC; IR (KBr, cm^{-1}) 3400, 2921, 2851, 2361, 2343, 1691, 1611, 1556, 1513, 1270, 1121, 838, 778, 553; ^1H NMR (500 MHz, Acetone-d_6) δ 8.60 (s, 1H), 7.64 (dd, J = 5.1, 2.0 Hz, 1H), 7.61 – 7.58 (m, 2H), 7.56 (dd, J = 6.7, 2.0 Hz, 1H), 6.90 – 6.86 (m, 2H), 6.45 (dd, J = 6.7, 5.1 Hz, 1H); ^{13}C NMR (126 MHz, Acetone-d_6) δ 161.9, 158.7, 151.4, 138.8, 130.4, 128.3, 127.1, 115.9, 107.6; HRMS (ESI) calcd. for $C_{11}H_9O_3$ [$(M + H)^+$] 189.0546, found: 189.0545.

3-(m-tolyl)-2H-pyran-2-one (3m). White solid (78%, 29 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 89–90 ^oC; IR (KBr, cm^{-1}) 3110, 3089, 2948, 1709, 1626, 1553, 1451, 1337, 1112, 785, 704, 585; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.39 (m, 4H), 7.30 (t, J = 7.6 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 6.33 (t, J = 5.8 Hz, 1H), 2.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 150.7, 139.3, 138.1, 134.7, 129.6, 128.9, 128.8, 128.4, 125.4, 106.8, 21.6; HRMS (ESI) calcd. for $C_{12}H_{11}O_2$ [$(M + H)^+$] 187.0754, found: 187.0751.

3-(o-tolyl)-2H-pyran-2-one (3n). [12a] Pale yellow oil (51%, 19 mg, eluent: petroleum ether/ethyl acetate = 10/1); IR (KBr, cm^{-1}) 3060, 2926, 1723, 1629, 1560, 1457, 1339, 1233, 967, 785, 754, 616; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 1H), 7.32 – 7.16 (m, 5H), 6.32 (t, J = 5.8 Hz, 1H), 2.27 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3, 151.3, 141.4, 136.8, 134.8, 130.4, 130.3, 129.8, 128.8, 126.0, 106.4,

20.0; EI-MS (*m/z*, relative intensity): 186 (M^+, 45), 158 (29), 129 (100), 115 (54), 91 (6), 51 (26).

3-(2-aminophenyl)-2H-pyran-2-one (3o). Pale yellow solid (44%, 16 mg, eluent: petroleum ether/ethyl acetate = 1/1), mp 145–146 °C; IR (KBr, cm^{-1}) 3370, 2922, 2851, 1703, 1624, 1552, 1494, 1453, 967, 749, 617; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (dd, J = 5.1, 2.1 Hz, 1H), 7.43 (dd, J = 6.7, 2.1 Hz, 1H), 7.20 (td, J = 8.0, 1.6 Hz, 1H), 7.09 (dd, J = 7.6, 1.4 Hz, 1H), 6.83 (td, J = 7.5, 1.1 Hz, 1H), 6.76 (dd, J = 8.0, 0.8 Hz, 1H), 6.37 (dd, J = 6.6, 5.1 Hz, 1H), 3.98 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.5, 151.2, 145.3, 142.8, 131.1, 130.1, 129.0, 122.0, 119.2, 117.5, 106.9; HRMS (ESI) calcd. for $C_{11}H_{10}O_2N$ [$(M + H)^+$] 188.0706, found: 188.0701.

3-(2-bromophenyl)-2H-pyran-2-one (3p). Pale yellow oil (69%, 35 mg, eluent: petroleum ether/ethyl acetate = 10/1); IR (KBr, cm^{-1}) 3100, 2921, 1725, 1631, 1561, 1089, 968, 852, 781, 756, 658; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 1H), 7.56 (dd, J = 5.1, 2.1 Hz, 1H), 7.39 – 7.29 (m, 3H), 7.28 – 7.21 (m, 1H), 6.34 (dd, J = 6.6, 5.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 151.9, 142.3, 135.8, 133.2, 131.3, 130.2, 129.2, 127.5, 123.5, 106.2; HRMS (ESI) calcd. for $C_{11}H_8O_2Br$ [$(M + H)^+$] 250.9702, found: 250.9700.

3-(naphthalen-1-yl)-2H-pyran-2-one (3q). White solid (78%, 35 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 144–145 °C; IR (KBr, cm^{-1}) 3058, 1716, 1630, 1558, 1508, 1234, 1096, 951, 774, 550; ^{1}H NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 2H), 7.75 – 7.69 (m, 1H), 7.61 (dd, J = 5.1, 2.1 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.46 – 7.38 (m, 2H), 6.38 (dd, J = 6.5, 5.2 Hz, 1H); ^{13}C

NMR (101 MHz, $CDCl_3$) δ 161.8, 151.6, 142.5, 133.7, 132.8, 131.4, 129.3, 128.8, 128.6, 127.6, 126.5, 126.1, 125.3, 125.2, 106.5; HRMS (ESI) calcd. for $C_{15}H_{11}O_2$ [$(M + H)^+$] 223.0754, found: 223.0750.

3-(thiophen-2-yl)-2H-pyran-2-one (3r). [12a] Pale yellow oil (76%, 27 mg, eluent: petroleum ether/ethyl acetate = 20/1); IR (KBr, cm^{-1}) 3103, 2921, 1710, 1617, 1543, 1425, 1236, 1086, 841, 771, 704, 687, 526; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 3.3 Hz, 1H), 7.66 – 7.60 (m, 1H), 7.50 – 7.43 (m, 1H), 7.38 (d, J = 5.0 Hz, 1H), 7.09 (t, J = 4.4 Hz, 1H), 6.38 – 6.30 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 149.6 135.9, 135.1, 127.6, 126.7, 122.6, 106.8; EI-MS (*m/z*, relative intensity): 178 (M^+, 96), 150 (29), 121 (100), 95 (6), 51 (10).

General procedure for Pd-catalyzed oxidative coupling reaction of terminal alkynes and vinyl diaoester 1. A 10 mL microwave tube was charged with $Pd(OAc)_2$ (5 mol%), $P(^tBu)_3{\cdot}HBF_4$ (20 mol%), BQ (0.4 mmol) and vinyl diaoester **2** (0.2 mmol) under argon atmosphere. Then 2 mL of 1, 4-dioxane, $^iPr_2NEt$ (0.6 mmol) and phenylacetylenes (0.3 mmol) were added *via* syringe. After the resulting solution was stirred at room temperature for 24 h, the mixture was filtered through a short path of silica gel, eluting with ethyl acetate. The volatile compounds were removed in *vacuo* and the residue was purified by column chromatography to give the coupling products.

3-(phenylethynyl)-2H-pyran-2-one (4a). Pale yellow solid (39%, 15.4 mg, eluent: petroleum ether/ethyl acetate = 10/1), mp 83–84 ^oC; IR (KBr, cm^{-1}) 3405, 3108, 2921, 2217, 1725, 1615, 1543, 1489, 1333, 1110, 1037, 834, 755, 587, 526; ^1H NMR (400

MHz, $CDCl_3$) δ 7.61 – 7.48 (m, 4H), 7.39 – 7.31 (m, 3H), 6.28 (dd, J = 6.7, 5.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.6, 151.3, 144.5, 132.0, 129.2, 128.5, 122.3, 114.0, 106.4, 96.3, 83.2; HRMS (ESI) calcd. for $C_{13}H_9O_2$ [$(M + H)^+$] 197.0597, found: 197.0595.

3-((4-chlorophenyl)ethynyl)-2H-pyran-2-one (4b). White solid (37%, 17 mg, eluent: petroleum ether/ethyl acetate = 5/1), mp 154–155 ^oC; IR (KBr, cm^{-1}) 3414, 3112, 2919, 1719, 1707, 1620, 1544, 1487, 1333, 1089, 1086, 824, 771, 604, 550; ^1H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.50 (m, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H), 6.29 (dd, J = 6.5, 5.4 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.4, 151.5, 144.7, 135.3, 133.2, 128.9, 120.8, 113.7, 106.4, 95.1, 84.1; HRMS (ESI) calcd. for $C_{13}H_8O_2Cl$ [$(M + H)^+$] 231.0207, found: 231.0213.

3-((4-methoxyphenyl)ethynyl)-2H-pyran-2-one (4c). Pale yellow oil (32%, 14.5 mg, eluent: petroleum ether/ethyl acetate = 5/1); IR (KBr, cm^{-1}) 3397, 3104, 2921, 2850, 2201, 1727, 1604, 1508, 1290, 1251, 1098, 1038, 833, 771, 546; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 – 7.46 (m, 4H), 6.90 – 6.85 (m, 2H), 6.26 (dd, J = 6.7, 5.2 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.8, 160.4, 150.9, 143.8, 133.6, 114.4, 114.3, 114.2, 106.5, 96.6, 82.1, 55.5; HRMS (ESI) calcd. for $C_{14}H_{11}O_3$ [$(M + H)^+$] 227.0703, found: 227.0703.

Synthesis of biphenyl 5. A mixture of **3a** (0.2 mmol, 37 mg), diethyl maleate (1 mmol) and 10% Pd/C (93 mg) in 2 mL of dodecane was heated to 200 ^oC under argon. After the reaction was completed, the mixture was filtered through a short path of silica gel and eluted with petroleum ether to remove most of dodecane. Then the

filtrate was collected by eluting with ethyl acetate. Biphenyl **5** was obtained as colorless oil (64%, 40 mg) through purification by column chromatography with petroleum ether/ethyl acetate (40/1) as the eluent. IR (KBr, cm^{-1}) 3438, 2983, 2927, 1720, 1516, 1450, 1366, 1266, 1149, 1064, 1016, 814, 761, 743, 563; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (dd, J = 6.9, 2.2 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.27 – 7.24 (m, 2H), 7.19 (d, J = 7.9 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 2.38 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 166.0, 140.7, 137.6, 136.6, 134.9, 134.1, 129.0, 129.0, 128.8, 128.7, 128.6, 61.6, 61.3, 21.3, 14.2, 13.8; HRMS (ESI) calcd. for $C_{19}H_{20}O_4Na$ [$(M + Na)^+$] 335.1254, found: 335.1256.

Synthesis of ethyl 4-(naphthalen-1-yl)benzoate 6. A solution of **3j** (0.2 mmol), CsF (1 mmol) and 2-(trimethylsilyl)phenyl trifluoromethanesulfonate (1 mmol) in anhydrous MeCN (2.0 mL) was heated to 100 °C. After the reaction was completed, the mixture was cooled to room temperature and the solvent removed *in vacuo*. The residue was purified by column chromatography to give product **6** as pale yellow oil (78%, 43 mg). IR (KBr, cm^{-1}) 3435, 3044, 2980, 2929, 1716, 1609, 1396, 1367, 1271, 1177, 1100, 1021, 862, 802, 779, 705, 642, 569; ^1H NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.15 (m, 2H), 7.97 – 7.84 (m, 3H), 7.63 – 7.58 (m, 2H), 7.57 – 7.50 (m, 2H), 7.49 – 7.42 (m, 2H), 4.47 (q, J = 7.1 Hz, 2H), 1.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.7, 145.6, 139.3, 133.9, 131.3, 130.2, 129.6, 129.5, 128.5, 128.4, 127.0, 126.4, 126.1, 125.7, 125.4, 61.1, 14.5; EI-MS (*m/z*, relative intensity): 276 (M^+, 100), 231 (52), 202 (80), 176 (2), 101 (20), 88 (2).

ASSOCIATED CONTENT

Supporting Information

Table S1, ^{1}H and ^{13}C NMR spectra of all products. 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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REFERENCES

1. a) Goel, A.; Ram, V. J. *Tetrahedron* **2009**, *65*, 7865. b) McGlacken, G. P.; Fairlamb, I. J. S. *J. Nat. Prod.* **2005**, *22*, 369.

2. a) Turner, S. R.; Strohbach, J. W.; Tommasi, R. A.; Aristoff, P. A.; Johnson, P. D.; Skulnick, H. I.; Dolak, L. A.; Seest, E. P.; Tomich, P. K.; Bohanon, M. J.; Horng, M.-M.; Lynn, J. C.; Chong, K.-T.; Hinshaw, R. R.; Watenpaugh, K. D.; Janakiraman, M. N.; Thaisrivongs, S. *J. Med. Chem.* **1998**, *41*, 3467. b) Thaisrivongs, S.; Janakiraman, M. N.; Chong, K.-T.; Tomich, P. K.; Dolak, L. A.; Turner, S. R.; Strohach, J. W.; Lynn, J. C.; Horng, M.-M.; Hinshaw, R. R.; Watenpaugh, K. D. *J.*

Med. Chem. **1996**, *39*, 2400.

3. Fairlamb, I. J. S.; Marrison, L. R.; Dickinson, J. M.; Lu, F.-J.; Schmidt, J. P. *Bioorg. Med. Chem.* **2004**, *12*, 4285.

4. Rao, P. N. P.; Amini, M.; Li, H.; Habeeb, A. G.; Knaus, E. E. *J. Med. Chem.* **2003**, *46*, 4872.

5. Marrison, L. R.; Dickinson, J. M.; Fairlamb, I. J. S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3509.

6. Evidente, A.; Cabras, A.; Maddau, L.; Serra, S.; Andolfi, A.; Motta, A. *J. Agric. Food Chem.* **2003**, *51*, 6957.

7. For reviews of DA cycloadditions of 2-pyrones, see: a) Afarinkia, K.; Vinader, V.; Nelson, T. D.; Posner, G. H. *Tetrahedron* **1992**, *48*, 9111. b) Komiyama, T.; Takaguchi, Y.; Tsuboi, S. *Synlett* **2006**, 124.

8. a) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 9015. b) Chung, S.-I.; Seo, J.; Cho, C.-G. *J. Org. Chem.* **2006**, *71*, 6701. c) Tam, N. T.; Chang, J.; Jung, E.-J.; Cho, C.-G. *J. Org. Chem.* **2008**, *73*, 6258. d) Rueping, M.; Merino, E.; Sugiono, E. *Adv. Synth. Catal.*, **2008**, 350, 2127. e) Tam, N. T.; Cho, C.-G. *Org. Lett.* **2008**, *10*, 601. f) Tam, N. T.; Jung, E.-J.; Cho, C.-G. *Org. Lett.* **2010**, *12*, 2012. g) Shin, H.-S.; Jung, Y.-G.; Cho, H.-K.; Park, Y.-G.; Cho, C.-G. *Org. Lett.* **2014**, *16*, 5718. h) Lee, J.-H.; Cho, C.-G. *Org. Lett.* **2016**, *18*, 5126.

9. For recent reviews on the synthesis of substituted 2-pyrones, see: a) Pratap, R.; Ram, V. J. *Tetrahedron* **2017**, *73*, 2529. b) Lee, J. S. *Mar. Drugs* **2015**, *13*, 1581.

10. a) Niyomchon, S.; Audisio, D.; Luparia, M.; Maulide, N. *Org. Lett.* **2013**, *15*,

2318. b) Souris, C.; Luparia, M.; Frébault, F.; Audisio, D.; Farès, C.; Goddard, R.; Maulide, N. *Chem. Eur. J.* **2013**, *19*, 6566.

11. a) Rosen, J. D.; Nelson, T. D.; Huffman, M. A.; McNamara, J. M. *Tetrahedron Lett.* **2003**, *44*, 365. b) Shi, X.; Leal, W. S.; Liu, Z.; Schrader, E.; Meinwald, J. *Tetrahedron Lett.* **1995**, *36*, 71. c) Boulanger, W. A.; Katzenellenbogen, J. A. *J. Med. Chem.* **1986**, *29*, 1159.

12. a) Frébault, F.; Oliveira, M. T.; Wöstefeld, E.; Maulide, N. *J. Org. Chem.* **2010**, *75*, 7962. b) Orimoto, K.; Tomizawa, T.; Namera, Y.; Oyama, H.; Niwa, T.; Nakada, M. *Heterocycles* **2013**, *87*, 827. c) Liu, Z.; Meinwald, J. *J. Org. Chem.* **1996**, *61*, 6693. d) Posner, G. H.; Harrison, W.; Wettlaufer, D. G. *J. Org. Chem.* **1985**, *50*, 5041. e) Lee, J.-H.; Kim, W.-S.; Lee, Y. Y.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 5779. f) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *Tetrahedron Lett.* **2002**, *43*, 9015.

13. Vijgen, S.; Nauwelaerts, K.; Wang, J.; Van Aerschot, A.; Lagoja, I.; Herdewijn, P. *J. Org. Chem.* **2005**, *70*, 4591.

14. For some reviews, see: a) Barluenga, J.; Valdés, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 7486. b) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236. c) Liu, Z.; Wang, J. *J. Org. Chem.* **2013**, *78*, 10024. d) Xia, Y.; Zhang, Y.; Wang, J. *ACS Catal.* **2013**, *3*, 2586. e) Xia, Y.; Wang, J. *Chem. Soc. Rev.* **2017**, *46*, 2306.

15. a) Chen, S.; Wang, J. *Chem. Commun.* **2008**, 4198. b) Xiao, Q.; Wang, B.; Tian, L.; Yang, Y.; Ma, J.; Zhang, Y.; Chen, S.; Wang, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 9305.

16. Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Adv. Synth. Catal.* **2010**,

352, 3235.

17. Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2012**, *14*, 922.

18. Xie, Y.; Zhang, P.; Zhou, L. *J. Org. Chem.* **2016**, *81*, 2128.

19. For interception of η^3-allylpalladium intermediate by nucleophiles, see: a) Devine, S. K. J.; Van Vranken, D. L. *Org. Lett.* **2008**, *10*, 1909. b) Zhou, P.-X.; Luo, J.-Y.; Zhao, L.-B.; Ye, Y.-Y.; Liang, Y.-M. *Chem. Commun.* **2013**, *49*, 3254. c) Ye, Y.-Y.; Zhou, P.-X.; Luo, J.-Y.; Zhong, M.-J.; Liang, Y.-M. *Chem. Commun*. **2013**, *49*, 10190.

20. Bykowski, D.; Wu, K.-H.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 16038.

21. Aryl triflate can hardly be activated by $Pd(PPh_3)_4$ in dioxane at room temperature: Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478.

22. Zhou, L.; Ye, F.; Ma, J.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2011**, *50*, 3510.