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Palladium catalyzed three component coupling reaction between chromones, alcohols, and allylic acetates: diversity-oriented synthesis of highly substituted chromones

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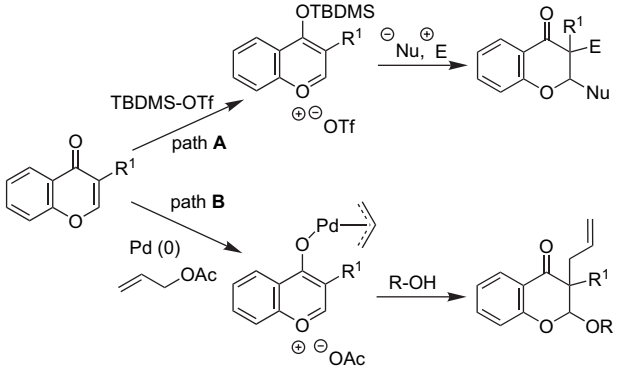
Abstract—This paper describes the palladium catalyzed highly efficient three component coupling (TCC) reactions between chromones, allylic acetates, and alcohols, which lead to a library of multiply substituted chromones. The activity of various palladium catalysts, such as $Pd(PPh_3)_4$ and $Pd_2dba_3 \cdot CHCl_3$ and their combination with various bisphosphine ligands, was investigated by using THF as a solvent, which revealed that $Pd(PPh_3)_4$ catalyst was the best one. The reaction most probably proceeds via the formation of benzopyrilium cation, generated from the reaction between chromones and allyl acetate, in the presence of palladium catalyst. The subsequent trapping of the benzopyrilium cation by alcohols would give the corresponding products in excellent yields. This alkoxy-allylation reaction was highly diastereoselective and only one diastereomer was obtained in all the cases.

1. Introduction

The generation of oxonium/benzopyrilium cations, followed by their subsequent trapping with carbon and heteroatom nucleophiles, is one of the valuable processes in organic synthesis.[1] The tendency of an oxonium cation to undergo various cascade reactions is also becoming an equally important area.[2] The generation of oxonium cations by using a transition metal as a catalyst is one of the powerful ways for generating them because the reaction can be performed under extremely mild conditions and with high atom economy.[3] Thus the organic transformation involving the metal mediated formation of oxonium ions and their in situ reactions are highly desirable.

Diversity-oriented synthesis (DOS) is an emerging field involving the synthesis of combinatorial libraries of diverse small molecules for biological screening.[4] Among various heterocycles, chromones are important structural motifs, which are often found in various natural products[5] and exhibit a wide range of biological activities.[6] Several methods are reported in the literature for the synthesis of chromones and their analogs. Two general approaches are commonly used for the preparation of substituted chromones: the first, functionalization of existing chromone containing precursors by introduction of new substituents,[7] and the second, formation of a new chromone ring by cyclization of suitable substrates.[8] Due to the importance of chromones as pharmacologically active molecules, a general and diversity-oriented approach toward these compounds is highly desirable.[9]

Chromones are structurally interesting compounds in which phenolic oxygen is attached to α,β-unsaturated ketone. The introduction of substituents at the C-2 and C-3 positions of chromones via activation by benzopyrylium cation formation by means of *tert*-butyldimethylsilyl triflate is the most popular way for the diversity-oriented synthesis of chromones (Scheme 1, path A).[7a] This led us to an idea that such process could be performed catalytically through the palladium technology and, if so, it is an interesting theme whether such a process shows high levels of



Scheme 1. Various modes of activation of chromones.

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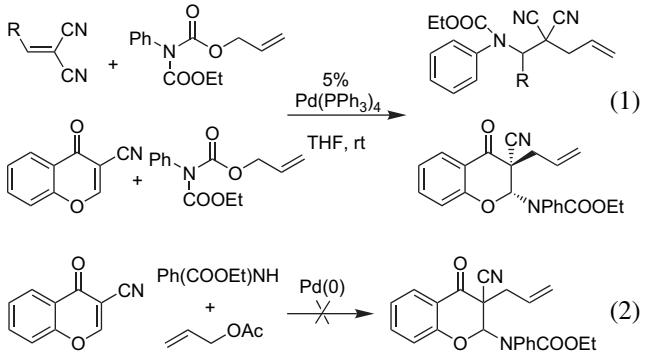
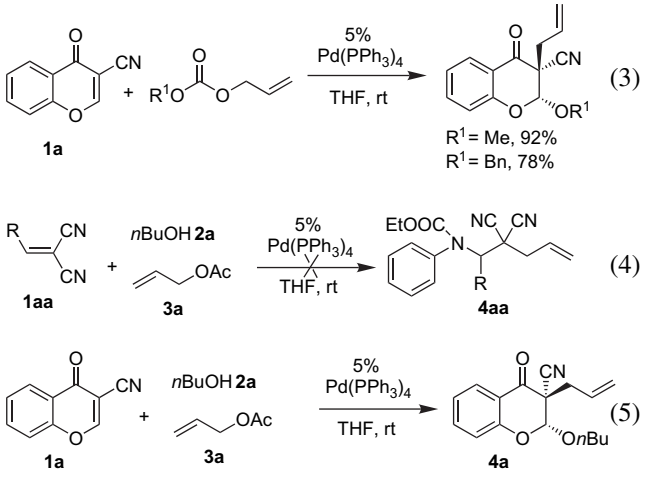
diastereoselection or not (Scheme 1, path B). A prime motivation for us was that, if successful, this would represent an efficient approach to highly substituted chromone analogs.

Recently, we reported the palladium catalyzed tandem amino-allylation of highly activated olefins and chromones via decarboxylative aza-Michael addition–allylation cascade (Eq. 1).[10] The use of allylic carbamate was the prime need for the reaction to proceed; the three component coupling reaction between chromones, allylic substrates, and amines did not give the products (Eq. 2). In a similar line, we were able to obtain the alkoxy-allylated chromones, via decarboxylative oxa-Michael addition–allylation cascade, in high yields and with excellent stereoselectivities (Eq. 3).[11] However, the three component coupling between chromones, allylic acetate, and alcohols is more desirable as it would reduce a step for the preparation of allylic carbonate from allylic alcohols. Accordingly, a mixture of benzylidenemalononitrile **1aa** (1 equiv), *n*-BuOH **2a** (1.2 equiv), and allyl acetate **3a** in the presence of $Pd(PPh_3)_4$ (5 mol %) was stirred in THF at rt for 12 h (Eq. 4). The desired product was not obtained at all and the starting material **1aa** was recovered. To our surprise, when the chromone **1a** was treated with **2a** and **3a** under identical conditions, the desired alkoxy-allylation product **4a** was obtained in an excellent yield. The detailed study of this work is described herein.



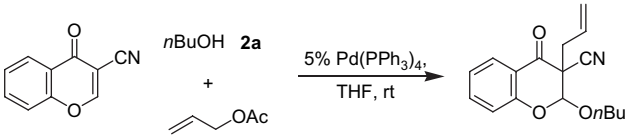


2. Results and discussion

At first, a mixture of the chromone **1a**, allyl acetate **3a**, and *n*-BuOH **2a** in the presence of $Pd(PPh_3)_4$ (5 mol %) was stirred in THF at rt for 12 h. The starting materials completely disappeared giving the alkoxy-allylation product **4a** in 88% isolated yield (Table 1, entry 1). In the absence of $Pd(PPh_3)_4$ no reaction took place even after heating at 100 °C for 24 h. The product was obtained as a single stereoisomer as can be judged from the ^1H NMR spectrum of the crude reaction mixture. Next, the activity of various palladium complexes obtained by mixing $Pd_2dba_3\cdot CHCl_3$ and various bisphosphine ligands was examined. When $Pd_2dba_3\cdot CHCl_3$ was employed alone as a palladium source, the reaction did not proceed (entry 2). The combination of $Pd_2dba_3\cdot CHCl_3$ and 40 mol % PPh_3 worked well and the desired compound was isolated in 82% yield (entry 3). As shown in entry 4, the use of dppb as a ligand in combination with $Pd_2dba_3\cdot CHCl_3$ gave the product **4a** in 57% yield. When dppf was employed as a ligand the reaction proceeded smoothly and the desired product was obtained in 88% yield (entry 5). However, the use of other bidentate ligands such as dppp, dppm, and dppe was proved unsatisfactory (entries 6–8).

Since the optimum reaction conditions for the formation of **4a** were in hand, we investigated the alkoxy-allylation reaction of various 2-cyano chromones **1**. The results are summarized in Table 2. Treatment of **1a** with MeOH **2b** under the standard conditions gave the desired product **4b** in 94% yield (entry 1). The reaction of cyclopropyl methyl alcohol **2c** with **1a** and **3a** also proceeded smoothly to produce **4c** in 79% yield (entry 2). The reaction of the olefinic alcohols such as **2d–2f** with **1a** and **3a** proceeded without problem to give the products **4d–4f** in excellent to good yields (entries 3–5). The use of benzyl alcohol **2g** also proved satisfactory giving the alkoxy-allylated chromone **4g** in 81% yield (entry 6). The secondary alcohol such as *i*-PrOH could also be employed as a nucleophile for this reaction without affecting the yield and reaction time (entry 7). However, in the case of *tert*-butanol **2i** a complex mixture of unidentified products was obtained indicating that the tertiary alcohol is not suitable nucleophile in this reaction (entry 8). All additional attempts to make feasible the reaction with tertiary alcohols

Table 1. Effect of various palladium complexes for TCC reaction[a]

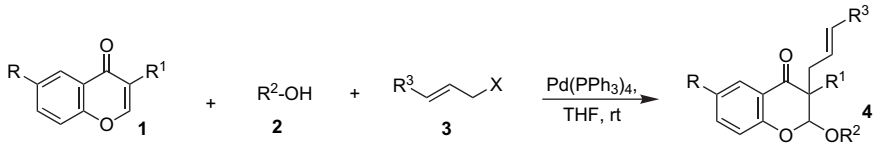


1a 3a 4a

Entry	Pd catalyst (5%)	Phosphine	NMR yield[b] (%)
1	$Pd(PPh_3)_4$	—	91 (88)[c]
2	$Pd_2dba_3\cdot CHCl_3$	—	0
3	$Pd_2dba_3\cdot CHCl_3$	PPh_3 (40 mol %)	82
4	$Pd_2dba_3\cdot CHCl_3$	dppb (20 mol %)	57
5	$Pd_2dba_3\cdot CHCl_3$	dppf (20 mol %)	88
6	$Pd_2dba_3\cdot CHCl_3$	dppp (20 mol %)	15
7	$Pd_2dba_3\cdot CHCl_3$	dppm (20 mol %)	5
8	$Pd_2dba_3\cdot CHCl_3$	dppe (20 mol %)	5

[a] *n*-Butanol **2a** of 1.5 equiv was added to a solution of **1a** (0.2921 mmol), 1.2 equiv allyl acetate **3a**, and 5 mol % $Pd(PPh_3)_4$ in THF and the mixture was stirred at rt for 12 h.
[b] NMR yield was calculated by using CH_2Br_2 as an internal standard.
[c] Yield in parenthesis shows isolated yield.

Table 2. Three component coupling between chromones, alcohols, and allylic substrates[a]



Entry	Carbamate (**1**)	R^2–OH (**2**)	Allylic substrate (**3**)	Product (**4**)	Yield[b] (%)
1	**1a**; R=H, R^1=CN	MeOH **2b**	**3a**; X=OAc, R^3=H	**4b**	94
2	**1a**; R=H, R^1=CN	HO **2c**	**3a**; X=OAc, R^3=H	**4c**	79
3	**1a**; R=H, R^1=CN	OH, 7 **2d**	**3a**; X=OAc, R^3=H	**4d**	78
4	**1a**; R=H, R^1=CN	OH **2e**	**3a**; X=OAc, R^3=H	**4e**	51
5	**1a**; R=H, R^1=CN	Ph, OH **2f**	**3a**; X=OAc, R^3=H	**4f**	70
6	**1a**; R=H, R^1=CN	Ph, OH **2g**	**3a**; X=OAc, R^3=H	**4g**	81
7	**1a**; R=H, R^1=CN	OH **2h**	**3a**; X=OAc, R^3=H	**4h**	88
8	**1a**; R=H, R^1=CN	OH **2i**	**3a**; X=OAc, R^3=H	**4i**	0[c]
9	**1a**; R=H, R^1=CN	OH **2j**	**3a**; X=OAc, R^3=H	**4j**	0[d]
10	**1a**; R=H, R^1=CN	Ph, OH **2k**	**3a**; X=OAc, R^3=H	**4k**	70
11	**1a**; R=H, R^1=CN	H_3C, OH **2l**	**3a**; X=OAc, R^3=H	**4l**	60
12	**1a**; R=H, R^1=CN	*n*-BuOH **2a**	**3b**; X=OAc, R^3=Ph	**4m**	99
13	**1a**; R=H, R^1=CN	*n*-BuOH **2a**	**3c**; X=OAc, R^3=CH_3	**4n**	96[e]
14	**1b**; R=CH_3, R^1=CN	*n*-BuOH **2a**	**3a**; X=OAc, R^3=H	**4o**	93
15	**1c**; R=F, R^1=CN	*n*-BuOH **2a**	**3a**; X=OAc, R^3=H	**4p**	86
16	**1d**; R=H, R^1=CHO	*n*-BuOH **2a**	**3a**; X=OAc, R^3=H	**4q**	73[f,g]
17	**1d**; R=H, R^1=CHO	OH **2h**	**3a**; X=OAc, R^3=H	**4r**	79[f,g]

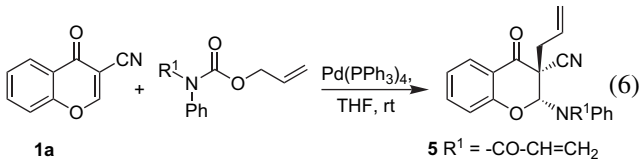
[a] Compound **2** of 1.5/1.2 equiv was added to a solution of **1a** (0.2921 mmol), 1.2 equiv allyl acetate **3a**, and 5 mol % $Pd(PPh_3)_4$ in THF and the mixture was stirred at rt for 12 h. In the case of MeOH, *i*-PrOH, and *n*-BuOH, 1.5 equiv of alcohol was used and for other alcohols only 1.2 equiv was used.
[b] Isolated yields.
[c] Starting material was recovered.
[d] Complex mixture was obtained.
[e] A mixture of *E*-(**4na**) and *Z*-(**4nb**) isomers in the ratio of 8:2 was obtained.
[f] Compounds **2a** (1.5 equiv), or **2h** (1.5 equiv), together with **3a** (2 equiv) were used.
[g] $Pd(PPh_3)_4$ catalyst of 10 mol % was used.

proved to be futile. This observation is in agreement to our previous reports wherein we showed that tertiary alcohols were not good nucleophiles for the trapping of oxonium cations.[1] It should be worth mentioning that the alcohol containing terminal alkyne was not tolerated under the reaction conditions. Thus, when **1a** was treated with propargyl alcohol **2j** and **3a**, the reaction did not afford the desired product; instead a complex mixture was obtained (entry 9). The formation of a complex mixture of unidentified products may be due to rapid oligomerization of the terminal alkyne by the palladium catalyst. Employing the substituted propargyl alcohols **2k** and **2l** as nucleophiles, the TCC reaction proceeded well with **1a** and **3a** to give the products **4k** and **4l** (entries 10 and 11). The three component coupling reaction also proceeded with cinnamyl acetate **3b** and crotyl acetate **3c** to give **4m** and **4n** in 99 and 96% yields, respectively (entries 12 and 13). It should be noted that the allylation with **3b** and **3c** took place exclusively at the α-position of the allylic acetate and no C–C bond forming product at the γ-position was obtained. The methyl and fluorine substituted chromones **1b** and **1c** also underwent smooth reaction with **2a** and **3a** giving the corresponding products **4o** and **4p** in 93 and 86% yields, respectively (entries 14 and 15). 2-Formyl chromone **1d** also reacted well when *n*-BuOH and *i*-PrOH were used as nucleophiles, however, excess amounts of the reagents and catalyst were necessary in order to complete the reactions (entries 16 and 17). It should be noted that the secondary allylic acetate, such as 2-cyclohexene-1-yl acetate, could not be used for these types of reactions.

2.1. Determination of stereochemistry

It proved difficult to assign the relative stereochemistry at the C-2 and C-3 positions of the products by using NMR

techniques. Therefore, the stereochemistry was assigned by chemical correlation as follows. The palladium catalyzed reaction of allyl carbamates with the chromone **1a** in THF gave the amino-allylation product **5** whose structure was unambiguously confirmed by X-ray crystallographic analysis (Eq. 6).[10] Under the similar reaction conditions, **1a** was treated with allyl methyl carbonate and allyl benzyl carbonate to give the alkoxy-allylation products (Eq. 3). Since the mechanistic feature of both the reactions mentioned in Eqs. 3 and 6 is similar, the same stereochemistry as observed in Eq. 6 was, therefore, assigned to the alkoxy-allylation products. The spectral data of these compounds were exactly in agreement with those of the compounds **4b** and **4g** obtained by the TCC reaction (Table 2, entries 1 and 6), indicating that same stereoselection as observed in Eq. 6 took place in the present case.



(6)

2.2. Mechanistic hypothesis

A plausible mechanism for the three component coupling reaction is shown in Figure 1. The oxidative addition of Pd(0) to allyl acetate **3a** leads to the formation of the π-allylpalladium complex **6**. The π-allylpalladium complex **6** thus formed would react with the species **1a′**, which is a resonance form of **1a**, either at the nucleophilic oxygen or at the carbon attached by CN group. The former mode of addition might produce **7a**, which in turn undergoes the tautomerization to **7** in the presence of palladium catalyst, and the latter mode of addition produces **7** directly. However, the intermediate **7a** was not detected even by a careful TLC analysis of the reaction progress; only the starting material, **3a**, and **7** were detected. The reaction of **7** with *n*-BuOH and concomitant reductive elimination of Pd(0) would afford the alkoxy-allylation product **4a** with the regeneration of Pd(0).

Alternatively, the π-allylpalladium acetoxy complex **6**, formed by the oxidative addition of Pd(0) to allyl acetate **3a**, reacts with an alcohol to form the π-allylpalladium alkoxy complex **8** after removal of AcOH.[12] The alkoxy anion

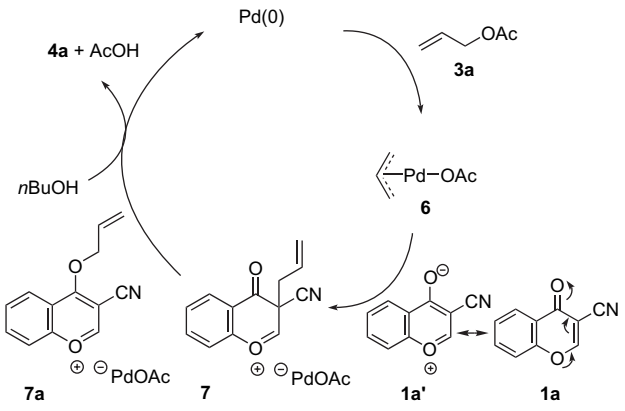


Figure 1. A proposed mechanism for the three component coupling reactions.

in **8** would react with the chromone **1a** to give the π-allylpalladium complexes **9** having the oxygen enolate. Ketolization of the palladium enolate **9** followed by reductive elimination,[13] or formation of the corresponding allyl ether through the direct reductive elimination from **9** followed by the allyl transfer from oxygen to carbon as mentioned in Figure 1, would give the product **4a** with the regeneration of Palladium(0).

Very high diastereoselectivity should be mentioned here. The stereochemical relation between the allyl group and OR group at the position beta to the allyl is trans. In the mechanism of Figure 1, OR attacks from the side opposite to the ally group, since CN is sterically far less bulky than $CH_2CH{=}CH_2$. In the mechanism of Figure 2, the allyl group attacks the carbon attached by CN from the side opposite to OR. Accordingly, the trans selectivity is obtained.

The precise mechanism of the present reaction is not known at present. However, it became clear that the presence of γ-oxygen in the Michael acceptor is very important for the reaction to occur. The highly activated olefins (Fig. 3), which lack γ-oxygen did not undergo the present alkoxy-allylation reaction although those olefins are known to be the best substrate[11] for the amino-allylation reactions. Accordingly, the oxonium ion mechanism proposed in Figure 1 might be operating here. Despite of the precise reaction mechanism, we are now in a position to synthesize various highly substituted chromone analogs, which might be useful for the diversity-oriented synthesis.

It can also be accounted that the activation of chromone first takes place in the presence of palladium catalyst forming the Michael addition product **10**.[14] The compound **10** containing an active methyne would then undergo Tsuji–Trost type allylation[15] to give **4a** (Scheme 2). However, the reaction of **1a** with *n*-BuOH in the presence of palladium catalysts [including Pd(II)] under the standard conditions did not

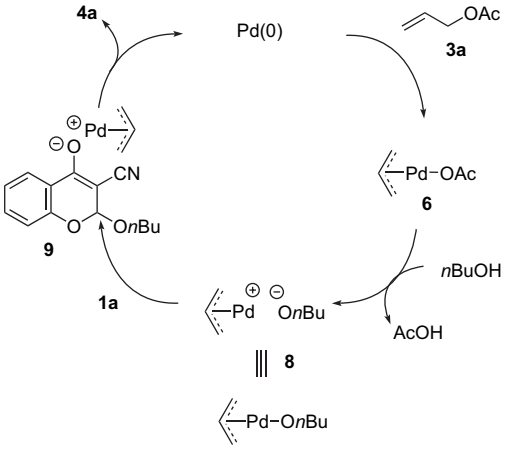


Figure 2. Alternative mechanism for the three component coupling reactions.

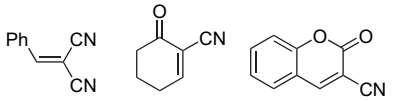
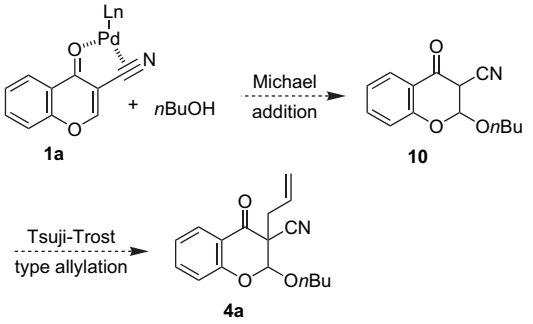


Figure 3. Structures of unreactive olefins.

give the Michael addition product **10**, clearly ruling out the possibility.



Scheme 2.

In conclusion, we have developed a new palladium catalyzed three component coupling reaction between chromones, allylic acetates, and alcohols. The yields are excellent in most cases, and the diastereoselectivities are very high. This work has not only discussed the development of a novel reaction but also described its usefulness for the diversity-oriented synthesis of chromones. Although these reactions are limited to 2-cyano and 2-formyl chromones, the utility of cyano and formyl groups for further structural manipulation is noteworthy.[16]

3. Experimental section

^{1}H and ^{13}C spectra were operated at 400 and 100 MHz, respectively, all referenced to internal tetramethylsilane (TMS) at 0.0 ppm. Reactions were monitored by thin-layer chromatography (Merck 60 F_{254}). Column chromatography was performed on neutral silica gel (60 N, 100–210 μm) and elution with hexane/AcOEt, 9:1 solvent system. All chromones and alcohols are commercially available and were used as such without further purifications. $Pd(PPh_3)_4$ was prepared according to the literature procedure.[17] TLC was performed on aluminum-precoated plates of silica gel 60 with an F_{254} indicator and visualized under UV light or developed by immersion in the solution of 0.6% $KMnO_4$ and 6% K_2CO_3 in water.

3.1. General procedure for three component coupling reaction

The preparation of **4a** is representative. To a 3 mL screw capped vial equipped with a magnetic stirring bar were added the chromone **1a** (0.050 g, 0.2921 mmol), allyl acetate **3a** (0.035 g, 0.3509 mmol), *n*-butanol **2a** (0.043 g, 0.5842 mmol), $Pd(PPh_3)_4$ (0.017 g, 0.0146 mmol), and THF (2 ml). After the mixture was stirred for 12 h at rt, TLC was taken in order to confirm whole disappearance of the starting material. The solvent was removed under reduced pressure, and the residue was purified by short silica gel column with eluant (hexane/ethyl acetate, 9:1) to give **4a** (0.73 mg) in 88% yield.

3.1.1. Compound 4a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.78 (t, J=7.0 Hz, 3H), 1.27–1.16 (m, 2H), 1.53–1.42 (m, 2H), 2.62 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.70 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 3.80–3.60 (m, 2H), 5.26 (dt, J=17.0, 1.0 Hz, 1H), 5.30 (dt, J=10.0, 1.0 Hz, 1H), 5.39 (s, 1H), 5.90 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 6.99 (d, J=8.0 Hz, 1H), 7.11 (t, J=8.0 Hz, 1H), 7.56 (t, J=8.0 Hz, 1H), 7.91 (dd, J=8.0, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 18.8, 31.0, 36.8, 54.5, 69.9, 101.3, 115.5, 118.0, 118.4, 121.7, 122.8, 127.5, 129.4, 137.0, 155.3, 184.2. IR (neat) 3150, 1616, 1610 cm^{-1}. ESI calcd for $C_{17}H_{19}NO_3$ (M^+): 285.1365. Found: 285.1368.

3.1.2. Compound 4b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.70 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 3.50 (s, 3H), 5.27 (dt, J=17.0, 1.0 Hz, 1H), 5.31 (s, 1H), 5.31 (dt, J=10.0, 1.0 Hz, 1H), 5.90 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 7.03 (d, J=8.0 Hz, 1H), 7.13 (t, J=8.0 Hz, 1H), 7.58 (t, J=8.0 Hz, 1H), 7.91 (dd, J=8.0, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 54.4, 57.0, 102.2, 115.5, 118.1, 118.4, 121.8, 122.9, 127.5, 129.3, 137.1, 155.1, 183.9. IR (neat) 2976, 2252, 1705, 1608, 1463, 1296, 991, 933 cm^{-1}. ESI calcd for $C_{14}H_{13}NO_3$ (M^+): 243.0895. Found: 243.0891.

3.1.3. Compound 4c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.22–0.03 (m, 2H), 0.52–0.39 (m, 2H), 1.04–0.93 (m, 1H), 2.62 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.70 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 3.50 (dd, J=11.0, 7.0 Hz, 1H), 3.57 (dd, J=11.0, 7.0 Hz, 1H), 5.25 (dt, J=17.0, 1.0 Hz, 1H), 5.29 (dt, J=10.0, 1.0 Hz, 1H), 5.50 (s, 1H), 5.99 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 6.98 (d, J=8.0 Hz, 1H), 7.10 (t, J=8.0 Hz, 1H), 7.55 (t, J=8.0 Hz, 1H), 7.85 (dd, J=8.0, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 2.7, 3.5, 9.8, 36.9, 54.6, 74.3, 100.6, 115.6, 118.0, 118.5, 121.7, 122.8, 127.5, 129.4, 136.9, 155.4, 184.2. IR (neat) 3270, 1621, 1618 cm^{-1}. ESI calcd for $C_{17}H_{17}NO_3$ (M^+): 283.1208. Found: 283.1205.

3.1.4. Compound 4d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36–1.11 (m, 10H), 1.53–1.45 (m, 2H), 2.04–1.95 (m, 2H), 2.62 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.70 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 3.63 (dt, J=10.0, 6.0 Hz, 1H), 3.74 (dt, J=10.0, 6.0 Hz, 1H), 4.99–4.87 (m, 2H), 5.26 (dt, J=17.0, 1.0 Hz, 1H), 5.31 (dt, J=10.0, 1.0 Hz, 1H), 5.39 (s, 1H), 5.78 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 5.96–5.84 (m, 1H), 6.99 (d, J=8.0 Hz, 1H), 7.12 (t, J=8.0 Hz, 1H), 7.59–7.53 (m, 1H), 7.91 (dd, J=8.0, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.6, 28.8, 28.9, 28.9, 28.9, 29.2, 33.6, 36.8, 54.5, 70.1, 101.3, 113.9, 115.5, 118.0, 118.4, 121.6, 122.7, 127.4, 129.4, 136.9, 138.9, 155.3, 184.1. IR (neat) 3078, 2927, 1705, 1610 cm^{-1}. ESI calcd for $C_{23}H_{29}NO_3$ (M^+): 367.2147. Found: 367.2148.

3.1.5. Compound 4e. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (d, J=7.0 Hz, 3H), 1.42–1.31 (m, 2H), 2.02–1.95 (m, 2H), 2.62 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.69 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 4.21–4.06 (m, 2H), 5.25 (dt, J=17.0, 1.0 Hz, 1H), 5.29 (dt, J=10.0, 1.0 Hz, 1H), 5.46 (s, 1H), 5.48–5.38 (m, 1H), 5.75–5.65 (m, 1H), 5.88 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 6.99 (d, J=8.0 Hz, 1H), 7.11 (t, J=8.0 Hz, 1H), 7.59–7.53 (m, 1H), 7.90 (dd, J=8.0, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 22.0, 34.2, 36.9, 54.5, 70.1, 99.7, 115.5, 118.1, 118.5, 121.7, 122.8, 123.8, 127.6, 129.4, 136.9, 137.0, 155.4, 184.1. IR (neat) 3200, 1620,

1615 cm^{-1}. ESI calcd for $C_{19}H_{21}NO_3$ (M^+): 311.1521. Found: 311.1522.

3.1.6. Compound 4f. ^1H NMR (400 MHz, $CDCl_3$) δ 2.64 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.72 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 4.44–4.33 (m, 2H), 5.25 (dt, J=17.0, 1.0 Hz, 1H), 5.29 (dt, J=10.0, 1.0 Hz, 1H), 5.52 (s, 1H), 5.89 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 6.16 (dt, J=16.0, 6.0 Hz, 1H), 6.59 (d, J=16.0 Hz, 1H), 7.01 (d, J=8.0 Hz, 1H), 7.13 (t, J=8.0 Hz, 1H), 7.35–7.20 (m, 5H), 7.57 (t, J=8.0 Hz, 1H), 7.93 (dd, J=8.0, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 54.5, 70.0, 100.2, 115.5, 118.1, 118.5, 121.8, 122.9, 123.1, 126.5, 127.6, 127.9, 128.4, 129.3, 134.0, 135.8, 137.0, 155.3, 184.0. IR (neat) 3082, 2937, 1705, 1608 cm^{-1}. ESI calcd for $C_{22}H_{19}NO_3$ (M^+): 345.1407. Found: 345.1408.

3.1.7. Compound 4g. ^1H NMR (400 MHz, $CDCl_3$) δ 2.59 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.66 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 4.77–4.66 (m, 2H), 5.19 (dt, J=17.0, 1.0 Hz, 1H), 5.23 (dt, J=10.0, 1.0 Hz, 1H), 5.44 (s, 1H), 5.82 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 6.92 (d, J=8.0 Hz, 1H), 7.08 (t, J=8.0 Hz, 1H), 7.29–7.18 (m, 5H), 7.55–7.49 (m, 1H), 7.83 (dd, J=8.0, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.8, 54.4, 71.1, 100.2, 115.5, 118.0, 118.5, 121.7, 122.9, 127.5, 127.7, 128.1, 128.4, 129.2, 135.3, 137.0, 155.1, 184.0. IR (neat) 3249, 1621, 1617 cm^{-1}. ESI calcd for $C_{20}H_{17}NO_3$ (M^+): 319.1208. Found: 319.1202.

3.1.8. Compound 4h. ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (d, J=6.0 Hz, 3H), 1.20 (d, J=6.0 Hz, 3H), 2.60 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.68 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 4.09–3.99 (m, 1H), 5.24 (dt, J=17.0, 1.0 Hz, 1H), 5.29 (dt, J=10.0, 1.0 Hz, 1H), 5.47 (s, 1H), 5.88 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 6.96 (d, J=8.0 Hz, 1H), 7.09 (t, J=8.0 Hz, 1H), 7.55 (t, J=8.0 Hz, 1H), 7.88 (dd, J=8.0, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 22.7, 36.8, 55.0, 73.3, 100.2, 115.7, 118.0, 118.4, 121.6, 122.6, 127.5, 129.5, 136.9, 155.6, 184.3. IR (neat) 3150, 1616, 1610 cm^{-1}. ESI calcd for $C_{16}H_{17}NO_3$ (M^+): 271.1208. Found: 271.1203.

3.1.9. Compound 4k. ^1H NMR (400 MHz, $CDCl_3$) δ 2.61 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.70 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 4.57–4.44 (m, 2H), 5.22 (dt, J=17.0, 1.0 Hz, 1H), 5.24 (dt, J=10.0, 1.0 Hz, 1H), 5.71 (s, 1H), 5.85 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 6.98 (d, J=8.0 Hz, 1H), 7.07 (t, J=8.0 Hz, 1H), 7.38–7.17 (m, 5H), 7.50 (t, J=8.0 Hz, 1H), 7.86 (d, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 36.9, 54.2, 57.3, 82.1, 88.1, 99.4, 115.2, 118.2, 118.4, 121.8, 121.9, 123.1, 127.6, 128.2, 128.7, 129.2, 131.6, 137.1, 155.2, 183.7. IR (neat) 3082, 2952, 1705, 1608 cm^{-1}. ESI calcd for $C_{22}H_{17}NO_3$ (M^+): 343.1208. Found: 343.1203.

3.1.10. Compound 4l. ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (t, J=2.0 Hz, 3H), 2.64 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.74 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 4.30–4.25 (m, 2H), 5.26 (dt, J=17.0, 1.0 Hz, 1H), 5.30 (dt, J=10.0, 1.0 Hz, 1H), 5.69 (s, 1H), 5.89 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 7.01 (d, J=8.0 Hz, 1H), 7.12 (t, J=8.0 Hz, 1H), 7.57 (t, J=8.0 Hz, 1H), 7.89 (dd, J=8.0, 1.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.7, 36.9, 54.1, 56.9, 72.3, 84.9, 99.0, 115.3, 118.1, 118.4, 121.8, 123.0, 127.6, 129.3, 137.0, 155.3, 183.8. IR (neat) 3130, 2985, 1705, 1608 cm^{-1}. ESI calcd for $C_{17}H_{15}NO_3$ (M^+): 281.1052. Found: 281.1053.

3.1.11. Compound 4m. ^1H NMR (400 MHz, $CDCl_3$) δ 0.78 (t, J=7.0 Hz, 3H), 1.28–1.15 (m, 2H), 1.53–1.43 (m, 2H), 2.79 (dd, J=14.0, 7.0 Hz, 1H), 2.86 (dd, J=14.0, 7.0 Hz, 1H), 3.80–3.59 (m, 2H), 5.42 (s, 1H), 6.26 (dt, J=16.0, 7.0 Hz, 1H), 6.57 (d, J=16.0 Hz, 1H), 7.03 (d, J=8.0 Hz, 1H), 7.13 (t, J=8.0 Hz, 1H), 7.40–7.22 (m, 5H), 7.59 (t, J=8.0 Hz, 1H), 7.93 (d, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 18.8, 31.0, 36.3, 54.8, 69.9, 101.3, 115.6, 118.1, 118.5, 120.4, 122.8, 126.4, 127.5, 127.9, 128.4, 135.8, 136.2, 137.0, 155.4, 184.2. IR (neat) 3359, 1620, 1610 cm^{-1}. ESI calcd for $C_{23}H_{23}NO_3$ (M^+): 361.1678. Found: 361.1678.

3.1.12. Compound 4na (*E*-isomer). ^1H NMR (270 MHz, $CDCl_3$) δ 1.75–1.68 (m, 3H), 2.63–2.54 (m, 2H), 3.49 (s, 3H), 5.31 (s, 1H), 5.59–5.43 (m, 1H), 5.75–5.62 (m, 1H), 7.02 (d, J=8.0 Hz, 1H), 7.12 (t, J=8.0 Hz, 1H), 7.61–7.53 (m, 1H), 7.94–7.87 (m, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 17.9, 36.0, 54.9, 57.0, 102.3, 115.8, 118.1, 118.6, 121.9, 123.0, 127.7, 133.0, 137.1, 155.2, 184.4. IR (neat) 2976, 1705, 1610, 1452, 933 cm^{-1}. ESI calcd for $C_{15}H_{15}NO_3$ (M+Na): 280.0944. Found: 280.0943.

3.1.13. Compound 4nb (*Z*-isomer). ^1H NMR (270 MHz, $CDCl_3$) δ 1.07–1.01 (m, 3H), 2.78–2.65 (m, 2H), 3.41 (s, 3H), 5.33–5.22 (m, 2H), 5.90–5.74 (m, 1H), 6.97 (d, J=8.0 Hz, 1H), 7.07 (t, J=8.0 Hz, 1H), 7.57–7.48 (m, 1H), 7.88–7.82 (m, 1H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 11.6, 23.1, 54.9, 57.0, 102.5, 115.8, 118.1, 118.6, 121.9, 123.0, 127.9, 133.0, 137.3, 155.2, 184.6. IR (neat) 2986, 1608, 1463, 991 cm^{-1}. ESI calcd for $C_{15}H_{15}NO_3$ (M+Na): 280.0944. Found: 280.0943.

3.1.14. Compound 4o. ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J=7.0 Hz, 3H), 1.28–1.17 (m, 2H), 1.53–1.43 (m, 2H), 2.32 (s, 3H), 2.61 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.68 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 3.78–3.58 (m, 2H), 5.25 (dt, J=17.0, 1.0 Hz, 1H), 5.30 (dt, J=10.0, 1.0 Hz, 1H), 5.36 (s, 1H), 5.89 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 6.89 (d, J=8.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 18.9, 20.4, 31.0, 37.0, 54.6, 69.8, 101.3, 115.7, 117.8, 118.1, 121.6, 127.2, 129.5, 132.4, 138.0, 153.3, 184.4. IR (neat) 3370, 1624, 1619 cm^{-1}. ESI calcd for $C_{18}H_{21}NO_3$ (M^+): 299.1521. Found: 299.1522.

3.1.15. Compound 4p. ^1H NMR (400 MHz, $CDCl_3$) δ 0.80 (t, J=7.0 Hz, 3H), 1.28–1.16 (m, 2H), 1.54–1.43 (m, 2H), 2.61 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.68 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 3.79–3.58 (m, 2H), 5.26 (dt, J=17.0, 1.0 Hz, 1H), 5.30 (dt, J=10.0, 1.0 Hz, 1H), 5.38 (s, 1H), 5.88 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 7.03–6.96 (m, 1H), 7.33–7.24 (m, 1H), 7.60–7.54 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 18.8, 31.0, 36.8, 54.4, 70.0, 101.5, 113.0, 115.3, 119.1, 119.8, 121.9, 124.5, 129.2, 151.4, 159.0, 183.6. IR (neat) 3359, 1620, 1610 cm^{-1}. ESI calcd for $C_{17}H_{18}FNO_3$ (M^+): 303.1271. Found: 303.1270.

3.1.16. Compound 4q. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.71 (t, J=7.0 Hz, 3H), 1.18–1.03 (m, 2H), 1.42–1.30 (m, 2H), 2.48 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.69 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 3.69–3.38 (m, 2H), 4.94 (dt, J=17.0, 1.0 Hz, 1H), 4.98 (dt, J=10.0, 1.0 Hz, 1H), 5.29 (s, 1H), 5.56 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 6.93 (d, J=8.0 Hz, 1H), 7.03 (t, J=8.0 Hz, 1H), 7.48 (t, J=8.0 Hz, 1H), 7.85 (dd, J=8.0, 1.0 Hz, 1H), 9.94 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 18.9, 31.0, 35.4, 62.4, 69.3, 103.5, 118.0, 119.7, 120.0, 122.2, 126.7, 130.6, 136.4, 156.2, 191.1, 199.5. IR (neat) 3343, 1726, 1697, 1608 cm^{-1}. ESI calcd for $C_{17}H_{20}O_4$ (M^+): 288.1362. Found: 288.1363.

3.1.17. Compound 4r. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (d, J=6.0 Hz, 3H), 1.02 (d, J=6.0 Hz, 3H), 2.47 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 2.70 (ddd, J=14.0, 7.0, 1.0 Hz, 1H), 3.96–3.86 (m, 1H), 4.94 (dt, J=17.0, 1.0 Hz, 1H), 4.99 (dt, J=10.0, 1.0 Hz, 1H), 5.38 (s, 1H), 5.56 (ddt, J=17.0, 10.0, 1.0 Hz, 1H), 6.91 (d, J=8.0 Hz, 1H), 7.03 (t, J=8.0 Hz, 1H), 7.48 (t, J=8.0 Hz, 1H), 7.86 (dd, J=8.0, 1.0 Hz, 1H), 9.93 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 22.9, 35.4, 62.3, 72.4, 102.2, 118.0, 119.6, 119.9, 122.1, 126.7, 130.6, 136.4, 156.4, 191.2, 199.8. IR (neat) 2976, 1728, 1689, 1608 cm^{-1}. ESI calcd for $C_{16}H_{18}O_4$ (M^+): 274.1205. Found: 274.1203.

References and notes

1. (a) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139; (b) Mondal, S.; Nogami, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2003**, *68*, 9496; (c) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764; (d) Patil, N. T.; Pahadi, N. K.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 10096; (e) Patil, N. T.; Wu, H.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 4531.
2. (a) Asao, N.; Nogami, T.; Lee, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 10921; (b) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650; (c) Asao, N.; Sato, K.; Menggenbateer; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 3682; (d) Sato, K.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 8977; (e) Dyker, G.; Hildebrandt, D. *J. Org. Chem.* **2005**, *70*, 6093; (f) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289; (g) Asao, N.; Aikawa, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **2004**, *126*, 7458; (h) Zhang, L. *J. Am. Chem. Soc.* **2005**, *127*, 16804; (i) Zhang, L.; Wang, S. *J. Am. Chem. Soc.* **2006**, *128*, 1442; (j) Furstner, A.; Hannen, P. *Chem. Commun.* **2004**, 2546; (k) Johansson, M. J.; Gorin, D. J.; Staben, S. T.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 18002; (l) Sato, K.; Yudha, S. S.; Asao, N.; Yamamoto, Y. *Synthesis* **2004**, 1409.
3. (a) Trost, B. M. *Science* **1991**, *254*, 1471; (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259; (c) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233.
4. For diversity-oriented synthesis, see: (a) Tan, D. S. *Nat. Chem. Biol.* **2005**, *1*, 74; (b) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46; (c) Schreiber, S. L. *Science* **2000**, *287*, 1964.
5. For reviews, see: (a) Saengchantara, S. T.; Wallace, T. W. *Nat. Prod. Rep.* **1986**, 465; (b) Houghton, P. J. *Alkaloids* **1987**, *31*, 67; (c) Houghton, P. J. *Stud. Nat. Prod. Chem.* **2000**, *21*, 123; For recent report, see: (d) Rukachaisirikul, V.; Chantaruk, S.; Pongcharoen, W.; Isaka, M.; Lapanum, S. *J. Nat. Prod.* **2006**, *69*, 980; (e) Yoon, J. S.; Lee, M. K.; Sung, S. H.; Kim, Y. C. *J. Nat. Prod.* **2006**, *69*, 290.
6. For representative reviews, see: (a) Havsteen, B. *Biochem. Pharmacol.* **1983**, *32*, 1141; (b) Edwards, A. M.; Howell, J. B. L. *Clin. Exp. Allergy* **2000**, *30*, 756; (c) Birt, D. F.; Hendrich, S.; Wang, W. *Pharmacol. Ther.* **2001**, *90*, 157; (d) Kim, H. P.; Son, K. H.; Chang, H. W.; Kang, S. S. *J. Pharm. Sci.* **2004**, *96*, 229; (e) Kosmider, B.; Osiecka, R. *Drug Dev. Res.* **2004**, *63*, 200.
7. (a) Lee, Y.-G.; Ishimaru, K.; Iwasaki, H.; Ohkata, K.; Akiba, K.-Y. *J. Org. Chem.* **1991**, *56*, 2058; (b) Kumar, K.; Kapoor, R.; Kapur, A.; Ishar, M. P. S. *Org. Lett.* **2000**, *2*, 2023; (c) Wallace, T. W. *Tetrahedron Lett.* **1984**, *25*, 4299; (d) Clarke, P. D.; Fitton, A. O.; Suschitzky, H.; Wallace, T. W.; Dowlatshahi, H. A.; Suschitzky, J. L. *Tetrahedron Lett.* **1986**, *27*, 91; (e) Saengchantara, S. T.; Wallace, T. W. *J. Chem. Soc., Chem. Commun.* **1986**, 1692; (f) Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *43*, 3075.
8. For some recent examples, see: (a) Lee, K. S.; Seo, S. H.; Lee, Y. H.; Kim, H. D.; Son, M. H.; Chung, B. Y.; Lee, J. Y.; Jin, C.; Lee, Y. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2857; (b) Zembower, D. E.; Zhang, H. *J. Org. Chem.* **1998**, *63*, 9300; (c) Krohn, K.; Vitz, J. *Eur. J. Org. Chem.* **2004**, *1*, 209; (d) Joo, Y. H.; Kim, J. K.; Kang, S. H.; Noh, M. S.; Ha, J. Y.; Choi, J. K.; Lim, K. M.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413; (e) Zhang, F.-J.; Lin, G.-Q.; Huang, Q.-C. *J. Org. Chem.* **1995**, *60*, 6427; (f) Lin, C.-F.; Duh, T.-H.; Lu, W.-D.; Lee, J.-L.; Lee, C.-Y.; Chen, C.-C.; Wu, M.-J. *J. Chin. Chem. Soc.* **2004**, *51*, 183; (g) Bhat, A. S.; Whetstone, J. L.; Brueggemeier, R. W. *Tetrahedron Lett.* **1999**, *40*, 2469; (h) Nakatani, K.; Okamoto, A.; Saito, I. *Tetrahedron* **1996**, *52*, 9427; (i) Seijas, J. A.; Vazquez-Tato, M. P.; Carballido-Reboredo, R. *J. Org. Chem.* **2005**, *70*, 2855; (j) Kabalka, G. W.; Mereddy, A. R. *Tetrahedron Lett.* **2005**, *46*, 6315; (k) Varma, R. S. *J. Heterocycl. Chem.* **1999**, *36*, 1565; (l) Liang, B.; Huang, M.; You, Z.; Xiong, Z.; Lu, K.; Fathi, R.; Chen, J.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 6097; (m) Miao, H.; Yang, Z. *Org. Lett.* **2000**, *2*, 1765.
9. For the reports focusing on the diversity-oriented synthesis of multiply substituted chromones, see: (a) Zhou, C.; Dubrovsky, A. V.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 1626; (b) Dahlen, K.; Wallen, E. A. A.; Grotli, M.; Luthman, K. *J. Org. Chem.* **2006**, *71*, ASAP.
10. Patil, N. T.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 6991.
11. Nakamura, H.; Sekido, M.; Ito, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6838.
12. Aoyagi, K.; Nakamura, H.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 5977.
13. (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044; (b) Trost, B. M.; Xu, J. *J. Am. Chem. Soc.* **2005**, *127*, 2846; (c) Minami, I.; Nisar, M.; Yuhara, M.; Shimizu, I.; Tsuji, J. *Synthesis* **1987**, 992; (d) Ohmori, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 755; (e) Nicolaou, K. C.; Vassilikogiannakis, G.; Magerlein, W.; Kranich, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2482; (f) Herrinton, P. M.; Klotz, K. L.; Hartley, W. M. *J. Org. Chem.* **1993**, *58*, 678.
14. The Lewis acid and transition metal catalyzed activation of carboalkynes is known, see: (a) Asao, N.; Asano, T.; Ohishi, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4817; (b) Asao, N.; Ohishi, T.; Sato, K.; Yamamoto, Y. *Tetrahedron* **2002**, *58*,

8195; (c) Yao, T.; Zhang, X.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 11164.
15. (a) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813; (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395; (c) Tsuji, J. *Transition Metal Reagents and Catalysts*; Wiley: New York, NY, 2000; Chapter 4.
16. Apart from the ability of cyano group to undergo various structural manipulation depending on the reagents used, it can be used for various reaction, see: Liu, H.-J.; Zhu, J.-L.; Shia, K.-S. *Tetrahedron Lett.* **1998**, *39*, 4183.
17. Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.