# An Efficient Approach to Original Substituted 2-Arylidene-2*H*-[1,4]-oxazin-3(4*H*)-ones via a Tandem Intramolecular P(O→C) Migration/Horner–Wadsworth–Emmons Olefination Sequence

Elise Claveau, Isabelle Gillaizeau,* Gérard Coudert*

Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, Rue de Chartres, B.P. 6759, 45067 Orléans, Cedex 2, France
Fax +33(2)38417281; E-mail: isabelle.gillaizeau@univ-orleans.fr; E-mail: gerard.coudert@univ-orleans.fr
*Received 23 September 2008*

**Abstract:** A useful tool for the synthesis of 2-arylidene-2*H*-[1,4]-oxazin-3(4*H*)-one derivatives is described. Starting from bisvinylphosphate intermediate, the key step is an intramolecular P(O→C) migration combined with a Horner–Wadsworth–Emmons olefination as a one-pot procedure.

**Key words:** vinylphosphate, Horner–Wadsworth–Emmons olefination, 1,3-phosphorus migration, oxazine, arylidene

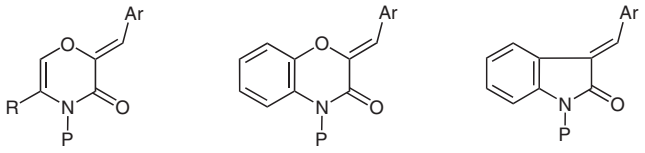



**Figure 1**

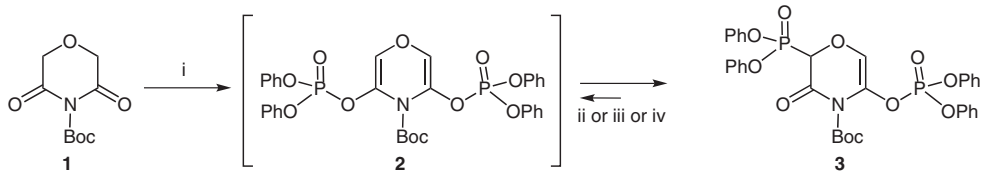
The versatility and synthetic utility of the enol phosphate function in organic synthesis have been largely demonstrated in the recent literature.[1] During the course of our studies directed toward the synthesis of new nitrogen containing derivatives, we intended to prepare 2-arylidene-2*H*-[1,4]-oxazin-3(4*H*)-ones derivatives **I** (Figure 1). While benzofused derivatives like 2-arylidene-2*H*-[1,4]-benzoxazin-3(4*H*)-ones **II**[2] or also arylidene-1,3-dihydroindol-2-ones **III**[3] have been largely studied because of their biological activities on the central nervous system or their efficiency as kinase inhibitors, there has been, to the best of our knowledge, no report on the synthesis of 2-arylidene-2*H*-[1,4]-oxazin-3(4*H*)-one derivatives **I**. In addition, in recent years the synthesis of α-methylene-γ-lactams, isosteric analogues of the naturally occurring α-methylene-γ-lactones, has received considerable attention as a consequence of the proven biological properties of this motif.[4] By using our previously described methodology based on palladium-catalyzed cross-coupling reactions of vinyl phosphate intermediates,[5] we want to report herein an efficient access to a variety of substituted 2-arylidene-2*H*-[1,4]-oxazin-3(4*H*)-one derivatives **I**. The latter might be not only of potential interest in terms of biological activity and of synthesis but also it would allow access to new heterocyclic scaffolds.

A few years ago, Wiemer et al.[6] demonstrated that enol phosphates derived from five- and six-membered rings undergo a 1,3-phosphorus migration to afford β-ketophosphonates upon deprotonation with LDA. Since Wiemer's initial report, the scope of this rearrangement has been expanded to include cyclic enones, esters, lactones, and lactams, some mechanistic information has been generated and diastereoselective variant has been unveiled.[7] This elegant rearrangement has given access to phosphono ketones that had been inaccessible or difficult to obtain by classical methods until then. Taking into account this result, we postulated that functionalized 2-arylidene-2*H*-[1,4]-oxazin-3(4*H*)-one derivatives **I** could be obtained via an intramolecular P(O→C) migration after basic treatment of the bisvinylphosphate **2** combined successively with a Horner–Wadsworth–Emmons olefination[8] and a palladium cross-coupling reaction on the remaining enol phosphate function.

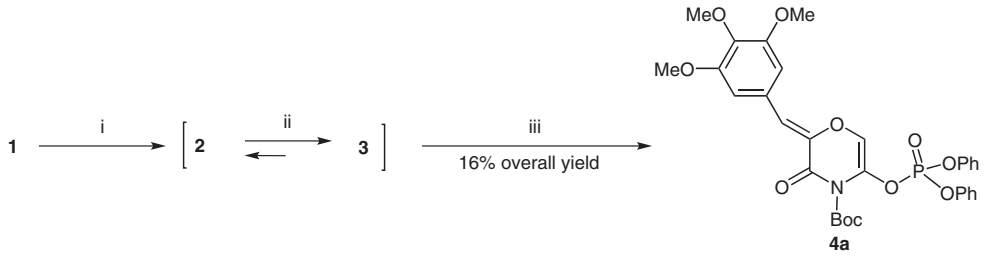
In order to demonstrate the feasibility of this strategy and to get the best yields, different approaches were tested. First of all, we tried to isolate the intermediary phosphonate **3** before performing the Horner–Wadsworth–Emmons olefination. To this aim and as previously reported,[5c] treatment of the *N*-Boc derivative **1** with KHMDS (2.5 equiv) in the presence of HMPA (2.5 equiv) in THF at –78 °C provided a bispotassium enolate which was immediately trapped by reaction with diphenylchlorophosphate (2.2 equiv, THF, –78 °C, 15 min). Without isolation, this mixture was exposed to additional KHMDS (1 equiv). After stirring for one hour at –78 °C, the bisvinylphosphate **2** rearranged through an intramolecular migration of the diphenyl phosphoryl group from oxygen to the α-carbon to provide the required α-phosphonolactam **3**.[9] After purification by silica gel chromatography, the α-phosphonolactam **3**[10] was isolated in only 20% yield together with 9% of the parent bisvinylphosphate **2**. Even if the conversion of vinylphosphate **2** into α-phosphonolactam **3** corresponds to a balanced reaction, a very clean rearrangement was observed based upon the TLC control of the mixture. So the low yield may be attributed to the instability of the α-phosphonolactam **3**.

As this step suffers from problem of reproducibility, alternative bases were studied. No improvement was observed when LiHMDS [(Scheme 1, (iii) conditions] was used as

*SYNLETT* 2009, No. 2, pp 0263–0267
Advanced online publication: 15.01.2009
DOI: 10.1055/s-0028-1087665; Art ID: D33908ST




**Scheme 1** *Reagents and conditions*: (i) KHMDS (2.5 equiv), HMPA (2.5 equiv), THF, $ClP(O)(OPh)_2$ (2.2 equiv), –78 °C, 15 min; (ii) KHMDS (1 equiv), THF, –78 °C, 1 h, **3** (20% via not isolated **2**), or (iii) LiHMDS (1 equiv), **3** (17% via not isolated **2**), or (iv) *n*-BuLi (1 equiv), **3** (32% via isolated **2**).




**Scheme 2** *Reagents and conditions*: (i) KHMDS (2.5 equiv), HMPA (2.5 equiv), THF, $ClP(O)(OPh)_2$ (2.2 equiv), –78 °C, 15 min (**2** not isolated); (ii) KHMDS (1 equiv), THF, –78 °C, 1 h (**3** not isolated); (iii) 3,4,5-trimethoxybenzaldehyde (2 equiv), 1 h, 0 °C (16% overall yield).

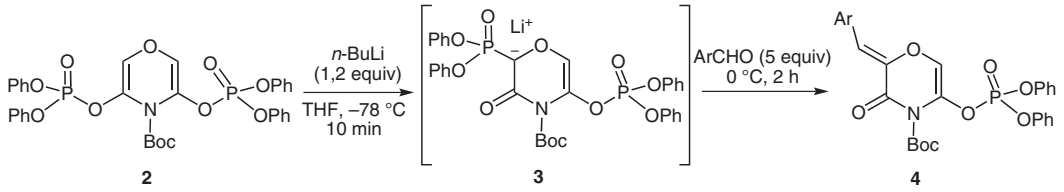
a base even when changing the sequence of reagent additions, and varying the temperature for enolate formation. More encouraging results were obtained by using *n*-butyllithium [Scheme 1, (iv) conditions]. In this case, the 1,3-phosphorus migration reaction was tested directly from the worked up bisvinylphosphate **2**, obtained in 64% yield the from *N*-Boc morpholine-3,5-dione **1**.[11] The desired α-phosphonolactam **3** was then isolated in just 32% yield as the only product.

To circumvent this problem and to improve the general yield, we attempted to perform the Horner–Wadsworth–Emmons olefination as a one-pot procedure without isolating the intermediary phosphonate **3** (Scheme 2). Starting from *N*-Boc morpholine-3,5-dione **1** and using KHMDS as a base, after a complete conversion of the vinylphosphate **2** into α-phosphonolactam **3** (TLC control), 3,4,5-trimethoxybenzaldehyde (2 equiv) was then added at –78 °C to induce the Horner–Wadsworth–Emmons olefination. The mixture was quickly warmed to 0 °C (1 h) and the desired exoarylidene derivative **4a** was isolated as a single stereoisomer.[12a] The small coupling constant ($J < 5$ Hz) observed between the exocyclic vinyl proton and the carbon of the carbonyl ($^3J_{C-H} = 3{,}5$ Hz) confirmed the *(Z)*-geometry of the introduced double bond.[12] Unfortunately, this one-pot procedure was characterized by a low yield (16%).

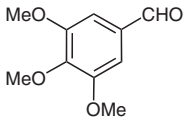
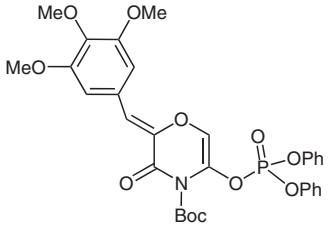
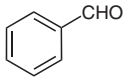
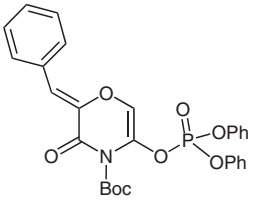
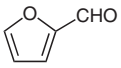
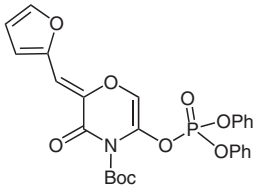
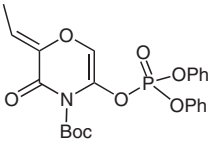
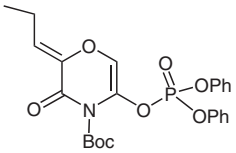
To achieve the intramolecular P(O→C) migration and the Horner–Wadsworth–Emmons olefination as a one-pot procedure, we next examined the protocol using *n*-BuLi as a base (Table 1). In this case, we started directly from the isolated bisvinylphosphate **2**, prepared as reported above. Treatment of **2** with *n*-BuLi (1.2 equiv) at –78 °C in THF for 10 minutes led to the formation of α-phosphonolactam **3** via an 1,3-phosphorus migration. The use of this intermediate in the Horner–Wadsworth–Emmons reaction was validated by addition of various aldehydes to the crude mixture to give the *exo*-alkylidene or -arylidene derivatives **4a**–**e**[13] which were isolated, albeit in fair or modest yields (Table 1). The slight instability of the alkylidene derivatives **4d** and **4e** could explain why the yields were so moderate in this case (Table 1, entries 4 and 5). Unfortunately, no improvement was observed by performing the Horner–Wadsworth–Emmons olefination as a separate step on the isolated α-phosphonolactam **3**. In fact, arylidenes **4** were thus obtained with comparable yields. Accordingly, it appears that this is the limiting step. In addition to the convenient tandem 1,3-phosphorus migration–Horner–Wadsworth–Emmons olefination sequence, one of the attractive features of our approach lies in its inherent versatility since a wide range of aldehydes could be used. The remaining enol phosphate function could eventually be subjected to various reactions.

In order to achieve our synthetic route to 2-arylidene-2*H*-[1,4]-oxazin-3(4*H*)-one derivatives **I**, palladium-catalyzed reactions were then investigated on enol phosphates **4**. The Stille coupling reaction[14] was performed with various tin reagents in the presence of catalytic $Pd(PPh_3)_4$ and anhydrous LiCl in refluxing THF. The desired original compounds **5a**–**c**[15] were isolated in modest yields (Table 2, entries 1–4). In addition, treatment of enol phosphate **4b** with triethylammonium formate, palladium acetate and triphenylphosphine[5c] in THF gave the basic heterocyclic system **5e** isolated in fair yield (48% yield, Table 2, entry 5). It is noteworthy that by submitting vinylphosphate **4** to classical basic Suzuki coupling conditions [$PhB(OH)_2$,$PdCl_2(PPh_3)_2$, $Na_2CO_3$ 2 M, THF], a degradation reaction was observed.

**Table 1** Rearrangement into α-Phosphonolactam **3** Combined with Horner–Wadsworth–Emmons Olefinations




**2** **3** **4**

| Entry | Aldehydes | Products **4** | Yield (%)[a] |
|---|---|---|---|
| 1 |  |  | **4a** 42 |
| 2 |  |  | **4b** 56 |
| 3 |  |  | **4c** 35 |
| 4 | MeCHO |  | **4d** 22 |
| 5 | $MeCH_2CHO$ |  | **4e** 36 |

[a] Yields are calculated for the two-step reaction starting with bisvinylphosphate **2**.

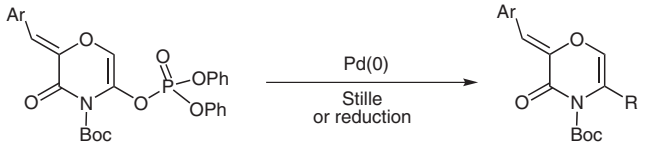
Because of their potential biological activity, the selected 2-arylidene-2*H*-[1,4]-oxazin-3(4*H*)-one derivatives **5a–e** were then tested on a variety of highly purified kinases (CK1, CDK5/p25, GSK-3α/β, DYRK1A)[16,17] (Table 3). In the CDK inhibitors family, the most advanced molecule is the purine analogue [R-roscovitine (CYC-202)].[18] Unfortunately, in all cases the kinases tested were poorly or not inhibited ($IC_{50}$ >10 μm).

To sum up, we have developed a new and easy method that provides a useful tool for the synthesis of 2-arylidene-2*H*-[1,4]-oxazin-3(4*H*)-one derivatives via an efficient tandem 1,3-phosphorus migration/Horner–Wadsworth–Emmons olefination sequence. In addition, it is worth noting that the presence of different functional groups in many positions of these heterocycles makes such compounds useful for further structural modifications and suitable as intermediates for more complex polycyclic structures (via Diels–Alder cycloaddition for instance). Experiments designed to explore the potentiality offered by this original heterocyclic system are in progress and will be described in due course.

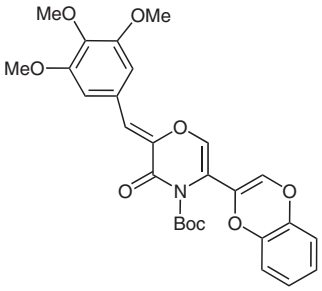
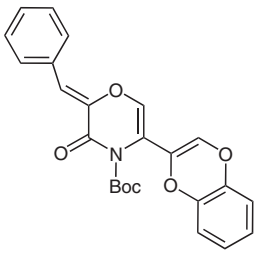
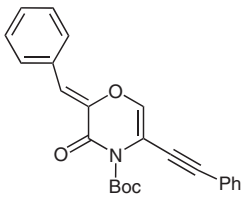
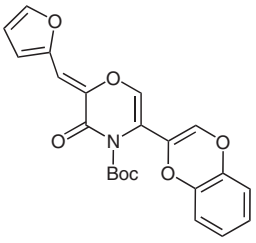
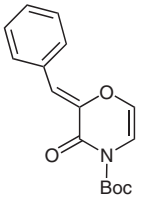
## Acknowledgement

This research was supported by La Ligue Contre le Cancer (comité du Loiret) and la FRM section Orléans. The authors thank Laurent

**Table 2** Preparation of Functionalized 2-Arylidene-2*H*-[1,4]-oxazin-3(4*H*)-one **5a–e** via Palladium-Catalyzed Reaction




**4** **5**

| Entry | Enol phosphate **4** | Product | Yield (%) |
|---|---|---|---|
| 1[a] | **4a** |  | **5a** 59 |
| 2[a] | **4b** |  | **5b** 27 |
| 3[a] | **4b** |  | **5c** 21 |
| 4[a] | **4c** |  | **5d** 39 |
| 5[b] | **4b** |  | **5e** 48 |

[a] Conditions: $Pd(PPh_3)_4$ (10 mol%), $RSnBu_3$ (2.5 equiv), LiCl (3 equiv), THF, 2–3 h, reflux.
[b] Conditions: HCOOH (4 equiv), $Et_3N$ (6 equiv), $Pd(OAc)_2$ (0.08 equiv), $Ph_3P$ (0.16 equiv), DME, reflux, 30 min.

**Table 3** Kinase Inhibition Values ($IC_{50}$ in μm) for Compounds **5a–e**

| Compounds | CK1 | CDK5/p25 | GSK-3α/β | DYRK1A |
|---|---|---|---|---|
| **5a–e** | >10 | >10 | >10 | >10 |
| (*R*)-roscovitine | 0.45 | 0.16 | 130 | 3.1 |

Meijer and Olivier Lozach (Cell Cycle Group UMR 7150 & UPS2682 Roscoff, France) for the biological tests on kinases.

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(9) α-Phosphonolactams analogous to **3** (Scheme 1) have been prepared previously, in a number of different ways, and used

in olefination processes. For recent representative examples, see: (a) Gois, P. M. P.; Afonso, C. A. M. *Eur. J. Org. Chem.* **2003**, 3798. (b) Gois, P. M. P.; Afonso, C. A. M. *Tetrahedron Lett.* **2003**, *44*, 6571. (c) Bower, J. F.; Svenda, J.; Williams, A. J.; Charmant, J. P. H.; Lawrence, R. M.; Szeto, P.; Gallagher, T. *Org. Lett.* **2004**, *6*, 4727. (d) Sudau, A.; Münch, W.; Bats, J.-W.; Nubbemeyer, U. *Eur. J. Org. Chem.* **2002**, 3315.

(10) The 1,3-phosphorus migration reaction was easily followed by TLC.

**Synthesis of 4-(*tert*-Butoxycarbonyl)-2-(diphenoxyphosphoryl)-5-(diphenoxyphosphoryloxy)-3-oxo-2,3-dihydro-4*H*-[1,4]-oxazine (3)**

A solution of KHMDS (13.94 mL, 0.5 M in toluene, 6.97 mmol) in THF (20 mL) was cooled to –78 °C under argon. Subsequently, a solution of **1** (0.500 g, 2.32 mmol), distilled diphenyl chlorophosphate (1.373 g, 5.11 mmol), and distilled HMPA (1.041 g, 5.81 mmol) in THF (15 mL) was added dropwise over 5 min. After 15 min at –78 °C, KHMDS was added (4.65 mL, 2.32 mmol). After an additional hour at –78 °C, the reaction mixture was diluted with $Et_2O$ (85 mL). Water (125 mL) was then added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over anhyd $MgSO_4$, and concentrated. Flash chromatography (PE–EtOAc, 7:3) afforded **3** (0.315 g, 20%) as a pale yellow oil; $R_f$ = 0.56 (PE–EtOAc, 6:4). IR (NaCl): 3068, 2988, 2930, 1790, 1489, 1206 $cm^{-1}$. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.07–7.26 (m, 20 H), 6.65 (d, $^4J_{HP}$ = 2.8 Hz, 1 H), 4.92 (d, $^2J_{HP}$ = 16.0 Hz, 1 H), 1.42 (s, 9 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 160.1 (s, $J_{C,P}$ = 4.5 Hz), 150.5 (s, $J_{C,P}$ = 7.5 Hz), 150.4 (s, $J_{C,P}$ = 6.5 Hz), 150.3 (s, $J_{C,P}$ = 7.6 Hz), 150.0 (s, $J_{C,P}$ = 9.6 Hz), 146.3 (s), 132.5 (s, $J_{C,P}$ = 8.9 Hz), 130.4 (d), 130.3 (d), 126.4 (d), 126.2(d), 122.9 (d, $J_{C,P}$ = 5.1 Hz), 121.1 (d), 121.0(d), 120.4 (d, $J_{C,P}$ = 2.1 Hz), 120.3 (d, $J_{C,P}$ = 2.1 Hz), 87.0(s), 74.8 (d, $J_{C,P}$ = 160.1 Hz), 28.0(q). MS (IS): *m/z* = 680.5 $[M + H]^+$, 702.0 $[M + Na]^+$.

(11) As previously reported, the synthesis of bisvinylphosphate **2** from *N*-Boc morpholine-3,5-dione **1** was optimal by using KHMDS as a base (cf. ref. [5c])

(12) (a) Yu, J. S.; Wiemer, D. F. *J. Org. Chem.* **2007**, *72*, 6263. (b) Vögeli, U.; Von Philipsborn, W.; Nagarajan, K.; Nair, M. D. *Helv. Chim. Acta* **1978**, *61*, 607. (c) Cabiddu, S.; Floris, C.; Melis, S.; Sotgiu, F.; Cerioni, G. *J. Heterocycl. Chem.* **1986**, *23*, 1815.

(13) **General Procedure for the Wiemer Rearrangement Followed by the Horner–Wadsworth–Emmons Reaction – Synthesis of (6*Z*)-4-(*tert*-Butoxycarbonyl)-6-(3,4,5-trimethoxybenzylidene)-5,6-dihydro-5-oxo-4*H*-[1,4]-oxazin-3-yl Diphenyl Phosphate (4a)**

A solution of the bisvinylphosphate **2**[5c] (0.500 g, 0.74 mmol) in THF (7.5 mL) was cooled to –78 °C under argon. Subsequently, *n*-BuLi (0.552 mL, 1.6 M in hexane, 0.88 mmol) was added dropwise, and the reaction mixture was stirred for 10 min at –78 °C. A solution of 3,4,5-trimethoxybenzaldehyde (0.722 g, 3.68 mmol) in THF (2 mL), previously dried over MS 4 Å, was then added dropwise. After 15 min at –78 °C and 150 min at 0 °C, the reaction mixture was diluted with $Et_2O$ (10 mL). Water (10 mL) was then added, and the mixture was extracted with EtOAc. The organic phase was washed with brine, dried over anhyd $MgSO_4$, and concentrated. Flash chromatog-raphy (PE–EtOAc, 8:2) afforded **4a** (0.193 g, 42%) as a yellow oil. IR (NaCl): 2926, 1693, 1446, 1240, 1043 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$): δ = 7.20–7.41 (m, 20 H), 6.90 (s, 2 H), 6.71 (d, $^4J_{HP}$ = 3.3 Hz, 1 H), 6.66 (s, 1 H), 3.87 (s, 3 H), 3.85 (s, 6 H), 1.50 (s, 9 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 156.2(s), 152.6 (s), 150.1 (s, $J_{C,P}$ = 7.4 Hz), 146.7 (s), 139.1 (s), 138.7 (s), 130.4 (s, $J_{C,P}$ = 7.6 Hz), 130.1(d), 127.1(s), 126.1(d), 124.5 (d), 121.4 (d, $J_{C,P}$ = 4.9 Hz), 120.0 (d, $J_{C,P}$ = 4.9 Hz), 108.0(d), 86.2 (s), 60.9 (q), 56.1 (q), 27.6(q). MS (IS): *m/z* = 626.5 $[M + H]^+$, 648.5 $[M + Na]^+$.

(14) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

(15) **General Procedure for Stille-Type Coupling Reactions – Synthesis of (2*Z*)-4-(*tert*-Butoxycarbonyl)-2-(3,4,5-trimethoxybenzylidene)-5-{benzo[*b*][1,4]dioxin-2-yl}-2,3-dihydro-3-oxo-[1,4]-oxazine (5a)**

To a stirred solution of enol phosphate **4a** (0.517 g, 0.83 mmol) in THF (16 mL), {benzo[*b*][1,4]dioxin-2-yl}tributylstannane (0.874 g, 2.07 mmol) and LiCl (0.105 g, 2.48 mmol) were added under argon. Then, the flask was evacuated and backfilled with argon three times. Under argon, $Pd(PPh_3)_4$ (0.096 g, 0.08 mmol) was added, and the mixture was heated at reflux during 150 min. After cooling, the reaction mixture was diluted with EtOAc. The organic phase was washed with brine, dried over anhyd $MgSO_4$, and concentrated. Flash chromatography (PE–EtOAc, 9:1 then 8:2) afforded **5a** (0.247 g, 59%) as a yellow solid; mp 151–152 °C. IR (NaCl): 2978, 2942, 2836, 1759, 1702, 1493, 1246 $cm^{-1}$. $^1H$ NMR (250 MHz, $CDCl_3$) δ = 6.95 (s, 1 H), 6.89 (s, 1 H), 6.83–6.87 (m, 2 H), 6.63–6.70 (m, 3 H), 6.20 (s, 1 H), 3.88 (s, 3 H), 3.87 (s, 6 H), 1.55 (s, 9 H). $^{13}C$ NMR (62.5 MHz, $CDCl_3$): δ = 156.1(s), 153.1(s), 148.0(s), 141.7 (s), 141.6(s), 140.2 (s), 139.1(s), 130.0(s), 128.5 (s), 128.0(d), 125.2 (d), 124.6 (d), 124.5 (d), 116.4 (d), 115.6 (d), 113.3 (s), 107.8 (d), 85.8 (s), 61.0(q), 56.2(q), 27.8 (q). ESI-HRMS: *m/z* calcd for $C_{27}H_{27}NO_9{}^{23}Na$ $[M+Na]^+$: 532.15835; found: 532.1582.

Compound **5b**: yellow solid; mp 140–141 °C. HRMS (EI): *m/z* calcd for $C_{19}H_{13}NO_4$ $[M – C_4H_8 – CO_2]^+$: 319.08446; found: 319.0838.

Compound **5c**: yellow oil. HRMS (EI): *m/z* calcd for $C_{17}H_{11}NO_5$ $[M – C_4H_8 – CO_2]^+$: 309.06372; found: 309.0642.

Compound **5d**: yellow oil. HRMS (EI): *m/z* calcd for $C_{19}H_{13}NO_2$ $[M – C_4H_8 – CO_2]^+$: 287.09463; found: 287.0969.

Compound **5e**: yellow oil. HRMS (EI): *m/z* calcd for $C_{16}H_{17}NO_4$ $[M]^+$: 287.11576; found: 287.1166.

(16) Minireview: Soos, T. J.; Meijer, L.; Nelson, P. J. *Drug News Perspect.* **2006**, *19*, 325.

(17) Kinase activities assay were performed as reported in ref. [15] and [17].

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