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Straightforward Synthesis of 2(5*H*)-Furanones as Promising Cross-Coupling Partners: Direct Furanone Annulation Utilizing Ti-Mediated Aldol Addition

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Abstract: Direct 2(5*H*)-furanone annulation produces promising cross-coupling partners incorporating *m*- or *p*-bromo- and *p*-tosyloxyphenyl groups into the 5-position of a notable 2(5*H*)-furanone pharmacore. The present one-pot annulation method involves two distinctive reactions: (i) a powerful and crossed Ti-direct aldol addition and (ii) an acid-induced characteristic cyclo-condensation, leading to 2(5*H*)-furanones. Suzuki-Miyaura cross-coupling of 5-(4-bromophenyl)-furan-2(5*H*)-ones, 5-(4-tosyloxyphenyl)-3,4-dimethylfuran-2(5*H*)-ones and a furan derivative successfully afforded the corresponding products with the 2(5*H*)-furanone skeleton.

Keywords: Cross-aldol reaction; titanium chloride; furanone; furanone annulation; Ti-mediated reaction; 1,1-dimethoxyacetone; bromophenyl ketone; tosyloxy ketone; cross-coupling partner; Suzuki-Miyaura cross-coupling

1. Introduction

2(5*H*)-Furanones (α,β-butenolides) are a well-recognized heterocyclic compound incorporated in natural products [1–3]. They also serve as useful precursors for the synthesis of lactones and furans by catalytic hydrogenation and hydride-reduction (LAH or DIBAL), respectively [2,3]. Several synthetic methods have been developed to date due to the relatively simple but promising candidate roles for 2(5*H*)-furanones as new pharmacores.

Current drug discovery is considerably based on cross-coupling methodologies, especially Suzuki-Miyaura cross-couplings, because large boronic acid libraries are supplied in a commercial base. Because this privileged approach representatively requires aromatics with leaving groups (-Br and -OTs) as latent scaffolds in various organic molecules, this background led us to investigate the convenient synthesis of attractive cross-coupling partner, 2(5*H*)-furanones **4** bearing bromophenyl and tosyloxyphenyl leaving groups.

A literature survey using SciFinder® revealed a two recent syntheses of **4a**; (i) Ru-catalyzed CO insertion into the corresponding allenic alcohol [4]; and (ii) SeBr-resin-mediated lactonization of β,γ-unsaturated carboxylic acids, followed by three oxidation (H_2O_2)-elimination-methylation (MeI/LDA) reaction sequences [5]. The first method requires three steps and special handling techniques and/or apparatuses using CO. The second synthetic method requires a less accessible SeBr-resin reagent and four steps. Other target molecules **4b**–**4f** are novel compounds.

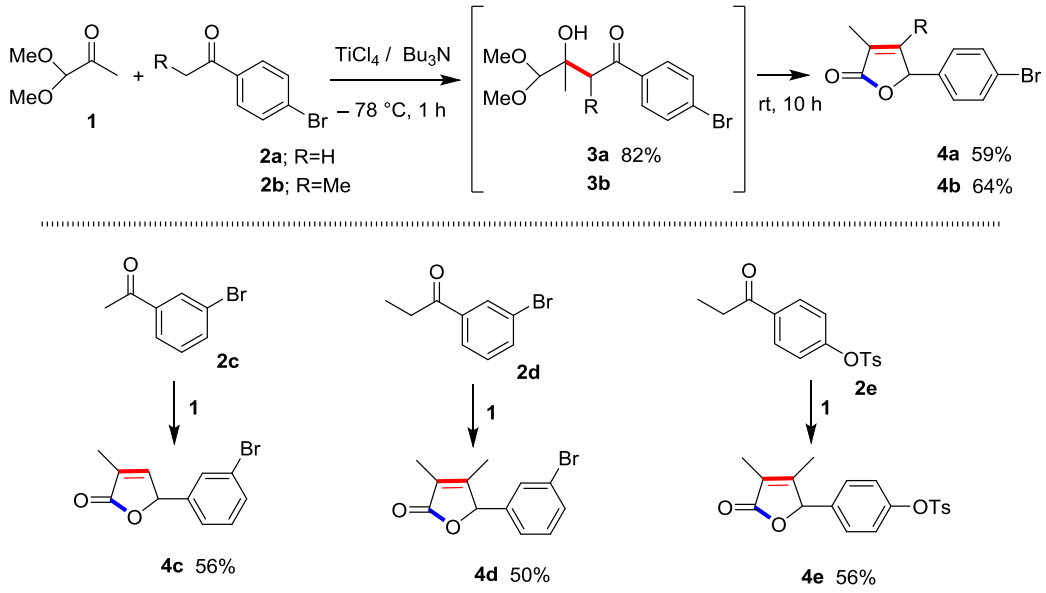
Consistent with our longstanding studies on $TiCl_4$/amine-mediated Claisen condensations (Ti-Claisen condensation) [6–11], its asymmetric version [12], related Ti-direct aldol reactions [13,14], and Ti-direct Mannich reactions [15], we already reported both a two-step method and a much improved one-step synthetic method for di- or trialkyl-substituted 2(5*H*)-furanones (direct

2(5*H*)-furanone *or* butenolide annulation) based on a $TiCl_4$-promoted direct aldol condensation between ketones and α,α-dimethoxyketones [16,17].

2. Results and Discussion

Crossed aldol reaction between acetophenones or propiophenones and carbonyl acceptors is pivotal in organic syntheses. Ti-direct aldol additions possess considerably powerful C-C bond forming ability allowing for the reaction between less reactive different ketones which would proceed with difficulty using other reaction systems [13]. Mukaiyama, Iwasawa, and their coworkers disclosed direct crossed aldol addition between different ketones mediated by $Sn(OTf)_2$/*N*-ethylpiperidine reagent, however, being limited to the reaction between both aromatic ketones [18].

In practice, Ti-direct aldol addition 1-(4-bromophenyl)ethan-1-one (*p*-bromoacetophenone) (**2a**) with 1,1-dimethoxypropan-2-one (1,1-dimethoxyacetone) (**1**) proceeded smoothly to produce the aldol adduct **3a** at −78 °C for 1 h in 82% isolated yield (Scheme 1). Gratifyingly, the reaction at −78 °C for 1 h and r.t. for 14 h produced 2(5*H*)-furanone **4a** directly in 59% yield in a one-pot procedure. The direct method using 4-bromophenyl-1-ethanone (*p*-bromopropiophenone) (**2b**) instead of **2a** similarly afforded the corresponding 2(5*H*)-furanone **4b** in 64% yield through **3b** under the identical conditions.



Scheme 1. Crossed Ti-direct aldol addition and successive cyclo-condensation (furanone annulation) leading to 2(5*H*)-furanone **4**.

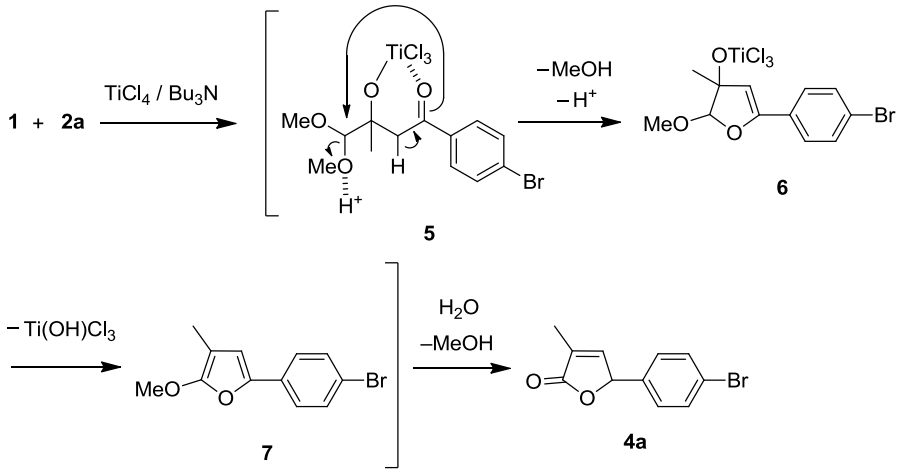
The reactions using *m*-bromoacetophenone (**2c**) and *m*-bromopropiophenone (**2d**) with **1** successfully afforded the corresponding 2(5*H*)-furanones **4c** and **4d**. In addition, 2(5*H*)-furanone **4e** bearing *p*-TsO- group as the related cross-coupling leaving group was also produced.

The present direct annulation methods utilize commercially available, inexpensive substrates and reagents, under accessible reaction conditions without any use of special apparatus and technique with sufficient substrate-generality [16,17]. Moreover, an application to the most straightforward total syntheses of (*R*)-mintlactone (a single step, 52%) and (*R*)-menthofuran (2 steps, overall 46%) was successfully performed [17]. Since the publication of these reports, three subsequent syntheses of (*R*)-mintlactone have been presented; however, these methods require (i) 3 steps, overall 7% [19]; (ii) formal synthesis, over 3 steps, accurate overall yield is unknown [20]; and (iii) 10 steps, overall 22%, [21]. The report [19] does not strictly evaluate our work [17], because it is categorized into

racemic mintlactone synthesis in the authors' reference part. The other reports [20,21] fail to refer to our work [17].

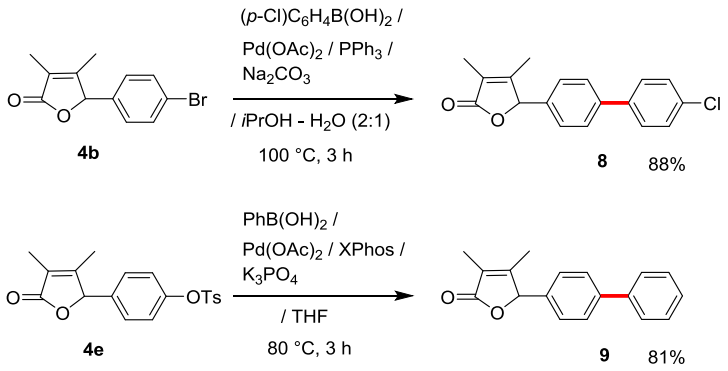
On the other hand, Mehta and Ramesh applied the present method exquisitely for the total syntheses of a series of lindenane-type sesquiterpenoids [22] and atractylenolide-type eudesmanolides [23], wherein these key skeletons are smoothly constructed, utilizing this direct 2(5*H*)-furanone annulation.

A plausible mechanism for the reaction sequences is proposed, exemplified by the production of **4a** (Scheme 2). The initially formed Ti-chelated cross aldol adduct **5** is transformed to dihydrofuran intermediate **6** with ring formation and elimination of MeOH. Intermediate **6** is converted to **4a** through methoxyfuran **7** with elimination of $Ti(OH)Cl_3$ before H_2O-workup.



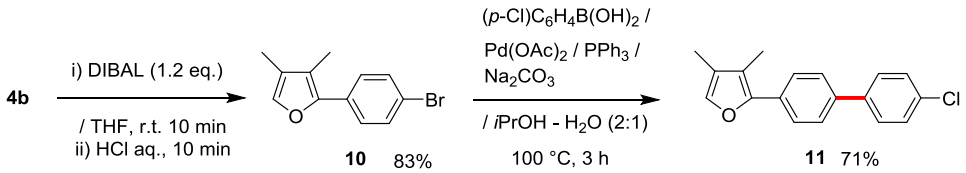
Scheme 2. Plausible mechanism for crossed Ti-direct aldol addition and successive cyclo-condensation (furanone annulation).

Finally, a useful derivatization of 2(5*H*)-furanones **4b** and **4e** by utilizing Suzuki-Miyaura cross-coupling was investigated (Scheme 3). A standard and accessible method using (*p*-Cl)$C_6H_4B(OH)_2$ with $Pd(OAc)_2/PPh_3/K_2CO_3$ catalysis could be successfully applied to the synthesis of biphenyl-substituted 2(5*H*)-furanone **8** in good 88% yield. *p*-Tosyloxy-substituted 2(5*H*)-furanones **4e** was also transformed to the desired compound **9** in 81% yield by utilizing Buchwald group's modified $Pd(OAc)_2/XPhos/K_3PO_4$ catalysis [24].



Scheme 3. Derivatization of 2(5*H*)-furanones **4b** and **4e** by utilizing Suzuki-Miyaura cross-coupling.

Notably, furan **10** derived from **4b** by DIBAL reduction (83%), similarly underwent Suzuki-Miyaura cross-coupling to produce the furan analogue **11** in 71% yield (Scheme 4).



Scheme 4. Derivatization of furan **10** derived from **4b** by utilizing Suzuki-Miyaura cross-coupling.

3. Experimental Section

3.1. General

All reactions were carried out in oven-dried glassware under an argon atmosphere. Flash column chromatography was performed with Silica Gel 60 (spherical) (63–210 μm, KANTO CHEMICAL, Tokyo, Japan). TLC analysis was performed on 0.25 mm Silicagel Merck 60 F254 plates. Melting points were determined on a hot stage microscope apparatus (ATM-01, AS ONE, Osaka, Japan) and were uncorrected. NMR spectra were recorded on a JEOLRESONANCE ECX-500II spectrometer (JEOL, Tokyo, Japan) operating at 500 MHz for ^{1}H-NMR and 125 MHz for ^{13}C-NMR. Chemical shifts (δ ppm) in $CDCl_3$ were reported downfield from TMS (= 0.00) for ^{1}H-NMR. For ^{13}C-NMR, chemical shifts were reported in the scale relative to $CDCl_3$ (77.0 ppm) as an internal reference. IR Spectra were recorded on a SHIMADZU IRAffinity-1S spectrophotometer (SHIMADZU, Kyoto, Japan). Mass spectra were measured on a JEOL JMS-T100LCP spectrometer (JEOL, Tokyo, Japan).

*3.2. Preparation of 1-(4-Bromophenyl)-3-hydroxy-4,4-dimethoxy-3-methylbutan-1-one (**3a**)*

$TiCl_4$ (0.82 mL, 7.5 mmol) and Bu_3N (2.38 mL, 10.0 mmol) were successively added to a stirred solution of *p*-bromoacetophenone (**2a**; 1.00 g, 5.0 mmol) in CH_2Cl_2 (5.0 mL) at −78 °C under an Ar atmosphere. After 15 min, 1,1-dimethoxyacetone (**1**; 1.18 g, 10.0 mml) in CH_2Cl_2 (5.0 mL) was added to the mixture at −78 °C, followed by being stirred at the same temperature for 1 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with 1M HCl aq., brine, dried (Na_2SO_4), and concentrated. The obtained crude product (1.97 g) was purified by SiO_2-column chromatography (hexane/AcOEt = 4:1) to give the desired product **3a** (1.31 g, 82 %).

Pale yellow oil; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 3H), 2.87 (d, *J* = 16.0 Hz, 1H), 3.36 (d, *J* = 16.0 Hz, 1H), 3.47 (s, 3H), 3.51 (s, 3H), 4.03 (s, 1H), 4.16 (s, 1H), 7.59–7.62 (m, 2H), 7.82–7.85 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 23.4, 42.3, 57.9, 75.3, 110.1 (2C), 128.3, 129.8 (2C), 131.7 (2C), 136.3, 200.7; IR (neat): ν_{max} = 3482, 2936, 2832, 1736, 1672, 1583, 1396, 1219, 1184 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{13}H_{17}O_4Br$ $[M + Na]^+$ 339.0208; found: 339.0205.

*3.3. Preparation of 5-(4-Bromophenyl)-3-methylfuran-2(5H)-one (**4a**) [4]*

$TiCl_4$ (0.82 mL, 7.5 mmol) and Bu_3N (2.38 mL, 10.0 mmol) were successively added dropwise to a stirred solution of *p*-bromoacetophenone (**2a**; 1.00 g, 5.0 mmol) in CH_2Cl_2 (5.0 mL) at −78 °C under an Ar atmosphere. After 15 min, 1,1-dimethoxyacetone (**1**; 1.18 g, 10.0 mml) in CH_2Cl_2 (5.0 mL) was added. Then the reaction mixture was stirred at the same temperature for 1 h and 20–25 °C for 14 h. Water was added to the mixture, which was extracted twice with Et_2O. The combined organic phase was washed with 1M HCl, brine, dried (Na_2SO_4), and concentrated. The obtained crude product (2.22 g) was purified by SiO_2-column chromatography (hexane/AcOEt = 5:1) to give the desired product **4a** (0.74 g, 59 %).

Pale yellow crystals (recryst. from *i*PrOH); mp 93–94 °C (lit. 94.0 °C [4]); ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.00 (t, *J* = 1.7 Hz, 3H), 5.82 (quin, *J* = 1.7 Hz, 1H), 7.09 (quin, *J* = 1.7 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 10.6, 81.3, 123.1, 128.0 (2C), 129.8, 132.0 (2C), 134.2, 147.8, 173.9; IR (neat): ν_{max} = 3084, 2928, 2363, 1748, 1661, 1587, 1485, 1406, 1319, 1294 cm^{-1}.

*3.4. Preparation of 5-(4-Bromophenyl)-3,4-dimethylfuran-2(5H)-one (**4b**)*

According to a similar procedure for preparing **4a**, the reaction of *p*-bromopropiophenone (**2b**; 1.07 g 5.0 mmol) with 1,1-dimethoxyacetone (**1**; 1.18 g, 10.0 mml), using $TiCl_4$ (0.82 mL, 7.5 mmol) and Bu_3N (2.38 mL, 10.0 mmol) in CH_2Cl_2 (10.0 mL) gave the desired product (**4b**; 0.86 g, 64 %).

Pale yellow crystals (recryst. from *i*PrOH); mp 112–114 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.81 (s, 3H), 1.89 (s, 3H), 5.56 (s, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 8.6, 12.1, 84.2, 123.2, 123.3, 128.4 (2C), 132.1 (2C), 134.0, 158.6, 174.4; IR (neat): ν_{max} = 2363, 1744, 1672, 1489, 1433, 1406, 1321, 1287 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{11}O_2Br$ $[M + Na]^+$ 288.9840; found: 288.9839.

*3.5. Preparation of 5-(3-Bromophenyl)-3-methylfuran-2(5H)-one (**4c**)*

According to a similar procedure for preparing **4a**, the reaction of *m*-bromoacetophenone (**2c**; 1.00 g, 5.0 mmol) with 1,1-dimethoxypropanone (**1**; 1.18 g, 10.0 mml), using $TiCl_4$ (0.82 mL, 7.5 mmol) and Bu_3N (2.38 mL, 10.0 mmol) in CH_2Cl_2 (10.0 mL) gave the desired product (**4c**; 0.74 g, 56 %).

Pale yellow crystals (recryst. from *i*PrOH); mp 97–98 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.00 (t, *J* = 1.7 Hz, 3H), 5.83 (quin, *J* = 1.7 Hz, 1H), 7.11 (quin, *J* = 1.7 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.26 (dd, *J* = 7.5, 8.0 Hz, 1H), 7.39–7.42 (m, 1H), 7.49 (d, *J* = 7.5 Hz, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 10.6, 81.0, 122.9, 125.0, 129.3, 129.9, 130.5, 132.1, 137.4, 147.7, 173.8; IR (neat): ν_{max} = 3063, 2357, 1748, 1661, 1593, 1566, 1471, 1429 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{11}H_9O_2Br$ $[M + Na]^+$ 274.9684; found: 274.9681.

*3.6. Preparation of 5-(3-Bromophenyl)-3,4-dimethylfuran-2(5H)-one (**4d**)*

According to a similar procedure for preparing **4a**, the reaction of *p*-bromopropiophenone (**2d**; 1.07 g 5.0 mmol) with 1,1-dimethoxyacetone (**1**; 1.18 g, 10.0 mml), using $TiCl_4$ (0.82 mL, 7.5 mmol) and Bu_3N (2.38 mL, 10.0 mmol) in CH_2Cl_2 (10.0 mL) gave the desired product (**4d**; 0.66 g, 50 %).

Pale yellow crystals (recryst. from *i*PrOH); mp 77–78 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.82 (s, 3H), 1.90 (s, 3H), 5.55 (s, 1H), 7.15 (d, J = 8.3 Hz, 1H), 7.27 (t, *J* = 8.3 Hz, 1H), 7.34–7.35 (m, 1H), 7.49–7.53 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 8.6, 12.1, 84.0, 122.9, 123.4, 125.5, 129.6, 130.4, 132.3, 137.3, 158.6, 174.3; IR (neat): ν_{max} = 3057, 2922, 1748, 1072, 997 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{12}H_{11}O_2Br$ $[M + Na]^+$ 267.0021, found 267.0023.

*3.7. Preparation of 5-(4-Tosyloxyphenyl)-3,4-dimethylfuran-2(5H)-one (**4e**)*

According to a similar procedure for preparing **4b** using *m*-tosyloxypropiophenone (**2f**; 1.52 g, 5.00 mmol) with 1,1-dimethoxyacetone (**1**; 1.18 g, 10.0 mml), using $TiCl_4$ (0.82 mL, 7.5 mmol) and Bu_3N (2.38 mL, 10.0 mmol) in CH_2Cl_2 (10.0 mL) gave the desired product (**4e**; 1.06 g, 56%).

Colorless crystals (recryst. from *i*PrOH); mp 128–129 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.79 (s, 3H), 1.88 (s, 3H), 2.45 (s, 3H), 5.56 (s, 1H), 6.99–7.04 (m, 2H), 7.12–7.16 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 8.5, 12.1, 21.6, 84.0, 122.9 (2C), 123.3, 128.1 (2C), 128.4 (2C), 129.8 (2C), 132.0, 133.9, 145.6, 150.0, 158.6, 174.3; IR (neat): ν_{max} = 1736, 1501, 1371, 1177, 1153, 1090, 1007, 868, 716 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}O_5S$ $[M + Na]^+$ 381.0773; found: 381.0783.

*3.8. Synthesis of 5-(4′-Chloro-[1,1′-biphenyl]-4-yl)-3,4-dimethylfuran-2(5H)-one (**8**)*

A mixture of **4b** (134 mg, 0.50 mmol), (*p*-Cl)$C_6H_4B(OH)_2$ (82 mg, 0.53 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), PPh_3 (3.9 mg, 0.015 mmol), and Na_2CO_3 (64 mg, 0.60 mmol) in *i*PrOH/H_2O (2:1, 1.4 mL) was stirred at 100–105 °C for 3 h under an Ar atmosphere. After cooling down to r.t., water was added to the mixture, which was extracted twice with AcOEt. The combined organic phase was washed with

water, brine, dried (Na_2SO_4), and concentrated. The obtained crude product (165 mg) was purified by SiO_2-column chromatography (hexane/AcOEt = 5:1) to give the desired product **8** (131 mg, 88%).

Colorless crystals (recryst. from *i*PrOH); mp 157–158 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.85 (s, 3H), 1.91 (s, 3H), 5.64 (s, 1H), 7.25–7.30 (m, 2H), 7.39–7.43 (m, 2H), 7.48–7.52 (m, 2H), 7.54–7.58 (m, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 8.6, 12.1, 84.7, 123.1, 127.3 (2C), 127.4 (2C), 128.2 (2C), 128.9 (2C), 133.7, 134.2, 138.6, 140.8, 159.0, 174.6; IR (neat): ν_{max} = 1748, 1674, 1483, 1319, 1080, 1013, 814, 760, 665 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{15}O_2Cl$ $[M + H]^+$ 299.0839; found: 299.0864.

*3.9. Synthesis of 5-(1,1′-Biphenyl-4-yl)-3,4-dimethylfuran-2(5H)-one (**9**) [25]*

A mixture of **4f** (179 mg, 0.50 mmol), $PhB(OH)_2$ (122 mg, 1.00 mmol), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol), XPhos (11.9 mg, 0.025 mmol), and K_3PO_4 (318 mg, 1.50 mmol) in THF (1.0 mL) was stirred at 80–85 °C for 3 h under an Ar atmosphere. A similar work up for the synthesis of **8** gave the desired product **9** (107 mg, 81%).

Yellow solid (recryst. from *i*PrOH); mp 121–122 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.86 (s, 3H), 1.92 (s, 3H), 5.65 (s, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.34–7.39 (m, 1H), 7.42–7.48 (m, 2H), 7.56–7.63 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 8.6, 12.2, 84.8, 123.2, 127.1 (2C), 127.2 (2C), 127.6 (2C), 128.8 (2C), 133.9, 140.3, 142.2, 159.0, 174.7; IR (neat): ν_{max} = 1742, 1678, 1086, 993, 756, 694 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{18}H_{16}O_2$ $[M + Na]^+$ 287.1048; found: 287.1038.

*3.10. Synthesis of 2-(4-Bromopheyl)-3,4-dimethylfuran (**10**)*

DIBAL (1.0 M in toluene; 0.60 mL, 0.60 mmol) was added dropwise to a stirred solution of **4b** (134 mg, 0.50 mmol) in THF (1.5 mL) at 0–5 °C under an Ar atmosphere. After 10 min, 1M-HCl aq. solution was added to the mixture at 0–5 °C, followed by being stirred at the same temperature for 10 min. Water was added to the mixture, which was extracted with Et_2O (×2). The combined organic phase was washed with 1M-HCl aq. solution (×2), $NaHCO_3$ aq. solution (×2), brine, dried (Na_2SO_4) and concentrated. The obtained crude product (164 mg) was purified by SiO_2 (Note: "60 N spherical, neutral" was used instead of standard type) -column chromatography (hexane/AcOEt = 5:1) to give the desired product **10** (105 mg, 83%).

Colorless solid; mp 44–46 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.99 (s, 3H), 2.16 (s, 3H), 7.21 (s, 1H), 7.45–7.54 (m, 4H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 8.3, 9.6, 117.5, 120.3, 122.9, 126.7 (2C), 131.0, 131.5 (2C), 138.0, 147.7; IR (neat): ν_{max} = 2922, 2866, 1545, 1483, 1393, 1074, 1003, 896, 824 cm^{-1}; HRMS (DART): *m/z* calcd for $C_{12}H_{11}OBr$ $[M + H]^+$ 251.0072; found: 251.0068.

*3.11. Synthesis of 2-(4′-Chloro-[1,1′-biphenyl]-4-yl)-3,4-dimethylfuran (**11**)*

The mixture of **10** (126 mg, 0.50 mmol), (*p*-Cl)$C_6H_4B(OH)_2$ (82 mg, 0.53 mmol), $Pd(OAc)_2$ (1.1 mg, 0.005 mmol), PPh_3 (3.9 mg, 0.015 mmol), and Na_2CO_3 (64 mg, 0.60 mmol) in *i*PrOH/H_2O (2:1, 1.4 mL) was stirred at 100–105 °C for 3 h under an Ar atmosphere. After cooling down to r.t., water was added to the mixture, which was extracted with AcOEt (×2). The combined organic phase was washed with water, brine, dried (Na_2SO_4) and concentrated. The obtained crude product (166 mg) was purified by SiO_2 (Note: "60 N spherical, neutral" was used instead of standard type)-column chromatography (hexane/AcOEt = 5:1) to give the desired product **11** (100 mg, 71%).

Pale green solid (recryst. from *i*PrOH); mp 126–129 °C; ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.01 (s, 3H), 2.22 (s, 3H), 7.24 (s, 1H7.41 (d, *J* = 8.6 Hz, 2H), 7.54 (d, *J* = 8.6 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 2H), 7.69 (d, *J* = 8.6 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$): δ = 8.4, 9.7, 117.4, 122.9, 125.6 (C), 126.9 (2C), 128.1 (2C), 128.9 (2C), 131.4, 133.3, 137.8, 137.9, 139.1, 148.3; IR (neat): ν_{max} = 2920, 2860, 1481, 1096, 1001, 816, 718 cm^{-1}; HRMS (DART): *m/z* calcd for $C_{18}H_{15}OCl$ $[M + H]^+$ 283.0890; found: 283.0890.

4. Conclusions

We developed an expedient synthetic approach to 5-(*m*- or *p*-bromo- and *p*-tosyloxyphenyl)-3-methyl-furan-2(5*H*)-ones and its 3,4-dimethyl analogues utilizing $TiCl_4$-mediated 2(5*H*)-furanone annulation. These molecules comprise a fundamentally important 2(5*H*)-furanone skeleton with *m*- or *p*-leaving moiety as a basic probe for the cross-coupling partner. Suzuki-Miyaura cross-coupling was successfully applied for *p*-bromo and *p*-tosyloxy substrates to afford the corresponding biphenyl products. In addition, a furan derivative prepared from a 2(5*H*)-furanone by DIBAL reduction underwent smoothly Suzuki-Miyaura cross-coupling to give the biphenyl analogue. The utility of the Ti-Claisen and the crossed Ti-direct aldol reactions is also demonstrated in recent asymmetric total syntheses of alternaric acid [11] and azaspirene [26].

Supplementary Materials: All materials (substrates and reagents) in this work are commercially available with inexpensive price. Copies of the ^1H, ^{13}C-NMR spectra for compounds **3a**, **4a**–**4e**, **8**–**11** are available in the supplementary information. They and molfiles can be found at http://www.mdpi.com/1422-8599/2016/4/M908.

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