Organic & Biomolecular Chemistry

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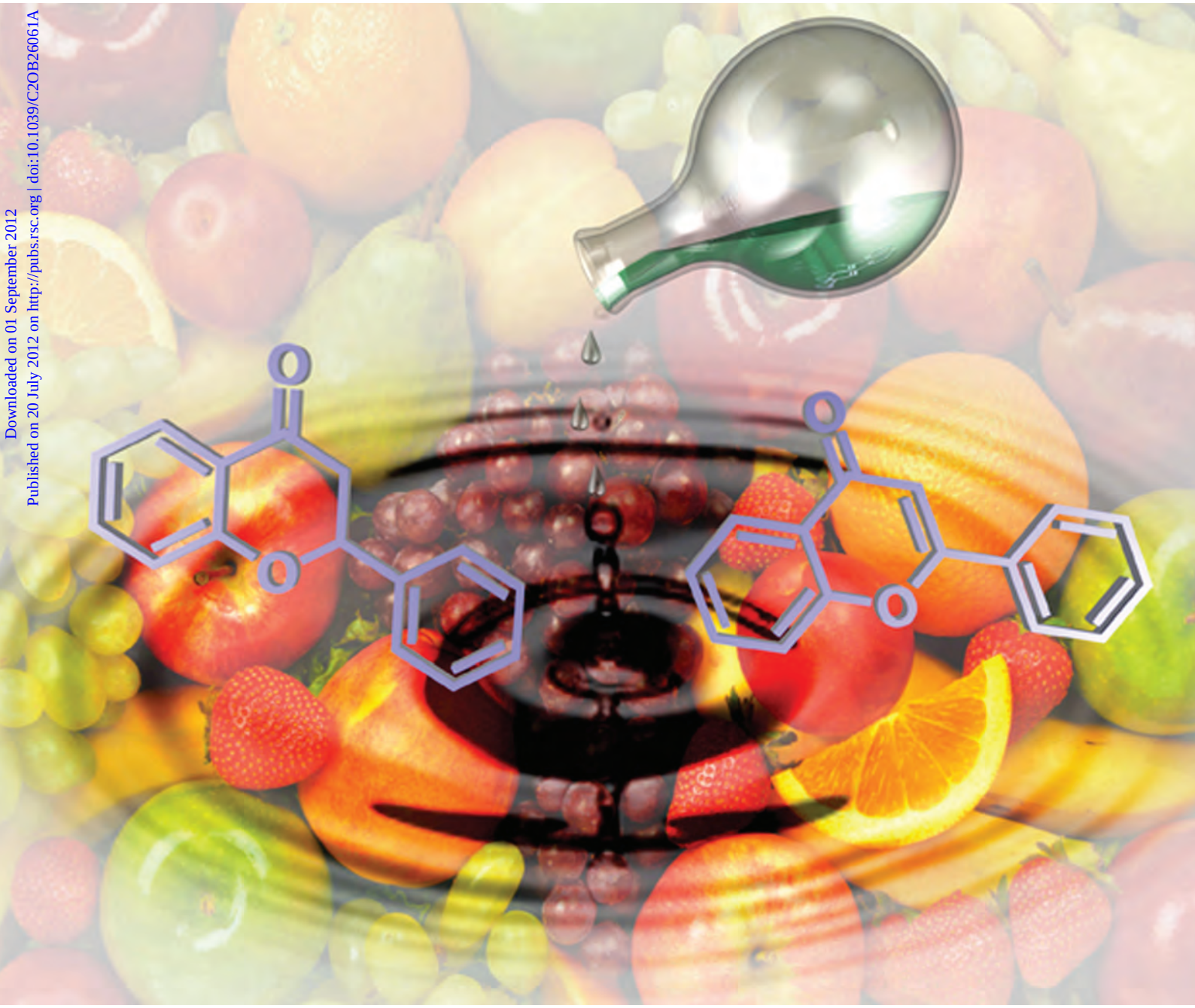
Volume 10 | Number 36 | 28 September 2012 | Pages 7229–7440



ISSN 1477-0520

RSC Publishing

PAPER

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1477-0520(2012)10:36;1-8

Organic & Biomolecular Chemistry

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Cite this: *Org. Biomol. Chem.*, 2012, **10**, 7305

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PAPER

Synthetic approach to flavanones and flavones *via* ligand-free palladium(II)-catalyzed conjugate addition of arylboronic acids to chromones†

Donghee Kim, Kyungrok Ham and Sungwoo Hong*

Received 1st June 2012, Accepted 17th July 2012
DOI: 10.1039/c2ob26061a

The remarkable catalytic effects of $Fe(OTf)_3$ in the context of the Pd(II)-catalyzed conjugate addition of arylboronic acids to chromones were observed to yield a variety of flavanones under mild conditions. The addition of catalytic amounts of DDQ and KNO_2 to the reactions exclusively yielded flavone analogs. The reaction scope for the transformation was fairly broad, affording good yields of a wide range of flavanones and flavones, which are privileged structures in many biologically active compounds.

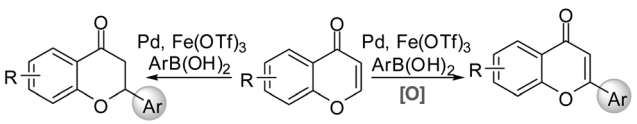
Introduction

Flavones and flavanones are widely present among natural products[1] and participate in a broad range of significant biological activities.[2] The importance of flavone and flavanone derivatives has led to the development of a variety of general approaches for synthesizing their varied derivatives.[3,4] Despite these advances, most methods can often suffer from the drawbacks of multiple steps, harsh reaction conditions, or low to moderate yields. We therefore sought a more straightforward methodology for synthesizing both the flavanones and flavones under mild reaction conditions.

The transition metal-catalyzed conjugate addition of organometallic reagents to α,β-unsaturated enones is one of the most useful methods for constructing C–C bonds. The 1,4-addition reactions of organoboron reagents to a wide variety of electron-deficient systems have been well reported, mainly with Rh species.[5,6] In addition to Rh catalysts, Pd is another catalyst for facilitating the conjugate addition of organoboron reagents to electron-deficient olefins.[7] In general, Pd-catalyzed conjugate addition reactions are performed in the presence of ligands[8] or $SbCl_3$ as a co-catalyst.[9]

Results and discussion

In light of the Pd-catalyzed 1,4-addition of arylboronic acids to α,β-unsaturated enones, we envisioned that the conjugate addition of arylboronic acids to chromones could proceed, if the electrophilic character of the C-2 position of chromone systems is properly enhanced. Moreover, subsequent oxidation of the resulting flavanones could be further transformed into the corresponding flavones (Scheme 1). During these efforts, we observed the remarkable catalytic effects of $Fe(OTf)_3$ in the context of the Pd(II)-catalyzed conjugate addition of arylboronic acids to chromones, and established a practical procedure for synthesizing flavones by simply employing a DDQ/KNO_2 catalytic system.



Scheme 1 Synthetic strategy for construction of various flavanones and flavones.

The feasibility of this process was tested through an investigation of the addition of phenyl boronic acid and chromone (**1**) as model substrates in the presence of $Pd(OAc)_2$ as a catalyst (Table 1). The 1,4-addition product **3a** was obtained in the presence of a pivalic acid, albeit in a product yield of only 6% (entry 1). To enhance the electrophilic character at the C-2 position of chromone systems, an intensive screening of Lewis acids was conducted with the goal of optimizing the conjugate addition. Conventional Lewis acid catalysts, such as $SbCl_3$, BF_3OEt_2, $SnCl_2$, LiOAc, $FeCl_3$, $CeCl_3$, or $AlCl_3$, fail to enhance reaction efficiency; however, a much improved yield of 72% was obtained in the presence of catalytic amounts of LiOTf. Under the reaction conditions, flavone **4a** was also observed from a Heck-type reaction[10,11] as a minor product (**3a**/**4a**, 3.8 : 1 in entry 2). A systematic investigation of more reactive catalytic systems was conducted by testing various OTf-based Lewis acids and temperatures, which led to the establishment of optimized conditions. In all cases (entries 2–9), the conjugate addition was accompanied by the formation of an appreciable amount of the Heck-type product **4a** (20–30% of the product).

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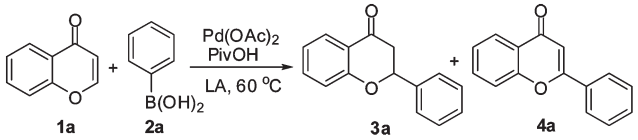
†Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra. See DOI: 10.1039/c2ob26061a

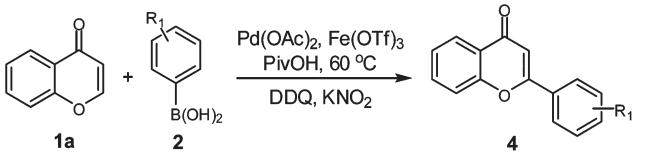
Table 1 Optimization of direct arylation of chromone[a]

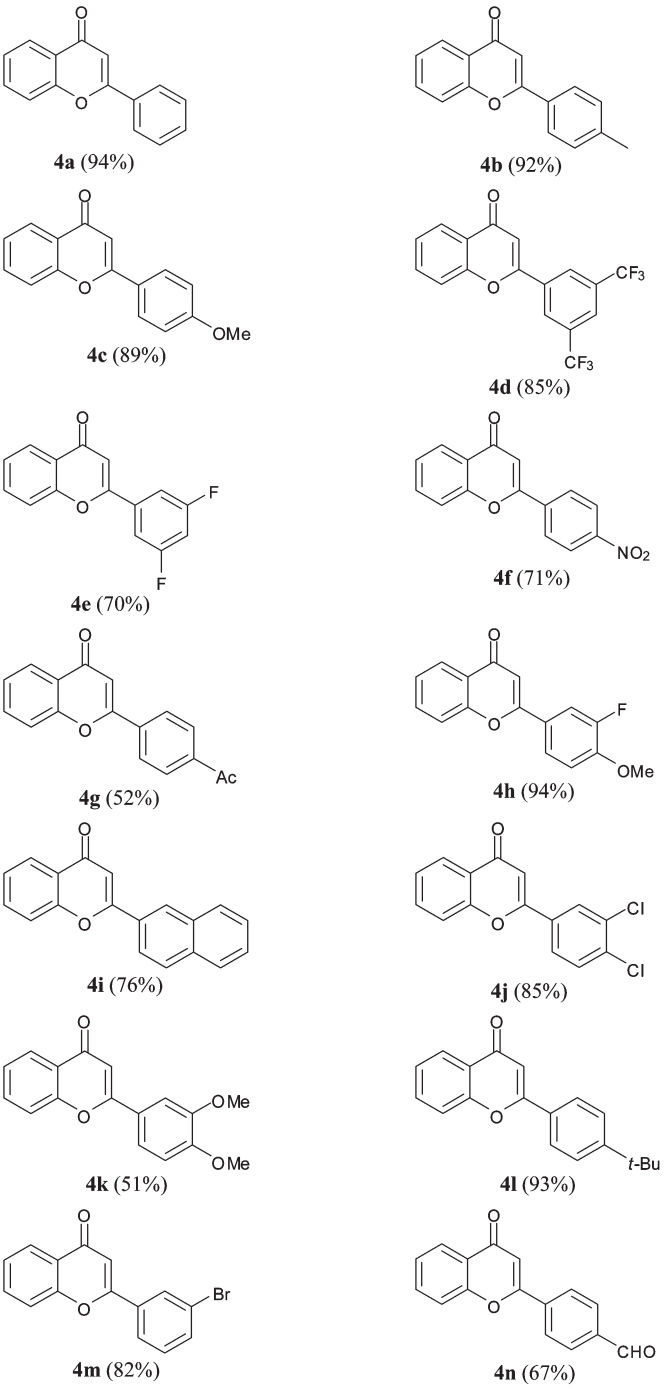


Entry	Lewis acid (0.1 equiv.)	Oxidant (equiv.)	3/4[b]	Yield 3 + 4[c] (%)
1	None	—	—	6
2	LiOTf	—	3.8 : 1	72
3	$Zn(OTf)_2$	—	3.9 : 1	86
4	TfOH	—	3.1 : 1	83
5	$Al(OTf)_3$	—	2.8 : 1	79
6	$Sm(OTf)_3$	—	3.2 : 1	84
7	$Yb(OTf)_3$	—	3.9 : 1	85
8	$Cu(OTf)_2$	—	4.8 : 1	86
9	$Fe(OTf)_3$	—	3.0 : 1	98
10	$Fe(OTf)_3$	DDQ (1)	>1 : 99	35
11	$Fe(OTf)_3$	Oxone® (1)	>1 : 99	55
12	$Fe(OTf)_3$	$(BzO)_2$ (1)	>1 : 99	62
13	$Fe(OTf)_3$	CrO_3 (1)	>1 : 99	71
14	$Fe(OTf)_3$	DDQ/KNO_2 (0.2)	>1 : 99	97

[a] Reactions were conducted with chromone (1 equiv.), phenylboronic acid (3 equiv.), $Pd(OAc)_2$ (0.2 equiv.), Lewis acid (0.1 equiv.) at 60 °C under an air atmosphere for 12–24 h. [b] The ratio was determined by ^1H NMR spectroscopy. [c] Yields are reported after isolation and purification by flash silica gel chromatography. DDQ = 2,3-dichloro-4,5-dicyanobenzoquinone.

Table 2 Direct arylation of chromone with various arylboronic acids[a]



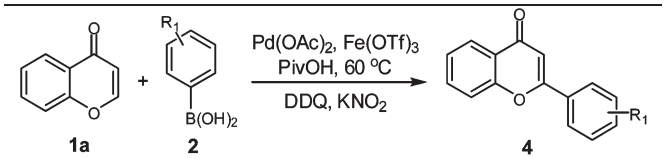


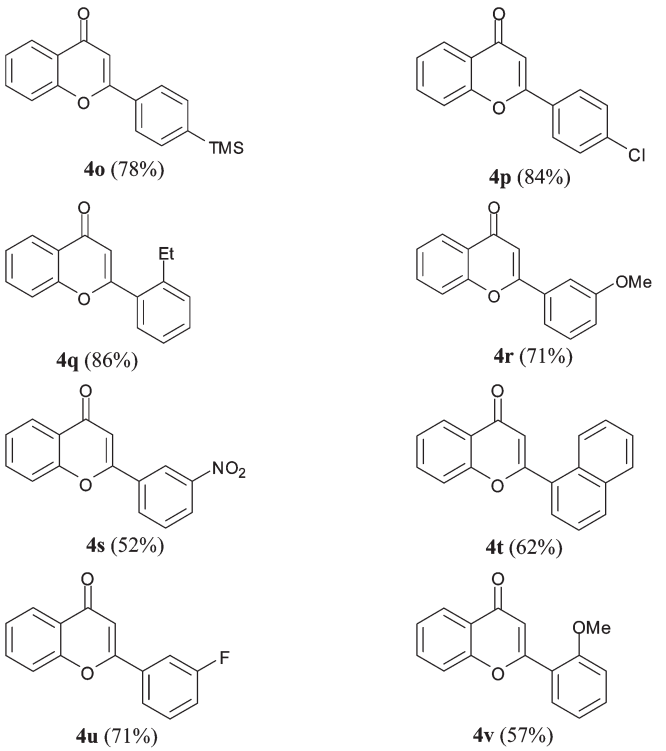
Notably, the best results were obtained with the use of 0.1 equiv. of $Fe(OTf)_3$ as a Lewis acid in pivalic acid. Thus, the treatment of a chromone (1 equiv.) with phenylboronic acid (3 equiv.), $Pd(OAc)_2$ (0.2 equiv.), and $Fe(OTf)_3$ (0.1 equiv.) in pivalic acid at 60 °C afforded flavanone **3a** (the conjugate addition product) in 73% yield, along with flavone **4a** (the Heck-type product) in 24% yield (entry 9). It was also found out that the use of $Fe(OTf)_3$ was essential to achieve a broad arylboronic acid scope.

Our efforts next focused on investigating the oxidation conditions required to efficiently convert flavanone **3a** into flavone **4a**. The presence of stoichiometric amounts of DDQ (1 equiv.) yielded flavone **4a** only, although the product yield was only 35% (entry 10). We next sought optimal conditions by screening of a variety of oxidants, such as oxone, $(BzO)_2$, CrO_3, benzoquinone (BQ), PDC, *etc*. (Table 1 and Table 1S in ESI†). The use of stoichiometric strong oxidants appears to have deleterious effects on substrates. It was eventually found out that the addition of catalytic amounts of DDQ (0.2 equiv.) and KNO_2 (0.2 equiv.)[12] to the reaction exclusively produced flavone **4a** with the highest yield (97%, entry 14).

With the optimized set of conditions in hand, the coupling reaction studies were extended to include a range of useful substituted arylboronic acids, as summarized in Table 2. To our delight, the conjugate addition/oxidation process worked well with a variety of arylboronic acids, tolerating various functional groups, including methyl, fluoro, chloro, bromo, nitro, methylketone, formyl, trimethylsilyl, methoxy, and naphthyl groups. The disubstituted phenyl boronic acid reacted well with chromone **1** to give the product in excellent yield. In all cases, flavanones

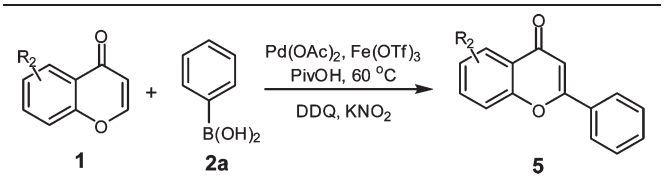
Table 2 *(Contd.)*

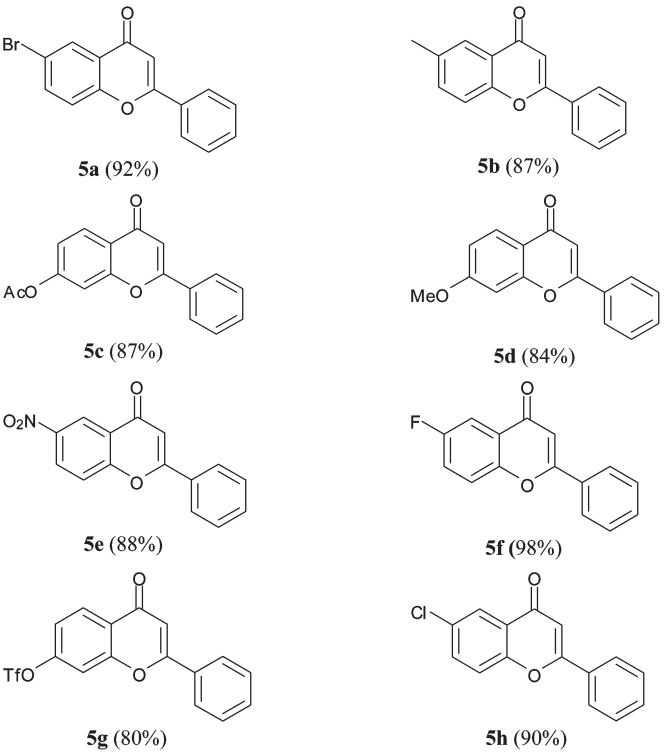




[a] Reactions were conducted with chromone (1 equiv.), phenylboronic acid (3 equiv.), $Pd(OAc)_2$ (0.2 equiv.), $Fe(OTf)_3$ (0.1 equiv.), DDQ (0.2 equiv.) and KNO_2 (0.2 equiv.) under an air atmosphere.

Table 3 Scope of direct arylation of various chromones[a]





[a] Reactions were conducted with chromone (1 equiv.), phenylboronic acid (3 equiv.), $Pd(OAc)_2$ (0.2 equiv.), $Fe(OTf)_3$ (0.1 equiv.), DDQ (0.2 equiv.) and KNO_2 (0.2 equiv.) under an air atmosphere.

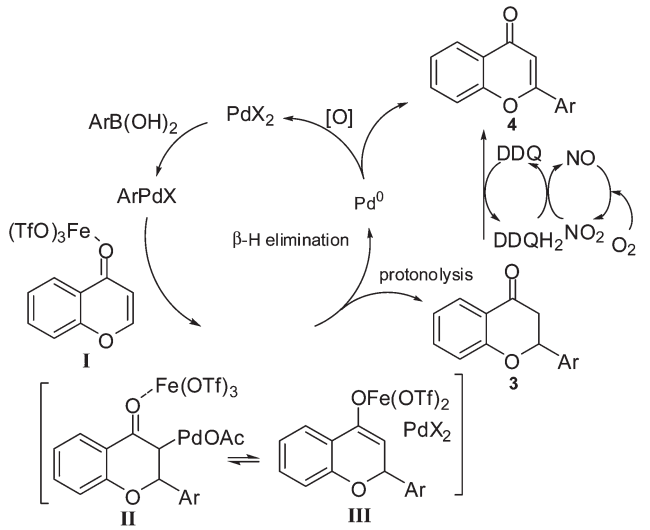
were readily obtained as the major products in the absence of the DDQ/KNO_2 catalytic system. Both the rate and yield of the reactions appeared to be insensitive to the electronic effects of the arylboronic acid. It should be noted that the nitro-substituted boronic acids were also tolerated, and products **4f** and **4s** were obtained in 71% and 52% yields, respectively. Because the recently reported Heck-type arylation[11] using nitro-substituted boronic acid was unsuccessful, our method offers a useful complementary route for the synthesis of various flavones.

Encouraged by the results, we further explored the generality of the coupling reaction and the scope of the chromone substrates is illustrated in Table 3. A relatively broad range of chromone derivatives (*e.g.*, alkyl, fluoride, bromide, chloride, nitro, methoxy, triflate, and ester) smoothly underwent the addition/oxidation process in good yields. Substitution of the electron-donating or -withdrawing group on the chromone has minimal impact on the reactivity. Of particular note were the chromones bearing bromo or triflate groups: the synthetically versatile **5a** and **5g** were isolated in good yields (in 92% and 80% yields, respectively) with intact bromo or triflate moieties, providing an opportunity for the further formation of C–C or C-heteroatom bonds.

$Fe(OTf)_3$ may coordinate to the carbonyl oxygen of chromone as a Lewis acid and activate the electrophilicity of the enolone system of chromone[9] (Scheme 2). Next, phenylpalladium, which is formed *in situ* by the transmetalation of the aryl group from boron to palladium,[13] adds to the 2 position of chromone to generate the alkylpalladium adduct **II** and the enolate **III**. The subsequent protonolysis of the enolate **III** leads to the conjugate addition product,[13] flavanone **3**. On the other hand, β-hydride elimination of the palladium adduct **II** directly generates a Heck-type product,[11] flavone **4**, as a minor product. The use of the DDQ/KNO_2 catalytic system as the oxidant exclusively provides flavone **4** *via* oxidation of the resulting flavanone **3**. In the presence of O_2, NO is readily oxidized to NO_2.[12] Finally, the reoxidation of Pd(0) to Pd(II) completes the catalytic cycle.

Conclusions

In summary, we developed a practical method for the palladium-catalyzed 1,4-addition of arylboronic acids to chromones, thereby yielding a variety of flavanone analogs as major products



Scheme 2 Plausible catalytic cycle for the direct arylation of chromone.

under mild conditions. The remarkable catalytic effects associated with the use of $Fe(OTf)_3$ in conjunction with PivOH were clearly observed in the transformation of the chromones. When catalytic amounts of DDQ and KNO_2 were added to the reactions, the flavone analogs were exclusively obtained. The reaction scope for the transformation was fairly broad, affording good yields of a wide range of flavanones and flavones, which are privileged structures in many biologically active compounds.

Experimental

General methods and materials

Unless stated otherwise, reactions were performed in flame-dried glassware under a positive pressure of oxygen. Solvents were used without purification or degassing. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F^{254} plates and visualization on TLC was achieved by UV light (254 and 354 nm). Flash column chromatography was undertaken on silica gel (400–630 mesh). ^{1}H NMR was recorded on 400 MHz and chemical shifts were quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.0 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, td = doublet of triplet. Coupling constants, *J*, were reported in hertz unit (Hz). ^{13}C NMR was recorded on 100 MHz and was fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm referenced to the center line of a triplet at 77.0 ppm of chloroform-d. Mass spectral data were obtained from the KAIST Basic Science Institute by using the EI method. Commercial grade reagents and solvents were used without further purification except as indicated below. Unless otherwise stated, all commercial reagents and solvents were used without additional purification.

General procedure (GP) for chromone arylation

Chromone derivative (0.205 mmol), $Fe(OTf)_3$ (0.1 equiv.) and arylboronic acid (3 equiv.), $Pd(OAc)_2$ (0.2 equiv.) were combined in PivOH (0.1 M). The reaction mixture was stirred at 60 °C under an air atmosphere for 12–24 h, yielding flavanones as the major product. For the flavone product, DDQ (0.2 equiv.), KNO_2 (0.2 equiv.) were added to the mixture. The mixture was monitored by TLC using EtOAc and *n*-hexane = 1 : 3 as the mobile phase and stirred until flavanone disappeared. The reaction mixture was diluted with CH_2Cl_2 and the excess aqueous $NaHCO_3$ was added to neutralize the PivOH. After stirring the mixture for 10 min, the residue was extracted with aqueous $NaHCO_3$, NH_4Cl (3 × 30 ml). The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified by flash chromatography on silica gel to give the desired product.

2-Phenylchroman-4-one (3a). The residue was purified by flash column chromatography (DCM : *n*-hexane = 2 : 1) to produce the desired product (33.4 mg, 73%) as a white solid; ^{1}H NMR (400 MHz, chloroform-d) δ 7.93 (dd, J = 8.0, 1.8 Hz, 1H), 7.54–7.33 (m, 6H), 7.08–7.01 (m, 2H), 5.47 (dd, J = 13.3, 2.9 Hz, 1H), 3.08 (dd, J = 16.9, 13.3 Hz, 1H), 2.88 (dd, J = 16.9, 2.9 Hz, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 191.9, 161.5, 138.7, 136.2, 128.8, 128.7, 127.0, 126.1, 121.6, 120.9, 118.1, 79.6, 44.6. [Ref] *Bull. Korean Chem. Soc.*, 2011, **32**, 4092–4094.

2-Phenyl-4*H*-chromen-4-one (4a). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (42.8 mg, 94%) as a white solid; mp 93–95 °C; IR: 1642, 1605, 1374, 1128 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.24 (dd, J = 8.0, 1.7 Hz, 1H), 8.02–7.87 (m, 2H), 7.73 (td, J = 8.6, 7.1, 1.7 Hz, 1H), 7.60 (dd, J = 8.4, 1.0 Hz, 1H), 7.56–7.49 (m, 3H), 7.45 (td, J = 8.1, 7.1, 1.1 Hz, 1H), 7.06 (s, J = 1.3 Hz, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.6, 164.5, 156.3, 134.4, 132.1, 131.3, 129.1, 126.5, 125.7, 125.6, 123.1, 118.1, 106.9. [Ref] *Angew. Chem., Int. Ed.* 2011, **50**, 3769–3773.

2-(*p*-Tolyl)-4*H*-chromen-4-one (4b). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 3) to produce the desired product (43.6 mg, 92%) as a yellowish solid; mp 106–109 °C; IR: 1640, 1465, 817 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.21 (dd, J = 7.9, 1.7 Hz, 1H), 7.81 (d, J = 8.3 Hz, 2H), 7.69 (td, J = 8.4, 7.2, 1.2 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.41 (td, J = 7.9, 0.8 Hz, 1H), 7.29 (d, 2H), 6.92 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.4, 16.7, 156.2, 142.7, 134.0, 129.8, 128.6, 126.4, 125.6, 125.4, 123.3, 118.0, 106.4, 104.0, 21.5; HRMS (EI$^+$) *m*/*z* calcd for $C_{16}H_{12}NaO_2^+$ [M + Na]$^+$: 259.0730, found: 259.0737.

2-(4-Methoxyphenyl)-4*H*-chromen-4-one (4c). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 2) to produce the desired product (46 mg, 89%) as a yellowish solid; mp 150–152 °C; IR: 1640, 1380, 827 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.22 (dd, J = 8.0, 1.7 Hz, 1H), 7.91 (d, 2H), 7.73 (td, J = 8.7, 7.1, 1.7 Hz, 1H), 7.59 (dd, J = 8.5, 1.0 Hz, 1H), 7.44 (td, J = 8.0, 7.1, 1.0 Hz, 1H), 7.11 (bs, 1H), 7.01 (d, 2H), 3.88 (s, 3H); ^{13}C NMR (100 MHz,

chloroform-d) δ 178.2, 165.4, 163.3, 156.2, 134.6, 131.0, 128.7, 125.8, 125.6, 123.1, 122.3, 118.1, 114.7, 113.8, 104.8, 55.6; HRMS (EI$^+$) *m/z* calcd for $C_{16}H_{12}NaO_3^+$ [M + Na]$^+$: 275.0679, found: 275.0689.

2-(3,5-Bis(trifluoromethyl)phenyl)-4*H*-chromen-4-one (4d). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 3) to produce the desired product (62 mg, 85%) as a white solid; mp 172–175 °C; IR: 1660, 1604, 1488, 1362, 1276, 900, 844 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.34 (d, *J* = 1.5 Hz, 2H), 8.23 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.03 (s, 1H), 7.75 (td, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.63 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.46 (td, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.90 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 177.79, 159.80, 156.08, 134.40, 134.12, 132.80 (q, *J* = 34.0 Hz), 126.24, 125.88, 124.79, 123.88, 122.8 (q, *J* = 272.0 Hz), 118.16, 109.21; HRMS (EI$^+$) *m/z* calcd for $C_{17}H_8F_6NaO_2^+$ [M + Na]$^+$: 381.0321, found: 381.0324.

2-(3,5-Difluorophenyl)-4*H*-chromen-4-one (4e). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 6) to produce the desired product (36.6 mg, 63%) as a yellowish solid; mp 145–148 °C; IR: 1638, 1376, 1121 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.20 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.71 (td, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.55 (dd, *J* = 8.6, 1.0 Hz, 1H), 7.50–7.37 (m, 3H), 6.97 (tt, 1H), 6.76 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.0, 164.6, 164.5, 162.1, 162.0, 160.6, 156.0, 135.0 (d, *J* = 9.4 Hz), 134.2, 125.8, 125.6, 123.8, 118.0, 109.5, 109.4, 109.3, 109.2, 108.5, 107.1, 106.8, 106.6; HRMS (EI$^+$) *m/z* calcd for $C_{15}H_8F_2NaO_2^+$ [M + Na]$^+$: 281.0385, found: 281.0395.

2-(4-Nitrophenyl)-4*H*-chromen-4-one (4f). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 3) to produce the desired product (39.4 mg, 66%) as a yellowish solid; mp 234–236 °C; IR: 1660, 1522, 1346, 857 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.37 (d, *J* = 9.0 Hz, 2H), 8.23 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.10 (d, *J* = 8.9 Hz, 1H), 7.74 (td, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.59 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.45 (td, *J* = 8.2, 7.1, 1.1 Hz, 1H), 6.89 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.0, 160.5, 156.1, 149.4, 137.6, 134.3, 127.2, 125.9, 125.7, 124.2, 123.9, 118.1, 109.6; HRMS (EI$^+$) *m/z* calcd for $C_{15}H_9NNaO_4^+$ [M + Na]$^+$: 290.0424, found: 290.0440.

2-(4-Acetylphenyl)-4*H*-chromen-4-one (4g). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 2) to produce the desired product (28.2 mg, 52%) as a yellowish solid; mp 151–153 °C; IR: 1680, 1642, 1266 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.22 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.08 (d, 2H), 8.01 (d, 2H), 7.71 (td, *J* = 8.6, 7.1, 1.7 Hz, 1H), 7.58 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.43 (td, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.87 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 197.1, 178.2, 161.9, 156.2, 139.0, 135.8, 134.0, 126.9, 126.5, 125.8, 125.5, 124.0, 118.1, 108.8, 26.8; HRMS (EI$^+$) *m/z* calcd for $C_{17}H_{12}NaO_3^+$ [M + Na]$^+$: 287.0679, found: 287.0682.

2-(3-Fluoro-4-methoxyphenyl)-4*H*-chromen-4-one (4h). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 1) to produce the desired product (52 mg, 94%) as a yellowish solid; mp 164–165 °C; IR: 1653, 1525, 1471, 1381, 1296, 1022 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.19 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.83–7.60 (m, 3H), 7.52 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.39 (td, *J* = 8.1, 7.1, 1.1 Hz, 1H), 7.05 (t, *J* = 8.6 Hz, 1H), 6.69 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.1, 162.0 (d, *J* = 2.7 Hz), 156.0, 153.5, 150.5 (d, *J* = 10.9 Hz), 133.7, 125.6, 125.2, 124.5 (d, *J* = 6.9 Hz), 123.8, 122.8 (d, *J* = 3.2 Hz), 117.9, 114.0 (d, *J* = 20.6 Hz), 113.3 (d, *J* = 2.3 Hz), 106.7, 56.3; HRMS (EI$^+$) *m/z* calcd for $C_{16}H_{11}FNaO_3^+$ [M + Na]$^+$: 293.0584, found: 293.0601.

2-(Naphthalen-2-yl)-4*H*-chromen-4-one (4i). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (42.5 mg, 76%) as a yellowish solid; mp 148–150 °C; IR: 1635, 1559, 1461 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.46 (s, 1H), 8.24 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.05–7.80 (m, 4H), 7.71 (td, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.62 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.59–7.53 (m, 2H), 7.42 (td, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.94 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.4, 163.3, 156.3, 134.6, 133.8, 132.9, 129.0, 129.0, 128.0, 127.8, 127.0, 126.9, 125.7, 125.2, 124.0, 122.5, 118.1, 107.9; HRMS (EI$^+$) *m/z* calcd for $C_{19}H_{12}NaO_2^+$ [M + Na]$^+$: 295.0730, found: 295.0736.

2-(3,4-Dichlorophenyl)-4*H*-chromen-4-one (4j). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (51 mg, 85%) as a yellowish solid; mp 196–198 °C; IR: 1662, 1605, 1472, 1131 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.20 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.01 (d, *J* = 2.2 Hz, 1H), 7.70 (td, *J* = 8.5, 6.5, 1.9 Hz, 2H), 7.57 (td, *J* = 9.3, 8.0 Hz, 2H), 7.43 (td, 1H), 6.76 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.0, 160.8, 156.1, 135.9, 134.1, 133.7, 131.7, 131.1, 128.0, 125.8, 125.5, 125.2, 123.9, 118.0, 108.2; HRMS (EI$^+$) *m/z* calcd for $C_{15}H_8Cl_2NaO_2^+$ [M + Na]$^+$: 312.9794, found: 312.9815.

2-(3,4-Dimethoxyphenyl)-4*H*-chromen-4-one (4k). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 2) to produce the desired product (29.5 mg, 51%) as a pink solid; mp 144–146 °C; IR: 1653, 1609, 1517, 1028 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.19 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.65 (td, 1H), 7.53 (dd, 2H), 7.38 (td, 2H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.72 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.3, 163.3, 156.1, 152.0, 149.2, 133.5, 125.6, 125.1, 124.2, 123.9, 119.9, 117.9, 111.1, 108.8, 106.4, 56.0. [Ref] *Angew. Chem., Int. Ed.*, 2011, **50**, 3769–3773.

2-(4-(*tert*-Butyl)phenyl)-4*H*-chromen-4-one (4l). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (53 mg, 93%) as a yellowish solid; mp 97–99 °C; IR: 1642, 1602, 1462, 1130 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.21 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.84 (dd, 2H), 7.67 (td, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.61–7.47 (m, 4H), 7.39 (td, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.4, 163.5, 156.2, 155.3, 133.6, 128.9, 126.1, 126.0, 125.6, 125.1, 124.0, 118.0, 107.0, 35.0, 31.1; HRMS (EI$^+$) *m/z* calcd for $C_{19}H_{18}NaO_2^+$ [M + Na]$^+$: 301.1199, found: 301.1205.

2-(3-Bromophenyl)-4*H*-chromen-4-one (4m). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (50.6 mg, 82%) as a

yellowish solid; mp 86–88 °C; IR: 1640, 1605, 1469, 1366 cm^{-1}; ^1H NMR (400 MHz, chloroform-d) δ 8.19 (dd, J = 8.0, 1.7 Hz, 1H), 8.04 (t, J = 1.9 Hz, 1H), 7.80 (td, J = 7.9, 1.8, 1.0 Hz, 1H), 7.69 (td, J = 8.6, 7.1, 1.7 Hz, 1H), 7.63 (td, J = 8.0, 2.0, 1.0 Hz, 1H), 7.55 (dd, 1H), 7.41 (td, 1H), 7.36 (t, 1H), 6.76 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.1, 161.6, 156.1, 134.4, 133.9, 133.7, 130.5, 129.2, 125.7, 125.4, 124.8, 123.9, 123.2, 118.0, 108.1; HRMS (EI^+) m/z calcd for $C_{15}H_9BrNaO_2^+$ $[M + Na]^+$: 322.9678, found: 322.9679.

4-(4-Oxo-4*H*-chromen-2-yl)benzaldehyde (4n). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 2) to produce the desired product (34.8 mg, 67%) as a yellowish solid; mp 166–168 °C; IR: 1702, 1637, 831 cm^{-1}; ^1H NMR (400 MHz, chloroform-d) δ 10.09 (s, 1H), 8.21 (dd, J = 8.0, 1.7 Hz, 1H), 8.08 (d, J = 8.5 Hz, 2H), 8.01 (d, J = 8.6 Hz, 1H), 7.71 (td, J = 8.7, 7.1, 1.7 Hz, 1H), 7.58 (dd, 1H), 7.43 (td, J = 8.1, 7.1, 1.1 Hz, 1H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 191.2, 178.1, 161.6, 156.2, 138.1, 137.1, 134.1, 130.1, 126.8, 125.8, 125.5, 123.9, 118.1, 109.1; HRMS (EI^+) m/z calcd for $C_{16}H_{10}NaO_3^+$ $[M + Na]^+$: 273.0522, found: 273.0518.

2-(4-(Trimethylsilyl)phenyl)-4*H*-chromen-4-one (4o). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 5) to produce the desired product (47 mg, 78%) as a yellowish solid; mp 78–80 °C; IR: 1640, 1463, 1360, 821 cm^{-1}; ^1H NMR (400 MHz, chloroform-d) δ 8.21 (dd, J = 8.0, 1.7 Hz, 1H), 7.87 (d, J = 8.2 Hz, 2H), 7.77–7.62 (m, 3H), 7.55 (dd, J = 8.4, 1.1 Hz, 1H), 7.40 (td, J = 8.1, 7.0, 1.1 Hz, 1H), 6.82 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.4, 163.5, 156.2, 145.4, 133.9, 133.7, 131.9, 125.7, 125.3, 125.2, 124.0, 118.1, 107.6, −1.3; HRMS (EI^+) m/z calcd for $C_{18}H_{18}NaO_2Si^+$ $[M + Na]^+$: 317.0968, found: 317.0980.

2-(4-Chlorophenyl)-4*H*-chromen-4-one (4p). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (44.1 mg, 84%) as a white solid; mp 176–179 °C; IR: 1662, 1374, 1092, 827, 754 cm^{-1}; ^1H NMR (300 MHz, chloroform-d) δ 8.21 (dd, J = 8.0, 1.6 Hz, 1H), 7.85 (d, 2H), 7.70 (td, J = 8.7, 7.1, 1.7 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.49 (d, 2H), 7.42 (t, J = 7.6 Hz, 1H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.2, 162.1, 156.1, 137.8, 133.9, 130.2, 129.3, 127.5, 125.7, 125.3, 123.9, 118.0, 107.6. [Ref] *Angew. Chem., Int. Ed.*, 2011, **50**, 3769–3773.

2-(2-Ethylphenyl)-4*H*-chromen-4-one (4q). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (44.4 mg, 86%) as a white solid; mp 50–52 °C; IR: 1645, 1620, 1469, 1367, 754 cm^{-1}; ^1H NMR (300 MHz, chloroform-d) δ 8.25 (dd, J = 8.0, 1.7 Hz, 1H), 7.68 (td, J = 8.6, 7.1, 1.7 Hz, 1H), 7.45 (t, 3H), 7.41 (dd, J = 8.0, 1.1 Hz, 1H), 7.35 (td, 1H), 7.30 (td, J = 7.4, 1.4 Hz, 1H), 6.46 (s, 1H), 2.77 (q, J = 7.6 Hz, 2H), 1.25 (t, J = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.2, 166.5, 156.4, 143.0, 133.7, 132.2, 130.9, 129.6, 129.5, 126.1, 125.8, 125.2, 123.8, 118.0, 112.0, 76.7, 26.7, 15.6; HRMS (EI^+) m/z calcd for $C_{17}H_{14}NaO_2^+$ $[M + Na]^+$: 273.0886, found: 273.0902.

2-(3-Methoxyphenyl)-4*H*-chromen-4-one (4r). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 8) to produce the desired product (36.9 mg, 71%) as a white solid; mp 125–128 °C; IR: 1652, 1604, 1464, 867, 767, 693 cm^{-1}; ^1H NMR (300 MHz, chloroform-d) δ 8.22 (dd, J = 8.0, 1.7 Hz, 1H), 7.69 (td, J = 8.7, 7.0, 1.7 Hz, 1H), 7.55 (d, 1H), 7.50 (dt, J = 7.7, 1.4 Hz, 1H), 7.44 (d, J = 3.2 Hz, 1H), 7.43–7.37 (m, 2H), 7.06 (ddd, J = 8.1, 2.6, 1.1 Hz, 1H), 6.81 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.4, 163.1, 159.9, 156.2, 133.7, 133.0, 130.1, 125.6, 125.2, 123.9, 118.7, 118.1, 117.1, 111.7, 107.7, 55.4; HRMS (EI^+) m/z calcd for $C_{16}H_{12}NaO_3^+$ $[M + Na]^+$: 275.0679, found: 275.0692.

2-(3-Nitrophenyl)-4*H*-chromen-4-one (4s). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (28.5 mg, 52%) as a white solid; mp 195–198 °C; IR: 1660, 1618, 1459, 1369 cm^{-1}; ^1H NMR (300 MHz, chloroform-d) δ 8.79 (t, J = 2.0 Hz, 1H), 8.38 (ddd, J = 8.2, 2.4, 1.0 Hz, 1H), 8.21 (dq, J = 7.8, 1.7 Hz, 2H), 7.78–7.69 (m, 2H), 7.62 (dd, J = 8.5, 1.1 Hz, 1H), 7.45 (td, J = 8.1, 7.0, 1.1 Hz, 1H), 6.89 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.0, 160.5, 156.1, 148.8, 134.3, 133.6, 131.7, 130.3, 125.9, 125.8, 125.7, 123.9, 121.2, 118.1, 108.8; HRMS (EI^+) m/z calcd for $C_{15}H_9NNaO_4^+$ $[M + Na]^+$: 290.0424, found: 290.0418.

2-(Naphthalen-1-yl)-4*H*-chromen-4-one (4t). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (34.7 mg, 62%) as a white solid; mp 107–109 °C; IR: 1667, 1614, 1464, 1374, 1128 cm^{-1}; ^1H NMR (300 MHz, chloroform-d) δ 8.30 (dd, J = 8.0, 1.7 Hz, 1H), 8.17–8.08 (m, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.98–7.90 (m, 1H), 7.76 (dd, J = 7.1, 1.3 Hz, 1H), 7.71 (td, J = 8.6, 7.0, 1.7 Hz, 1H), 7.62–7.54 (m, 3H), 7.52 (d, 1H), 7.46 (td, 1H), 6.68 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 181.1, 178.2, 165.4, 156.7, 133.8 (d, J = 14.6 Hz), 131.5, 130.6, 130.3, 128.7, 127.9, 127.4, 126.6, 125.8, 125.3, 124.9 (d, J = 19.6 Hz), 124.0, 118.2, 113.0, 76.7; HRMS (EI^+) m/z calcd for $C_{19}H_{12}NaO_2^+$ $[M + Na]^+$: 295.0730, found: 295.0736.

2-(3-Fluorophenyl)-4*H*-chromen-4-one (4u). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (37.6 mg, 76%) as a white solid; mp 96–98 °C; IR: 1663, 1643, 1509, 1376 cm^{-1}; ^1H NMR (300 MHz, chloroform-d) δ 8.20 (dd, J = 7.9, 1.7 Hz, 1H), 7.70 (dd, J = 8.5, 1.6 Hz, 1H), 7.66 (dt, 1H), 7.61 (dt, J = 9.7, 2.2 Hz, 1H), 7.54 (dd, J = 8.5, 1.0 Hz, 1H), 7.52–7.44 (m, 1H), 7.41 (tt, 1H), 7.21 (td, 1H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.2, 163.0 (d, J = 241.7 Hz), 156.1, 134.0, 133.9, 133.9, 130.7 (d, J = 8.1 Hz), 125.7, 125.4, 123.9, 121.9 (d, J = 3.1 Hz), 118.4 (d, J = 21.2), 118.0, 113.3 (d, J = 23.9 Hz), 108.1; HRMS (EI^+) m/z calcd for $C_{15}H_9FNaO_2^+$ $[M + Na]^+$: 263.0479, found: 263.0480.

2-(2-Methoxyphenyl)-4*H*-chromen-4-one (4v). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 3) to produce the desired product (29.5 mg, 57%) as a white solid; mp 96–98 °C; IR: 1637, 1613, 1462 cm^{-1}; ^1H NMR (400 MHz, chloroform-d) δ 8.21 (dd, J = 8.0, 1.7 Hz, 1H), 7.88 (dd, J = 7.8, 1.8 Hz, 1H), 7.65 (td, J = 8.7, 7.1, 1.7 Hz, 1H), 7.50 (d, 1H), 7.45 (td, 1H), 7.38 (td, J = 8.1, 7.1, 1.1 Hz, 1H), 7.12 (s, 1H), 7.09 (td, J = 7.6, 1.0 Hz, 1H), 7.02

(d, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.9, 160.8, 158.0, 156.5, 133.5, 132.4, 129.2, 125.6, 124.9, 123.8, 120.8, 120.7, 118.0, 112.6, 111.7, 55.6; HRMS (EI$^+$) *m/z* calcd for $C_{16}H_{12}NaO_3^+$ [M + Na]$^+$: 275.0679, found: 275.0692.

6-Bromo-2-phenyl-4*H*-chromen-4-one (5a). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 5) to produce the desired product (38 mg, 92%) as a yellowish solid; mp 170–175 °C; IR: 1650, 1599, 1452, 1434 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.34 (d, *J* = 2.4 Hz, 1H), 7.90 (dd, *J* = 8.0, 1.7 Hz, 2H), 7.77 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.59–7.49 (m, 3H), 7.47 (d, *J* = 8.9 Hz, 1H), 6.88 (s, 1H); ^{13}C NMR (101 MHz, chloroform-d) δ 177.1, 164.0, 155.0, 136.9, 132.0, 131.3, 129.1, 128.4, 126.4, 125.1, 120.0, 118.8, 107.4. [Ref] *Angew. Chem., Int. Ed*., 2011, **50**, 3769–3773.

6-Methyl-2-phenyl-4*H*-chromen-4-one (5b). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 3) to produce the desired product (39 mg, 87%) as a yellowish solid; mp 112–116 °C; IR: 1642, 1607, 1502, 1260 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.00 (s, 1H), 7.94–7.86 (m, 2H), 7.51 (d, *J* = 1.9 Hz, 2H), 7.49 (dd, *J* = 8.0, 2.2 Hz, 3H), 7.44 (d, *J* = 8.5 Hz, 1H), 6.79 (s, 1H), 2.45 (s, 3H); ^{13}C NMR (100 MHz, chloroform-d) δ 178.5, 163.2, 154.5, 135.2, 135.0, 131.9, 131.5, 129.0, 126.2, 125.0, 123.6, 117.8, 107.4, 20.9. [Ref] *Angew. Chem., Int. Ed.*, 2011, **50**, 3769–3773.

4-Oxo-2-phenyl-4*H*-chromen-7-yl acetate (5c). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 2) to produce the desired product (36 mg, 87%) as a pink solid; mp 117–119 °C; IR: 1758, 1638, 1599, 1437, 1371, 1205, 1143 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.24 (d, *J* = 8.7 Hz, 1H), 7.90 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.64–7.46 (m, 3H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.16 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.88 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 177.8, 168.4, 165.1, 156.9, 155.2, 132.3, 131.0, 129.2, 127.1, 126.6, 120.7, 120.0, 111.1, 106.8, 21.2; HRMS (EI$^+$) *m/z* calcd for $C_{17}H_{12}NaO_4^+$ [M + Na]$^+$: 303.0628, found: 303.0642.

7-Methoxy-2-phenyl-4*H*-chromen-4-one (5d). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 2) to produce the desired product (36 mg, 84%) as a white solid; mp 85–88 °C; IR: 1650, 1626, 1444, 1151, 1018 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.14–8.05 (m, 1H), 7.89 (dd, *J* = 7.8, 1.9 Hz, 2H), 7.61–7.41 (m, 3H), 6.98 (d, *J* = 2.3 Hz, 1H), 6.94 (d, *J* = 15.2 Hz, 2H); ^{13}C NMR (100 MHz, chloroform-d) δ 177.8, 164.5, 163.7, 158.1, 131.7, 131.5, 129.0, 127.0, 126.3, 117.1, 114.9, 106.8, 100.3, 55.9. [Ref] *Angew. Chem., Int. Ed.*, 2011, **50**, 3769–3773.

6-Nitro-2-phenyl-4*H*-chromen-4-one (5e). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 3) to produce the desired product (37 mg, 88%) as a yellow solid; mp 184–187 °C; IR: 1647, 1613, 1510, 1456, 1338, 1018 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 9.07 (d, *J* = 2.8 Hz, 1H), 8.51 (dd, *J* = 9.2, 2.8 Hz, 1H), 7.91 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.71 (d, *J* = 9.2 Hz, 1H), 7.63–7.45 (m, 4H), 6.86 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 176.6, 164.1, 159.0, 144.8, 132.3, 130.7, 129.2, 128.1, 126.4, 124.0, 122.4, 119.8, 107.8. [Ref] *Angew. Chem., Int. Ed.*, 2011, **50**, 3769–3773.

6-Fluoro-2-phenyl-4*H*-chromen-4-one (5f). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 5) to produce the desired product (43 mg, 98%) as a yellow solid; mp 123–127 °C; IR: 1657, 1359 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 7.88 (dd, *J* = 7.7, 1.9 Hz, 1H), 7.83 (dd, *J* = 8.1, 3.1 Hz, 1H), 7.61–7.46 (m, 3H), 7.39 (td, *J* = 9.1, 7.6, 3.1 Hz, 1H), 6.78 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 177.5, 163.6, 160.8, 158.3, 152.4, 131.6 (d, *J* = 30.6 Hz), 129.1, 126.3, 125.1 (d, *J* = 7.1 Hz), 121.9 (d, *J* = 25.4 Hz), 120.1 (d, *J* = 8.1 Hz), 110.6 (d, *J* = 23.6 Hz), 106.9. [Ref] *Angew. Chem., Int. Ed.*, 2011, **50**, 3769–3773.

4-Oxo-2-phenyl-4*H*-chromen-7-yl trifluoromethanesulfonate (5g). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (19.5 mg, 80%) as a white solid; mp 128–131 °C; IR: 1168, 1646, 1622, 1430, 1216, 1136, 1115 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.32 (d, *J* = 8.9 Hz, 1H), 7.91 (ddd, 2H), 7.59–7.51 (m, 4H), 7.32 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.84 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 176.8, 164.2, 156.4, 152.2, 132.1, 131.0, 129.2, 128.4, 126.3, 123.7, 123.4, 120.3, 118.5, 117.1, 113.9, 111.5, 108.0; HRMS (EI$^+$) *m/z* calcd for $C_{16}H_9F_3NaO_5S^+$ [M + Na]$^+$: 393.0015, found: 393.0029.

6-Chloro-2-phenyl-4*H*-chromen-4-one (5h). The residue was purified by flash column chromatography (EtOAc : *n*-hexane = 1 : 4) to produce the desired product (38.5 mg, 90%) as a yellow solid; mp 178–180 °C; IR: 1650, 1602, 1434, 1130, 679 cm^{-1}; ^{1}H NMR (400 MHz, chloroform-d) δ 8.17 (d, *J* = 2.5 Hz, 1H), 7.89 (dd, 2H), 7.61 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.55–7.47 (m, 4H), 6.80 (s, 1H); ^{13}C NMR (100 MHz, chloroform-d) δ 177.1, 163.6, 154.5, 133.9, 131.8, 131.4, 131.2, 129.1, 126.3, 125.1, 124.9, 119.8, 107.4. [Ref] *Angew. Chem., Int. Ed.*, 2011, **50**, 3769–3773.

Acknowledgements

This research was supported by the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (NRF-2011-0026680, 0020322 and 0016436).

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