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Synthesis of Flavones Derivatives through Versatile Palladium-catalyzed Cross-coupling Reactions of Tosyloxy and Mesyloxyflavones

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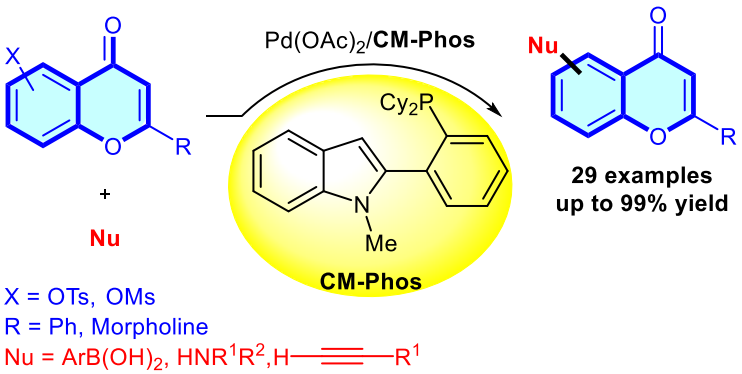

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Abstract In this study, tosyloxy- and mesyloxyflavones that are derived from abundant and biologically important hydroxyflavones were used to the synthesis of a series of functionalized flavones through versatile palladium-catalyzed cross-coupling reactions. $Pd(OAc)_2$/CM-Phos catalytic system was found to be an effective catalyst system for a broad range of tosyloxy- and mesyloxyflavones as electrophilic coupling partners with different types of nucleophiles to give the corresponding products in good-to-excellent yields. A catalyst loading down to 0.1 mol% Pd was also successfully achieved. Importantly, we demonstrated the applicability of this protocol with a significantly improved efficiency to synthesize potential chromen-4-one-based inhibitors of the DNA-PK's analog.

Key words palladium, phosphine ligands, cross-coupling reactions, tosylates, mesylates, flavones

Flavones represent a class of flavonoids based on the backbone of 2-phenylchromen-4-one. Their scaffold is a "skeleton key," as it is an important motif in many compounds with various substitution patterns showing versatile biological activities; for example, flavones have antioxidant, anti-inflammation, antiulcer, and antimicrobial properties and are applicable in asthma, cardiovascular system, cancer, and neuroprotection therapy (Figure 1).[1] Due to the wide range of flavones' biological activities, medicinal chemists have focused considerably on their structural-activity relationships.[2] Hence, the design of synthetic strategies is crucial in dealing with large bundles of flavones.

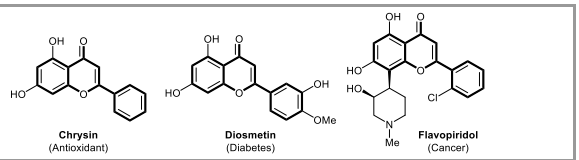
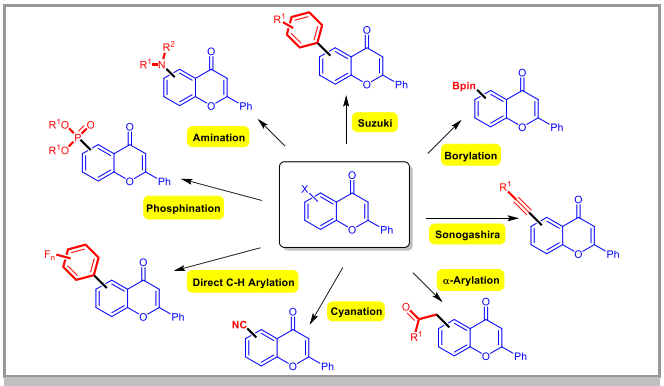


Figure 1 Therapeutic activity of flavones

Traditional organic synthesis methods, such as Claisen–Schmidt condensation,[3] Baker–Venkataraman rearrangement,[4] ionic liquid-promoted synthesis,[5] Allan–Robinson reaction,[6] the Vilsmeier–Haack reaction,[7] and the Wittig reaction[8] have been developed for the synthesis of flavones. However, they are subject to low product yields, as the reactions are conducted in a strong basic and/or acidic conditions with prolonged reaction time.

Palladium-catalyzed cross-coupling reactions have become a versatile technology in organic synthesis for the rapid connection of electrophilic and organometallic fragments through the formation of either carbon–carbon or carbon–heteroatom bonds; thus, it offers a platform for the rapid synthesis of the desired functionalized flavones (Scheme 1).[9] The appropriate choice of palladium catalysts and fine-tuning of reaction conditions are necessary for the transformation of halo- and sulfonyloxyflavones into their target compounds.

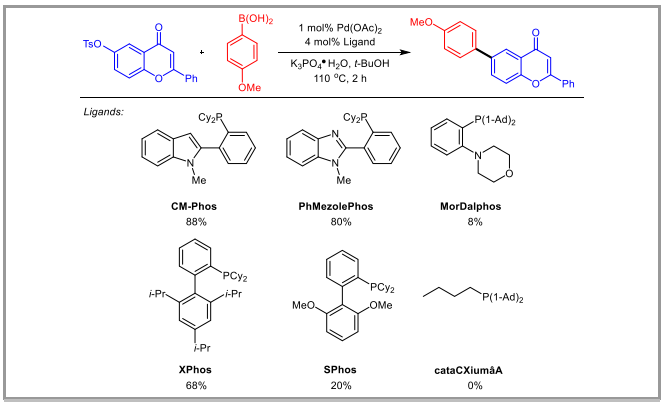


Scheme 1 Rapid synthesis of functionalized flavones via cross-coupling reactions

In the past few years, Leméire,[10] Pal,[11] Caddick,[12] and Langer, Kónya, and Patonay[13] have reported palladium-catalyzed cross-coupling reactions (Suzuki–Miyaura reaction, Stille coupling,

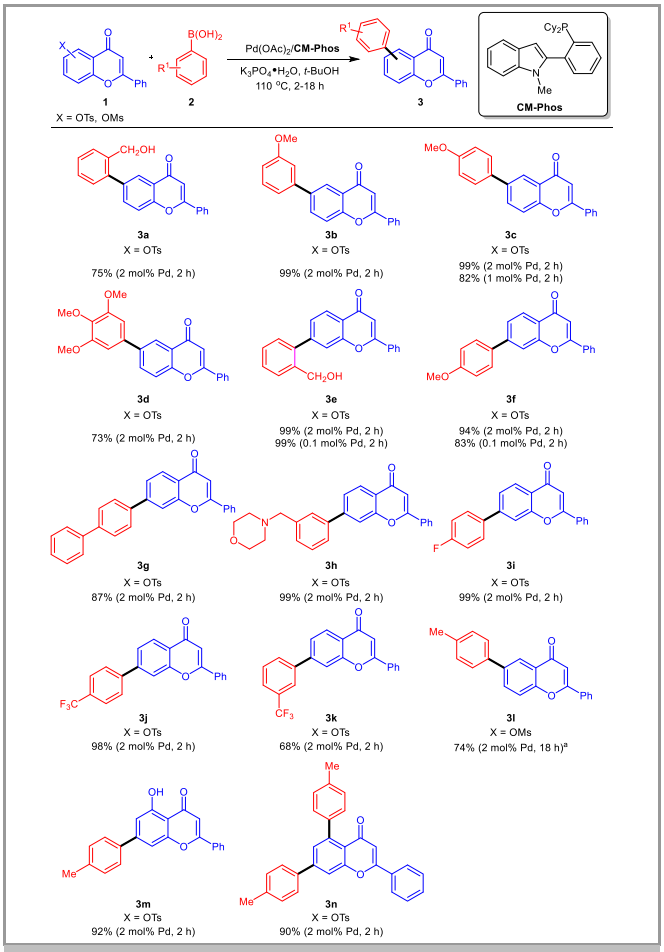
Sonogashira reaction, and amination) of iodo-, bromo-, and triflyloxyflavones. However, these reports tend to have the following potential shortcomings: 1) high catalyst loading (3–10 mol% Pd catalysts were commonly used); 2) only halo- and triflyloxyflavones were demonstrated. Flavones containing –OH groups are widespread in nature; despite the availability of haloflavones, many flavones exist only in their phenolic form.[14] Hence, sulfonyloxyflavones are desirable complements to haloflavones. They can be prepared from a variety of commercially available hydroxyflavones, which are not accessible by their halide counterparts. Although triflating agents can offer a route for transforming hydroxyflavones to electrophiles, triflyloxyflavones have high cost and low hydrolytic stability. Indeed, the use of tosyloxy- and mesyloxyflavones is much more desirable due to their cost-effectiveness[15] and high stability.[16] Hence, we envision that the use of tosyloxy- and mesyloxyflavones through advanced cross-coupling technology may provide the key to success in tackling the existing limitations and offer an efficient route for medicinal chemistry. In view of our phosphine ligand synthesis and application,[17] we aimed to develop an efficient catalyst system to diversify synthesized functionalized flavones using tosyloxy- and mesyloxyflavones.

We initially chose the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction of tosyloxy- and mesyloxyflavones to synthesize functionalized flavones. To investigate the effect of phosphine ligands, 6-tosyloxyflavone and 4-anisylboronic acid were chosen as benchmark substrates (Scheme 2). Indolylphosphine ligand, CM-Phos, was first examined. CM-Phos showed excellent catalytic activity toward the coupling reaction, and an 88% product yield was obtained. The benzimidazolyl phosphine PhMezolePhos provided a slightly lower product yield (80%). Other commercially available and well-recognized ligands, such as MorDalphos, XPhos, SPhos, and cataCXium®A, were further evaluated, and moderate product yields were obtained.



Scheme 2 Evaluation of ligand efficacy. Reaction conditions: ArOTs (0.5 mmol), Ar'B(OH)$_2$ (1.0 mmol), Pd(OAc)$_2$ (1 mol%), Ligand (4 mol%), K_3PO_4•H_2O (1.5 mmol) and *t*-BuOH (1.5 mL) were stirred at 110°C for 2 h under nitrogen. GC yields were reported using dodecane as the internal standard.

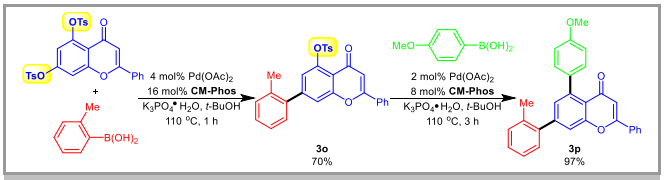
Using the identified Pd(OAc)$_2$/CM-Phos catalyst system, we next evaluated the efficacy of this catalyst system in the substrate scope of the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction using tosyloxy- and mesyloxyflavones (Scheme 3). A diverse set of arylboronic acids was successfully coupled with tosyloxyflavones. Free –OH group in 2-(hydroxymethyl)phenylboronic acid was found compatible in these reaction conditions, giving excellent product yields (Table 2, compounds **3a** and **3e**). Electron-rich (4-OMe), neutral (3-OMe), and poor (4-F, 4-CF_3 and 3-CF_3) arylboronic acids were suitable counterparts, and they afforded the corresponding products in good-to-excellent product yields (Scheme 3, compounds **3b**, **3c**, **3f**, **3i, 3j and 3k**). Tri-OMe-substituted arylboronic acid was also successfully converted to the corresponding product (Scheme 3, compound **3d**). Moreover, 4-biphenylboronic acid underwent the transformation smoothly, and part of the terphenyl-containing flavone was given (Scheme 3, compound **3g**). 3-(Morpholinomethyl)phenylboronic acid was also well-coupled with 7-tosyloxyflavone, and an excellent product yield was obtained (Scheme 3, compound **3h**). Aryl mesylates are more challenging substrates than aryl tosylates, because they are less susceptible to oxidative addition. With the use of this catalyst system, 6-mesyloxyflavone also proceeded smoothly, giving the corresponding product in good yield (Scheme 3, compound **3l**). Free –OH group in 5-hydroxy-7-tosyloxyflavone was found to be compatible under this reaction condition (Scheme 3, compound **3m**). Particular noteworthy is that the tolerance of –OH group can offer an avenue for further versatile functionalization using traditional cross-coupling protocols.[9] Diarylation of chrysin also proceeded smoothly. 5,7-Diarylflavone was obtained in excellent yield (Scheme 3, compound **3n**).



Scheme 3 Palladium-catalyzed Suzuki–Miyaura reaction of tosyloxy and mesyloxyflavones. Reaction conditions: ArOTs/ArOMs (0.5 mmol), Ar'B(OH)$_2$ (1.0 mmol), Pd(OAc)$_2$:CM-Phos = 1:4, K_3PO_4•H_2O (1.5 mmol) and *t*-BuOH (1.5 mL) were stirred at 110°C for the indicated time under nitrogen. Isolated yields

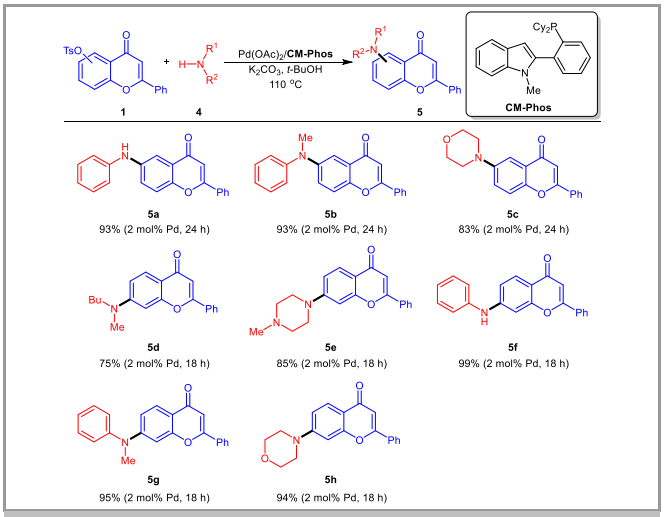
were reported. [a]Anhydrous K_3PO_4 was used instead of $K_3PO_4•H_2O$.

To examine the site selectivity of our catalyst system towards the flavones which contain multiple hydroxyl groups, ditosylated chrysin was employed in Suzuki-Miyaura reaction (Scheme 4). With only 1.0 equivalence of *o*-tolylboronic acid, the reaction rate was slightly reduced and some starting material was remained after 1 h. However, an excellent selectivity was observed and 7-arylated Chrysin was isolated in good yield (Scheme 4, compound 3o). Afterwards, 4-anisylboronic acid was employed as the second coupling partner resulting in 5,7-diarylated chrysin with different aryl rings in 97% product yield (Scheme 4, compound 3p). One-pot addition of 2.5 equivalence of *o*-tolylboronic acid led to the formation of 5,7-diarylated chrysin in 80% yield.



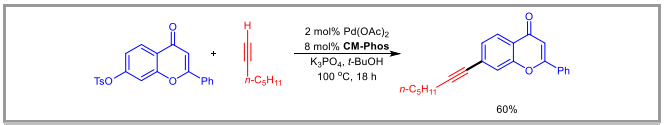
Scheme 4 Site-selective Suzuki-Miyaura reaction of ditosylated Chrysin. 1st Step reaction condition: ArOTs (0.5 mmol), Ar'B(OH)$_2$ (0.5 mmol), Pd(OAc)$_2$ (4 mol%), CM-Phos (16 mol%), $K_3PO_4•H_2O$ (1.5 mmol) and *t*-BuOH (1.5 mL) were stirred at 110°C for 1 h under nitrogen. 2nd Step reaction condition: ArOTs (0.5 mmol), Ar'B(OH)$_2$ (1.0 mmol), Pd(OAc)$_2$ (2 mol%), CM-Phos (8 mol%), $K_3PO_4•H_2O$ (1.5 mmol) and *t*-BuOH (1.5 mL) were stirred at 110°C for 3 h under nitrogen. Isolated yields were reported.

To further explore the wide-ranging effectiveness of our catalyst system in coupling reactions of tosyloxyflavones, we next turned our attention to using amines as the nucleophilic coupling partners (Scheme 5). Arylamines, such as aniline and *n*-methylaniline, were coupled smoothly with tosyloxyflavones, and excellent product yields were afforded (Scheme 5, compounds **5a**, **5b**, **5f**, and **5g**). Secondary cyclic amines, including morpholine and 1-methylpiperazine, gave the corresponding products in a good-to-excellent yield (Scheme 5, compounds **5c**, **5e**, and **5h**). Secondary acyclic amine was also found to be a feasible cross-coupling partner, but a lower yield was given (Scheme 5, compound **5d**).



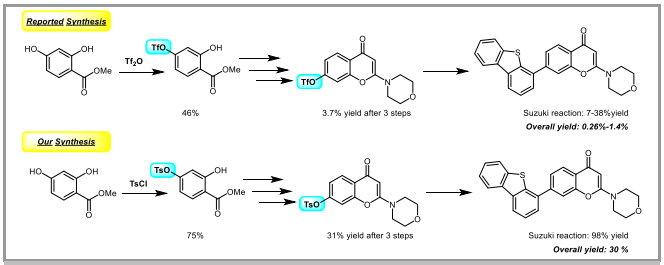
Scheme 5 Palladium-catalyzed amination of tosyloxyflavones. Reaction conditions: ArOTs (0.5 mmol), amines (0.75 mmol), Pd(OAc)$_2$:CM-Phos (1:4), PhB(OH)$_2$ (0.02 mmol), K_2CO_3 (1.25 mmol) and *t*-BuOH (1.5 mL) were stirred at 110°C for the indicated time under nitrogen. Isolated yields were reported.

Encouraged by the former success, we decided to further expand the scope. We synthesized another functionalized flavone to demonstrate the applicability of our system. 7-Tosyloxyflavone and 1-heptyne smoothly furnished the corresponding coupling product under a mild reaction condition (Scheme 6).



Scheme 6 Palladium-catalyzed Sonogashira coupling of 7-tosyloxyflavone Reaction condition: ArOTs (0.5 mmol), 1-heptyne (1.0 mmol), Pd(OAc)$_2$ (2 mol%), CM-Phos (8 mol%), K_3PO_4 (1.5 mmol) and *t*-BuOH (1.0 mL) were stirred at 100°C for 18 h under nitrogen. Isolated yield was reported.

To demonstrate the advantages of the use of tosylates and our current catalyst system, we selected 7-(dibenzo[b,d]thiophen-4-yl)-2-morpholino-4H-chromen-4-one which was found to be an analog for the potent inhibitor of the DNA-dependent protein kinase (DNA-PK) as our example (Scheme 7).[18] In the originally reported synthesis, extremely poor overall product yield (low as 0.26%) after four-step synthesis was obtained. It may suffer from the poor stability and tolerance of the triflate group. Being beneficial from high stability of tosylate group as well as the high efficiency of our catalyst system, by using a similar synthetic pathway, we have achieved an overall 30% yield after the four-step synthesis which improved over 100 times compared with the original synthesis (See the Supporting Information, Scheme S1). This promising result offered a convenient pathway for the rapid and effective synthesis to access flavones derivatives so as to accelerate the investigation of its biological activity.



Scheme 7 Synthesis of analogue for potent inhibitor of the DNA-dependent protein kinase (DNA-PK). Reaction condition: ArOTs (0.5 mmol), Ar'B(OH)$_2$ (1.0 mmol), Pd(OAc)$_2$ (2 mol%), CM-Phos (8 mol%), $K_3PO_4•H_2O$ (1.5 mmol) and *t*-BuOH (1.5 mL) were stirred at 110°C for 3 h under nitrogen. Isolated yield was reported.

In summary, we have developed the first general, efficient protocol for the rapid synthesis of functionalized flavones through palladium-catalyzed cross-coupling reactions using tosyloxy- and mesyloxyflavones as electrophiles. The combination of Pd(OAc)$_2$ and the CM-Phos ligand exhibited good compatibility with a wide range of tosyloxy- and mesyloxyflavones with different types of nucleophiles, including arylboronic acids, amines, and alkyne. Excellent product yields and a particular catalyst loading down to 0.1 mol% Pd were achieved. This protocol provided a straightforward, rapid and diversified modification of biologically active flavones. We believe that this palladium-catalyzed cross-coupling technology using the Pd(OAc)$_2$ and CM-Phos catalyst system would be a

useful tool for development of a drug library for lead optimizations and fine-tuning the biological properties of chromen-4-one-based compounds.

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Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

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(14) The commercial availability of 7-bromoflavone is far less than that of 7-hydroxylflavone.

(15) According to the 2018 Aldrich catalog: mesyl chloride ($173.5/1 L), tosyl chloride ($85.1/1 kg), triflic anhydride ($1620/1 kg).

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(19) **General procedure for Suzuki-Miyaura coupling of tosyloxy and mesyloxyflavones and representative characterization data (6-(2-(Hydroxymethyl)phenyl)-2-phenyl-4H-chromen-4-one (Scheme 3, compound 3a)) :** $Pd(OAc)_2$ (2.24 mg, 0.010 mmol) and CM-Phos (Pd:L = 1:4) were added into a Schlenk tube containing a Teflon-coated magnetic stir bar. The tube was then evacuated and flushed with nitrogen for three times. Precomplexation was conducted by adding freshly distilled dichloromethane (1.0 mL) and triethylamine (0.1 mL) into the tube. The solution was stirred and placed in a preheated oil bath (50°C) for around 1 to 2 minutes until the solvent started boiling. The solvent was then evaporated under high vacuum. Tosyloxy or mesyloxyflavones (0.5 mmol), arylboronic acid (1.0 mmol) and $K_3PO_4{\cdot}H_2O$ (345 mg, 1.5 mmol) or K_3PO_4 (318 mg, 1.5 mmol) were added into the tube, and the mixture was evacuated and flushed with nitrogen for three times again. *t*-BuOH (1.5 mL) was added finally. The sealed tube was stirred at room temperature for one minute and then placed in a preheated oil bath (110 °C) for the reaction time indicated in Table 2. After the completion of the reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate or dichloromethane (~10 mL) and water (~3 mL) were added. The organic layer was subjected to GC analysis. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product. Eluents (Ethyl acetate: Hexane= 1: 4, R_f= 0.10) was used for flash column chromatography. White solid; m.p.=157.6-161.5 °C; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 2.17 (bs, 1H), 4.64 (s, 2H), 6.85 (s, 1H), 7.35-7.48 (m, 3H), 7.57-7.63 (m, 4H), 7.68 (d, *J*= 8.6 Hz, 1H), 7.80-7.82 (m, 1H), 8.00-8.03 (m, 2H), 8.20 (d, *J*= 2.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 62.7, 107.4, 118.0, 123.6, 125.6, 126.3, 127.7, 128.1, 128.8, 129.0, 130.1, 131.6, 131.8, 135.0, 138.0, 138.5, 139.7, 155.5, 163.5, 178.1; MS (EI): m/z (relative intensity) 326.4 (M+, 100), 298.3 (81), 196.2 (65), 168.2 (18), 139.2 (44); HRMS: calcd. for $C_{22}H_{17}O_3$+: 329.1172, found 329.1181.

(20) **General procedure for palladium-catalyzed amination of tosyloxy and mesyloxyflavones and representative characterization data (2-Phenyl-6-(phenylamino)-4H-chromen-4-one (Scheme 5, compound 5a)):** $Pd(OAc)_2$ (2.24 mg, 0.010 mmol) and CM-Phos (Pd:L = 1:4) were added into a Schlenk tube containing a Teflon-coated magnetic stir bar. The tube was then evacuated and flushed with nitrogen for three times. Precomplexation was conducted by adding freshly distilled dichloromethane (1.0 mL) and triethylamine (0.1 mL) into the tube. The solution was stirred and placed in a preheated oil bath (50°C) for around 1 to 2 minutes until the solvent started boiling. The solvent was then evaporated under high vacuum. Tosyloxy or

mesyloxyflavones (0.5 mmol), K_2CO_3 (172.5 mg, 1.25 mmol), amines (if solid, 0.75 mmol) and phenylboronic acid (2.44 mg, 0.02 mmol) were added into the tube, and the mixture was evacuated and flushed with nitrogen for three times again. Amines (if liquid, 0.75 mmol) and *t*-BuOH (1.5 mL) were added finally. The sealed tube was stirred at room temperature for one minute and then placed in a preheated oil bath (110 °C) for the reaction time indicated in Table 3. After the completion of reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate or dichloromethane (~10 mL) and water (~3 mL) were added. The organic layer was subjected to GC analysis. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product. Eluents (Ethyl acetate: DCM= 1: 4, R_f= 0.80) was used for flash column chromatography. Orange solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.99 (t, *J*= 7.3 Hz, 1H), 7.13 (d, *J*= 7.6 Hz, 2H), 7.28-7.32 (m, 2H), 7.41-7.53 (m, 5H), 7.81 (s, 1H), 7.90-7.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 106.8, 110.7, 118.5, 119.1, 122.0, 124.1, 124.8, 126.2, 129.0, 129.5, 131.4, 132.0, 141.2, 142.3, 151.0, 163.1, 178.2; MS (EI): *m/z* (relative intensity) 312.4 (M^+, 100), 207.2 (6), 154.2 (25), 128.2 (4), 78.2 (5).

(21) **General procedure for palladium-catalyzed Sonogashira reaction of tosyloxyflavone and representative characterization data (7-(Hept-1-yn-1-yl)-2-phenyl-4H-chromen-4-one (Scheme 6)):** $Pd(OAc)_2$ (2.24 mg, 0.010 mmol) and CM-Phos (Pd:L = 1:4) were added into a Schlenk tube containing a Teflon-coated magnetic stir bar. The tube was then evacuated and flushed with nitrogen for three times. Precomplexation was conducted by adding freshly distilled dichloromethane (1.0 mL) and triethylamine (0.1 mL) into the tube. The solution was stirred and placed in a preheated oil bath (50°C) for around 1 to 2 minutes until the solvent started boiling. The solvent was then evaporated under high vacuum. 7-Tosyloxyflavones (196.0 mg, 0.5 mmol) and K_3PO_4 (318.0 mg, 1.50 mmol) were added into the tube, and the mixture was evacuated and flushed with nitrogen for three times again. 1-Heptyne (131.2 μL, 1.0 mmol) and *t*-BuOH (1.0 mL) were added finally. The sealed tube was stirred at room temperature for one minute and then placed in a preheated oil bath (100 °C) for 18 h. After the completion of reaction, the reaction tube was allowed to reach room temperature. Ethyl acetate or dichloromethane (~10 mL) and water (~3 mL) were added. The organic layer was subjected to GC analysis. The filtrate was concentrated under reduced pressure. The crude products were purified by flash column chromatography on silica gel (230-400 mesh) to afford the desired product. Eluents (Ethyl acetate: Hexane= 1: 4, R_f= 0.5) was used for flash column chromatography. Light orange solid; m.p.=105.4-106.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (t, *J*= 7.3 Hz, 3H), 1.35-1.41 (m, 2H), 1.42-1.48 (m, 2H), 1.61-1.67 (m, 2H), 2.45 (t, *J*= 7.2 Hz, 3H), 6.79 (s, 1H), 7.39 (d, *J*= 8.2 Hz, 1H), 7.49-7.53 (m, 3H), 7.57 (s, 1H), 7.89 (d, *J*= 7.0 Hz, 2H), 8.11 (d, *J*= 8.2 Hz, 1H); ^{13}C NMR (1205 MHz, $CDCl_3$) δ 13.9, 19.5, 22.2, 28.1, 31.1, 79.4, 95.1, 107.7, 120.7, 122.8, 125.4, 126.2, 128.5, 129.0, 129.9, 131.6, 155.9, 163.4, 177.9; MS (EI): *m/z* (relative intensity) 316.1 (M^+, 64), 301.1 (14), 287.1 (100), 273.1 (56), 261.1 (74), 231.1 (35); HRMS: calcd. for $C_{22}H_{21}O_2^+$: 317.1536, found 317.1539.