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# Palladium-Catalyzed Cross-Coupling Reaction and Gold-Catalyzed Cyclization for Preparation of Ethyl 2-Aryl 2,3-Alkadienoates and α-Aryl γ-Butenolides†

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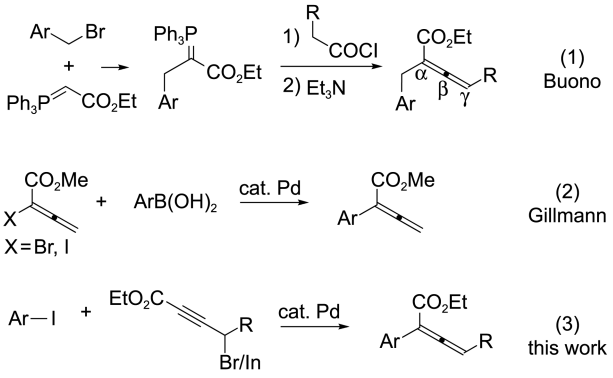
Efficient synthetic method for the preparation of ethyl 2-aryl-2,3-alkadienoates through Pd-catalyzed selective allenyl cross-coupling reactions of aryl iodides with organoindiums generated *in situ* from indium and ethyl 4-bromo-2-alkynoate was developed. The cyclization reaction of ethyl 2-aryl-2,3-alkadienoates catalyzed by $AuCl_3$ and AgOTf in the presence of AcOH or TfOH produced various α-aryl γ-butenolides or γ-substituted α-aryl γ-butenolides.

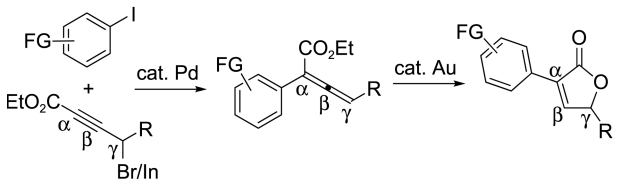
**Key Words :** Palladium, Gold, Indium, Cross-coupling reaction, Cyclization

## Introduction

Transition metal-catalyzed cross-coupling reactions represent an extremely versatile tool in organic synthesis.[1] Cross-coupling reactions leading to C-C bond formation are often key steps in a wide range of organic processes.[2] During the past decades, a variety of organometallic reagents, such as alkyl-, allyl-, allenyl-, benzyl-, vinyl- and arylmetals, have been used as nucleophiles in cross-coupling reactions.[1] Recently, because allenes have been widely used in organic reactions, development of novel synthetic methods of allenes has been required.[3] Especially, preparation of 2,3-alkadienoates is of synthetic importance and still a very challenging problem since they have been utilized in a variety of molecular transformations such as Michael addition, lactonization, cyclization and cycloaddition reactions.[3] Although several methods for preparation of 2,3-alkadienoates are known,[4] they seem to lack generality as far as 2-aryl substituted analogs are concerned. Traditionally, 2,3-alkadienoates were prepared from reaction of stabilized ylide with derivatives of benzyl bromide followed by treatment of acid chloride in the presence of triethylamine (eq 1).[5] Unfortunately, this method can not be applied in preparation of alkyl 2-aryl-2,3-alkadienoates because ylide do not react with aryl halide. Gillmann reported silver oxide-assisted Pd-catalyzed cross-coupling reaction of Pd-catalyzed cross-coupling reaction of methyl 2-halo-2,3-butadienoate with arylboronic acid to produce methyl 2-aryl-2,3-butadienoates (eq 2).[6] However, not only preparation of ethyl 2-halo-2,3-butadienoate but also introduction of substituent on γ-position is difficult.[7] Moreover, yield of cross-coupling reaction of methyl 2-halo-2,3-butadienoate with phenylboronic acid is variable (Br: 0 ~ 52%, I: 52 ~ 98%).[6] Recently, Pd-catalyzed cross-coupling reactions using organoindium reagents have been described.[8]




In addition, we reported Pd-catalyzed cross-coupling reactions,[9] addition reactions, and substitutions[10] of allylindiums, allenylindiums, 1,3-butadien-2-ylindiums, tetra(organo)indates and indium tri(organothiolates) with a variety of electrophiles. During the course of our research program aimed at finding new indium-mediated organic reactions,[11] we envisioned the possibility of ethyl 2,3-alkadien-2-yl cross-coupling reactions by using indium and ethyl 4-bromo-2-alkynoates.[12] Herein, we report that cross-coupling reaction of a variety of aryl iodides with organoindium reagents generated *in situ* from indium and ethyl 4-bromo-2-alkynoate produced ethyl 2-aryl-2,3-alkadienoates with complete regioselectivity and chemoselectivity (Scheme 1). In addition, subsequent treatment of these compounds with gold catalyst gave α-aryl γ-butenolides or γ-substituted α-aryl γ-butenolides showing antifungal activity (Scheme 1).[13]




**Scheme 1.** Preparation of ethyl 2-aryl-2,3-alkadienoates and their cyclization to α-aryl γ-butenolides having γ-substituent

†This paper is dedicated to Professor Eun Lee on the occasion of his honourable retirement.

**Table 1.** Optimization of Pd-catalyzed cross-coupling reactions[a]


| Entry | Met | Lignd | Solvent | Additive (equiv) | Time (h) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 | In | 16 mol % $Ph_3P$ | DMF | LiI (3) | 18 | 0 |
| 2 | In | 16 mol % $Ph_3P$ | DMF | LiCl (3) | 18 | 0 |
| 3 | In | 8 mol % Xantphos | DMF | LiI (3) | 24 | 0 |
| 4 | In | 8 mol % Xantphos | THF | LiI (3) | 15 | 0 |
| 5 | In | 8 mol % DPEphos | DMF | LiI (3) | 15 | 0 |
| 6 | In | 16 mol % (4-$CH_3O$-$C_6H_4$)$_3$P | DMF | LiI (3) | 12 | 0 |
| 7 | In | 16 mol % (4-$CH_3O$-$C_6H_4$)$_3$P | THF | NaI (1) | 12 | 0 |
| 8 | In | 16 mol % (4-$CF_3$-$C_6H_4$)$_3$P | DMF | LiI (3) | 3 | 0 |
| 9 | In | 16 mol % (4-$CF_3$-$C_6H_4$)$_3$P | THF | NaI (1) | 3 | 56 |
| 10 | In | 16 mol % (4-$CF_3$-$C_6H_4$)$_3$P | THF | NaI (1.5) | 3 | 58 |
| 11 | In | 16 mol % (4-$CF_3$-$C_6H_4$)$_3$P | DMF | NaI (1.5) | 5 | 0 |
| 12 | In | 16 mol % (4-$CF_3$-$C_6H_4$)$_3$P | THF | NaI (1.5) | 3 | 79[c] |
| 13 | In | - | DMF | LiI (3) | 10 | 0[d] |
| 14 | Mg | 16 mol % (4-$CF_3$-$C_6H_4$)$_3$P | THF | NaI (1.5) | | 0 |
| 15 | Zn | 16 mol % (4-$CF_3$-$C_6H_4$)$_3$P | THF | NaI (1.5) | | 0 |

[a]Reactions performed with In (1 equiv) and **2a** (1.5 equiv). [b]Isolated yield. [c]In (1.5 equiv) and **2a** (2.3 equiv) was used. [d]Pd(dppf)$Cl_2$ was used as a catalyst.

## Results and Discussion

Our initial study focused on Pd-catalyzed cross-coupling reactions of ethyl 4-iodobenzoate (**1a**) with organoindium reagent generated *in situ* from indium and ethyl 4-bromo-2-butynoate (**2a**)[14] (Table 1). Reaction of **1a** with organoindium did not proceed with 2 mol % $Pd_2dba_3CHCl_3$ and a variety of ligands such as $Ph_3P$, Xantphos,[15] DPEphos,[16] (4-$CH_3O$-$C_6H_4$)$_3$P and (4-$CF_3$-$C_6H_4$)$_3$P in the presence of MX (M = Li and Na, X = Cl and I) as an additive in DMF or THF (entries 1- 8). However, 2 mol % $Pd_2dba_3CHCl_3$ and 16 mol % (4-$CF_3$-$C_6H_4$)$_3$P in the presence of NaI (1 equiv) afforded selectively ethyl 2-(4-ethoxycarbonylphenyl)-2,3-butadienoate **3a** in 56% yield in THF, indicating that electron poor ligand is better than electron rich ligand (entry 7 *vs*. 9). In addition, comparison of solvents suggests that THF is critically important for a successful reaction (entry 11 *vs.* 12). Of the catalytic systems examined, the best results were obtained with 2 mol % $Pd_2dba_3CHCl_3$ and 16 mol % (4-$CF_3$-$C_6H_4$)$_3$P in the presence of NaI (1.5 equiv) in THF at 70 °C for 3 h, producing selectively **3a** in 79% yield (entry 12). There is no propargylic cross-coupling product formed. Organoindium generated *in situ* from indium (1.5 equiv) and **2a** (2.3 equiv) gave the best result as a coupling partner. The high selectivity of the present reaction was compared to Mg and Zn reagents. Under the optimum reaction conditions, reaction of **1a** with **2a** (1.8 equiv) and Mg (1.5 equiv) or Zn (1.5 equiv) in refluxing THF did not proceed (entries 14 and 15).

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to reactions of a variety of aryl iodides with organoindium reagent generated *in situ* from indium and ethyl 4-bromo-2-alkynoates (Table 2). Reaction of iodobenzene (**1b**) with **2a** and indium gave selectively ethyl 2-phenyl-2,3-butadienoate (**3b**) in 85% yield (entry 1). However, bromobenzene and chlorobenzene did not react with **2a**. Electronic variation on the aromatic substituents, such as methoxy, acetyl, formyl, ethoxycarbonyl and *N*-benzylamido group, did not diminish the efficiency and selectivity in Pd-catalyzed cross-coupling reactions (entries 2-9). Treatment of **1c** having electron-donating group (MeO) with organoindium produced the desired products **3c** in 65% yield (entry 2). 4-Iodoacetophenone (**1d**) was subjected to cross-coupling reaction with **2a** and indium, affording **3d** in 81% yield (entry 3). The reaction conditions were mild enough to tolerate a formyl group, which would be incompatible with other organometallic reagents (entry 4). Ethyl iodobenzoate (**1a**) and *N*-benzyl 4-iodobenzamide (**1f**) worked equally well with organoindium generated *in situ* from **2b** and indium, producing 2-aryl-2,3-pentadienoates (**3f** and **3g**) in 79% and 76% yields, respectively (entries 5 and 6). Subjecting **1b** to ethyl 4-bromo-2-heptynoate (**2c**) and indium provided **3h** in 85% yield (entry 7). 3-Iodoanisole (**1c**) turned out to be compatible with the employed reaction conditions, producing **3i** in 64% yield (entry 8). We were pleased to obtain ethyl 2-(4-ethoxycarbonylphenyl)-2,3-heptadienoate **3j** in 77% yield from the reaction of **1a** with organoindium under the optimum reaction conditions (entry 9). Treatment of vinyl triflate **1g** with **1a** and indium in the presence of KBr (1.5 equiv) instead of NaI provided selectively the corresponding products **3k** in 63% yield (entries 10).

Next, synthetic utility of 2-aryl-2,3-alkadienoates was demonstrated by applying them in the efficient synthesis of α-aryl γ-butenolides or γ-substituted α-aryl γ-butenolides which are important skeleton of antifungals.[13] γ-Substituted α-aryl γ-butenolides were prepared by Pd-catalyzed cross-coupling reaction of α-bromo-γ-butenolides with arylboronic acid under microwave heating condition (eq 4).[17] Recently,

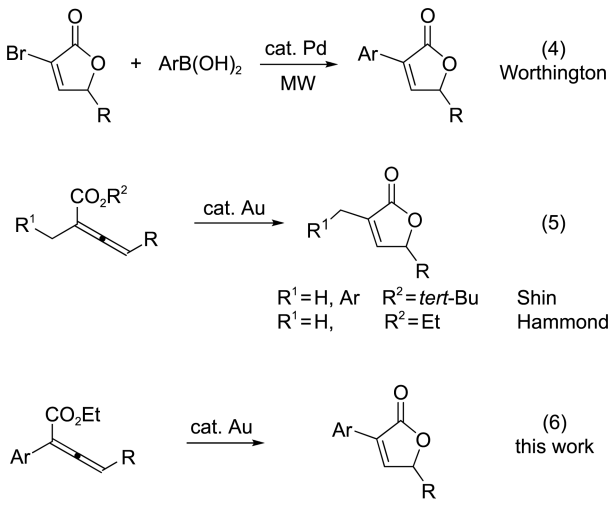
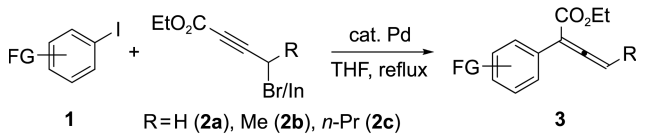
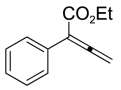
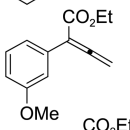
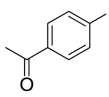
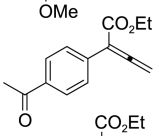
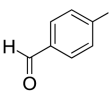
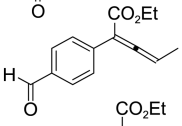
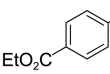
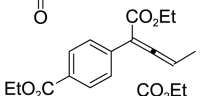
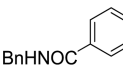
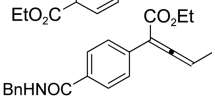
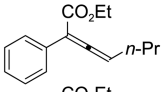
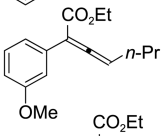
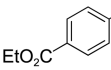
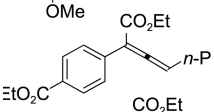
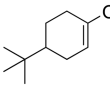
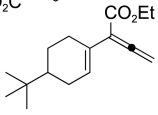


**Table 2.** Preparation of ethyl 2-aryl-2,3-alkadienoates *via* Pd-catalyzed cross-coupling reactions with organoindium[a]




**1** R=H (**2a**), Me (**2b**), *n*-Pr (**2c**) **3**

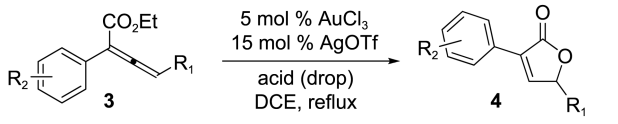
| Entry | Aryl Halide | | R | Time (h) | Lignd | | Yield[b] (%) |
|---|---|---|---|---|---|---|---|
| 1 |  | **1b** | H | 2 |  | **3b** | 85 |
| 2 |  | **1c** | H | 2 |  | **3c** | 65 |
| 3 |  | **1d** | H | 1 |  | **3d** | 81 |
| 4 |  | **1e** | Me | 2 |  | **3e** | 72 |
| 5 |  | **1a** | Me | 1 |  | **3f** | 79 |
| 6 |  | **1f** | Me | 1 |  | **3g** | 76 |
| 7 |  | **1b** | *n*-Pr | 2 |  | **3h** | 85 |
| 8 |  | **1c** | *n*-Pr | 2 |  | **3i** | 64 |
| 9 |  | **1a** | *n*-Pr | 1 |  | **3j** | 77 |
| 10 |  | **1g** | H | 2 |  | **3k** | 63[c] |

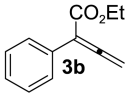
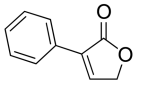
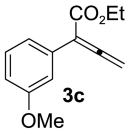
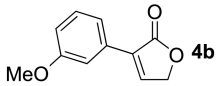
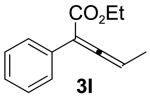
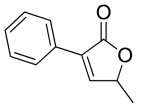
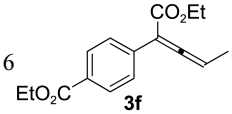
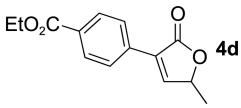
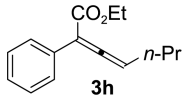
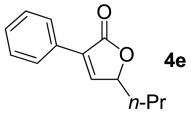
[a]Reactions performed with 2 mol % $Pd_2dba_3CHCl_3$ and 16 mol % (4-$CF_3$-$C_6H_4$)$_3$P in the presence of NaI (3 equiv) in refluxing THF. Organoindium was obtained from In (1.5 equiv) and **2** (2.3 equiv). [b]Isolated yields. [c]KBr (1.5 equiv) was used instead of NaI.

Shin and Hammond reported gold-catalyzed cyclization of *tert*-butyl or ethyl 2-methyl or 2-benzyl-2,3-alkadienoates (eq 5).[18]

Encouraged by these and our results related to Au-catalyzed cyclization,[10b,19] the present method was applied in gold-catalyzed cyclization resulting in the formation of γ-substituted α-aryl γ-butenolides. The results are summarized in Table 3. Although gold-catalyzed cyclization of *tert*-butyl 2,3-alkadienoates was reported (eq 5),[18a] this shows only the synthetic method of α-methyl or α-benzyl γ-butenolides because synthesis of 2-aryl-2,3-alkadienoates is impossible.[5] Reaction of **3b** with a variety of gold catalysts, such as 5 mol

**Table 3.** Cyclization of ethyl 2-aryl-2,3-alkadienoates catalyzed by gold




| Entry | Substrate | Acid[a] | Time (h) | Product | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 |  **3b** | AcOH | 2 |  **4a** | 85 (67)[c] |
| 2 |  **3c** | AcOH | 3 | | 70 |
| 3 | | TfOH | 3 |  **4b** | 50 |
| 4 | | TfOH | 5 | | 0[d] |
| 5 |  **3l** | TfOH | 1 |  **4c** | 75 |
| 6 |  **3f** | TfOH | 2 |  **4d** | 72 |
| 7 |  **3h** | TfOH | 3 |  **4e** | 59 |

[a]Acid of one drop (ca. 10 mol %) as an additive was used. [b]Isolated yield. [c]5 mol % AuCl and 5 mol % AgOTf was used as a catalyst. [d]Au catalyst was not used.

% $AuCl_3$/15 mol % AgOTf, 5 mol % $AuCl_3$/15 mol % $AgBF_4$, 5 mol % $Ph_3PAuCl$/5 mol % AgOTf, 5 mol % $Ph_3PAuCl$ /5 mol % $AgBF_4$ or 5 mol % $Ph_3PAuCl$ /5 mol % $AgSbF_6$, did not proceed in DCE or $CH_2Cl_2$. However, when alkadienota **3b** was treated with 5 mol % $AuCl_3$ and 15 mol % AgOTf in the presence of acetic acid (one drop) in DCE (110 °C, 2 h), α-phenyl γ-butenolide (**4a**) was producedin 85% yield (entry 1). The use of 5 mol % AuCl/5 mol % AgOTf afforded **4a** in 67% yield. Role of acid in cyclization might accelerate protonation of vinyl gold intermediate that is converted to γ-butenolide. Under the optimum reaction conditions, 2-(3-methoxyphenyl)-2,3-butadienoate **3c** was converted to α-(3-methoxyphenyl)-γ-butenolide in 70% (AcOH) and 50% (TfOH) yield (entries 2 and 3). A control experiment with AcOH or TfOH (one drop or 1 equiv) in the absence of $AuCl_3$ and AgOTf did not afford the desired product, indicating that gold catalyst is essential for cyclization (entry 4). In the case of 2-aryl-2-alkadienoates (**3l** and **3f**) having methyl group on C4-position, the desired products (**4c** and **4d**) was produced in 75% and 72% yields, respectively, using TfOH (entries 5 and 6). Alkadienoate **3h** was cyclized by 5 mol % $Ph_3PAuCl$/5 mol % AgOTf in the presence of TfOH, producing the corresponding γ-butenolide **4e** in 59% yield (entry 7).

## Conclusion

In conclusion, we have developed an efficient synthetic method for the preparation of ethyl 2-aryl-2,3-alkadienoates through Pd-catalyzed selective allenyl cross-coupling reactions of aryl iodides with organoindiums generated *in situ* from indium and ethyl 4-bromo-2-alkynoate. Because introduction of aryl group to C2-position of 2,3-alkadienoate is difficult, this method would pave a new way to the synthesis of a wide range of functionalized 2-aryl-2,3-alkadienoates. The cyclization reaction of ethyl 2-aryl-2,3-alkadienoates catalyzed by $AuCl_3$ and AgOTf in the presence of AcOH or TfOH produced various α-aryl γ-butenolides or γ-substituted α-aryl γ-butenolides. Because these compounds are important skeleton of antifungals, the study of further applications of this methodology is now underway.

## Experimental Section

**Ethyl 2-(4-ethoxycarbonylphenyl)-2,3-butadienoate (3a):** To a suspension of $Pd_2dba_3CHCl_3$ (6.2 mg, $0.6 \times 10^{-2}$ mmol) and ($p$-$CF_3$-$C_6H_4$)$_3$P (22.0 mg, $4.8 \times 10^{-2}$ mmol) in THF (0.5 mL) was added ethyl 4-iodobenzoate (**1a**) (50.5 mL, 0.3 mmol) at room temperature under nitrogen atmosphere. After being stirred for 30 min, organoindium reagent generated in situ from indium (52.0 mg, 0.45 mmol), sodium iodide (67.5 mg, 0.45 mmol) and **2a** (129.0 mg, 0.68 mmol) in THF (1.0 mL) was added and the mixture was stirred at 70 °C for 2 h. The reaction mixture was quenched with saturated $NaHCO_3$. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc:hexane = 1:30) to give **3a** (62.0 mg, 0.24 mmol, 79%). $^1$H NMR (400 MHz, $CDCl_3$) δ 8.02 ( d, $J$ = 8.44 Hz, 2H), 7.60 (d, $J$ = 8.44 Hz, 2H), 5.48 (s, 2H), 4.38 (q, $J$ =7.09 Hz, 2H), 4.30 (q, $J$ = 7.12 Hz, 2H), 1.39 (t, $J$ = 7.09 Hz, 3H), 1.33 (t, , $J$ = 7.12 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 216.2, 166.7, 165.9, 137.1, 129.90, 129.86, 128.7, 103.0, 81.1, 61.9, 61.4, 14.7, 14.6; IR (film) 2982, 1953, 1716, 1607, 1447, 1366, 1275, 1104, 1021, 704 cm$^{-1}$; HRMS (EI) calcd for $C_{15}H_{16}O_4$ $M^+$ 260.1049, found 260.1046.

**3-Phenyl-5*H*-furan-2-one (4a):** A suspension of $AuCl_3$ (4.5 mg, $1.5 \times 10^{-2}$ mmol, 5 mol %) and AgOTf (11.6 mg, $4.5 \times 10^{-2}$ mmol, 15 mol %) in DCE (0.8 mL) was stirred at 25 °C for 5 min. A solution of ethyl 2-phenyl-2,3-butadienoate (**3b**) (56.0 mg, 0.3 mmol) in DCE (0.4 mL) and AcOH (one drop) were added to catalyst under nitrogen atmosphere. After being stirred for 2 h at 70 °C, the reaction mixture was quenched with water. The aqueous layer was extracted with $CH_2Cl_2$ (15 mL × 2) and the combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc: hexane = 1:5 ) gave **4a** (41mg, 0.26 mmol, 85%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, $J$ = 4.02 Hz, 2H), 7.65 (t, $J$ = 1.95 Hz, 1H), 7.45-7.37 (m, 3H), 4.92 (d, $J$ = 4.02 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.7, 144.8, 132.0, 129.9, 129.8, 129.1, 127.4, 70.0; IR (film) 3095, 1747, 1493, 1447, 1345, 1115, 1057, 958, 828 cm$^{-1}$; HRMS (EI) calcd for $C_{10}H_8O_2$ $M^+$ 160.0524, found 160.0525.

**3-(3-Methoxy-phenyl)-5*H*-furan-2-one (4b):** $^1$H NMR (400 MHz, $CDCl_3$) d 7.65 (s, 1H), 7.45 (d, $J$ = 1.97, 1H), 7.41 (d, $J$ = 7.71, 1H), 7.33 (t, $J$ = 7.93 Hz, 1H), 6.94 (d, $J$ = 8.15, 1H), 4.92 (d, J = 1.97 Hz, 2H), 3.84 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.5, 160.1, 145.1, 131.8, 131.2, 130.1, 119.8, 115.5, 112.8, 69.9, 55.7; IR (film) 2938, 1751, 1601, 1580, 1487, 1347, 1217, 1113, 793 cm$^{-1}$; HRMS (EI) calcd for $C_{11}H_{10}O_3$ $M^+$ 190.0630, found 190.0630.

**5-Methyl-3-phenyl-5*H*-furan-2-one (4c):** $^1$H NMR (400 MHz, $CDCl_3$) δ 7.87-7.84 (m, 2H), 7.55 (d, $J$ = 1.80 Hz, 1H), 7.42-7.38 (m, 3H), 5.16 (td, $J$ = 6.83, 1.80 Hz, 1H), 1.52 (d, $J$ = 6.83 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.1, 149.4, 131.8, 129.9, 129.7, 129.1, 127.5, 19.6; IR (film) 2981, 1754, 1492, 1449, 1321, 1132, 1112, 972 cm$^{-1}$; HRMS (EI) calcd for $C_{11}H_{10}O_2$ $M^+$ 174.0681, found 174.0681.

**Ethyl 4-(5-methyl-2-oxo-2,5-dihydrofuran-3-yl)benzoate (4d):** $^1$H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, $J$ = 6.68 Hz, 2H), 7.94 (d, $J$ = 6.68 Hz, 2H), 7.68 (d, $J$ = 1.79 Hz, 1H), 5.19 (td, J = 6.89, 1.79 Hz, 1H), 4.40 (q, $J$ = 7.12 Hz, 3H), 1.54 (d, $J$ = 6.89 Hz, 3H), 1.41 (t, $J$ = 7.12 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 171.6, 166.5, 151.2, 134.0, 131.4, 131.1, 130.2, 127.4, 61.6, 19.4, 14.7; IR (film) 2982, 1756, 1714, 1368, 1276, 1184, 1108, 974 cm$^{-1}$; HRMS (EI) calcd for $C_{14}H_{14}O_4$ $M^+$ 246.0892, found 246.0894.

**3-Phenyl-5-propyl-5*H*-furan-2-one (4e):** $^1$H NMR (400 MHz, $CDCl_3$) δ 7.86-7.84 (m, 2H), 7.55 (d, $J$ = 1.78 Hz, 1H), 7.41-7.38 (m, 3H), 5.07-5.03 (m, 1H), 1.80-1.71 (m, 2H), 1.58-1.52 (m, 2H), 1.00 (t, $J$ = 7.33 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 172.2, 148.5, 131.9, 130.0, 129.7, 129.1, 127.4, 80.8, 36.0, 18.9, 14.3; IR (film) 2961, 1754, 1492, 1449, 1329, 1118, 1028, 965, 795 cm$^{-1}$; HRMS (EI) calcd for $C_{11}H_{10}O_2$ $M^+$ 202.0994, found 202.0990.

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