Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2011, **9**, 6265

www.rsc.org/obc

PAPER

Generation of diverse 2-pyrones *via* palladium-catalyzed site-selective Suzuki-Miyaura couplings of 3-bromo-4-tosyloxy-2-pyrone†

Xiaoli Lei,[a] Liang Gao,[a] Qiuping Ding,[a] Yiyuan Peng*[a] and Jie Wu*[b]

Received 19th May 2011, Accepted 8th June 2011
DOI: 10.1039/c1ob05783a

Based on different reactivity of the (pseudo)halide substituents in the 2-pyrone (3-Br and 4-OTs), palladium-catalyzed sequential site-selective Suzuki–Miyaura cross-coupling reactions of 3-bromo-6-methyl-4-tosyloxy-2-pyrone are described, which afford the diverse 2-pyrones in good yields.

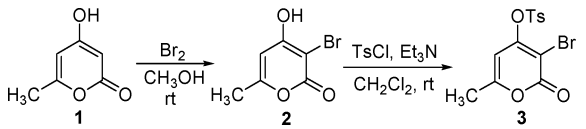
Introduction

2-Pyrone is the structural unit in various biologically active natural products.[1] Compounds with different substitutions on the 2-pyrone scaffold show diverse biological activities (such as anticancer and antimicrobial agents, HIV-protease inhibitor and selective cyclooxygenase-2 inhibitor).[2] Meanwhile, 2-pyrone is a versatile building block in organic synthesis.[3] For example, it has been utilized as a diene component in Diels–Alder reactions,[4] and as a precursor for the synthesis of other heterocyclic systems.[5] So far, various methods have been developed for the synthesis of substituted 2-pyrones. However, the formation of substituted 2-pyrones usually suffered from multi-steps, harsh reaction conditions and generally low yields.[6] Alternatively, halogenated 2-pyrones have been used for direct couplings.[7–10] Additionally, they can be converted into organometallic reagents (such as tin,[11] boron,[12] zinc,[13] and copper-based reagents[14]) for couplings with electrophilic partners. Although the above research has focused on the use of palladium-catalyzed C–C bond formation for introduction of substituent 2-pyrones, most of these methods are centered on mono-substituted 2-pyrones. Applications of transition metal-catalyzed reactions for the synthesis of 3,4-disubstituted 2-pyrones are limited, which is due to the restrictions of regioselectivity problems. Therefore, the development of an effective strategy for the synthesis of diverse 2-pyrones, especially for 3,4-disubstituted 2-pyrones is highly desirable.

Recently, transition-metal-catalyzed site-selective cross-coupling reactions have been developed for the compounds bearing two or more leaving groups, especially dihaloheteroarenes.[15,16] We also applied the palladium-catalyzed site-selective cross-coupling reactions for the synthesis of 3,4-disubstituted coumarins, which include 3,4-diaryl-coumarins, 3-amino-4-arylcoumarins, and 3-aryl-4-aminocoumarins.[16f] Prompted by these results, we conceived that the generation of differentially 3,4-disubstituted 2-pyrones could be accessed by using the similar strategy. Thus, the key step in our program is to introduce leaving groups with different reactivities to the electronically different C-3 and C-4 positions of 2-pyrones. We envisioned that based on the controllable chemoselectivity of two leaving groups, substituents would be expected to be successively installed into the 2-pyrone moiety. Herein, we would like to describe our recent efforts for the synthesis of 3,4-disubstituted 2-pyrones through palladium-catalyzed site-selective couplings of 3-bromo-4-tosyloxy-2-pyrone.

Results and discussion

As mentioned above, our strategy is based on the elaboration of the readily available 2-pyrone core structure using site-selective cross-coupling reactions. Thus, 4-hydroxy-2-pyrone **1** was selected as the target for further development due to its easy availablility. After halogenation and sulfonylation of 4-hydroxy-2-pyrone, 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** could be prepared easily with a total yield of 86% (Scheme 1).



Scheme 1 Synthesis of 3-bromo-4-tosyloxy-2-pyrone **3** from 4-hydroxy-2-pyrone **1**.

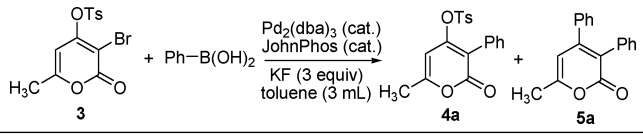
Due to the great functional group tolerance of Suzuki-Miyaura cross-coupling reaction,[17] initial studies were performed for the palladium-catalyzed reaction of 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** with phenylboronic acid (Table 1). To test the C3 and C4 selectivity, the reaction was carried out in the presence of $Pd_2(dba)_3$, JohnPhos, and KF in toluene. A mixture of mono-coupled product **4a** and di-coupled product **5a** were obtained

[a]*Key Laboratory of Functional Small Organic Molecules, Ministry of Education and College of Chemistry and Chemical Engineering, Jiangxi Normal University, Nanchang, Jiangxi, 330022, China. E-mail: yypeng@jxnu.edu.cn; Fax: +86 791 812 0396; Tel: +86 791 812 0396*

[b]*Department of Chemistry, Fudan University, 220 Handan Road, Shanghai, 200433, China. E-mail: jie_wu@fudan.edu.cn; Fax: +86 21 6564 1740; Tel: 86 21 6510 2412*

† Electronic supplementary information (ESI) available: General experimental information, characterization data, ^1H and ^{13}C NMR spectra of compounds **4–6**. See DOI: 10.1039/c1ob05783a

Table 1 Initial studies for palladium-catalyzed reaction of 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** with phenylboronic acid



Entry	$Pd_2(dba)_3$ (mol%)	JohnPhos (mol%)	$PhB(OH)_2$ (equiv.)	T/°C	Yield (%)[a] (**4a**/**5a**)
1	2.5	5	1.5	85	38/10
2	2.5	5	1.5	75	35/6
3	2.5	5	1.5	60	49/0
4	2.5	5	1.5	40	15/0
5	2.5	5	1.5	rt	5/0
6	2.5	5	1.1	60	40/0
7	2.5	5	2.0	60	45/0
8	2.5	5	3.0	60	46/0
9	5.0	10	1.5	60	40/0
10	7.5	15	1.5	60	50/0

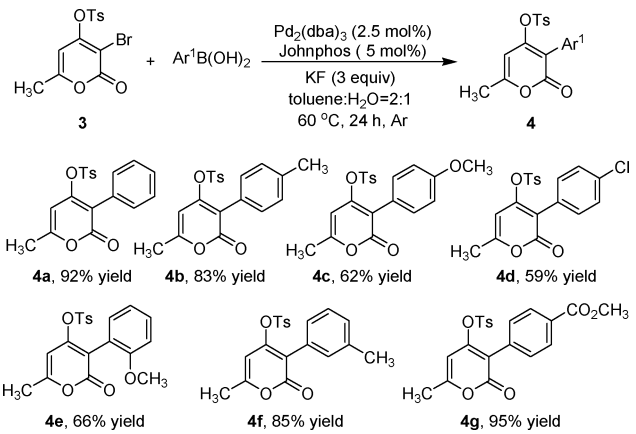
[a] Isolated yield based on 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3**.

in 38% and 10% yield, respectively (Table 1, entry 1) when the reaction occurred at 85 °C catalyzed by 2.5 mol% of $Pd_2(dba)_3$ and 5 mol% of JohnPhos. The amount of compound **5a** was reduced when the temperature decreased (Table 1, entry 2). Only product **4a** was generated when the reaction was performed at 60 °C with a 49% isolated yield (Table 1, entry 3). However, the reaction was retarded when the temperature was lower (Table 1, entries 4 and 5). No obvious influence was observed when the amount of phenylboronic acid or palladium catalyst was changed (Table 1, entries 6–10).

To further improve the reaction, we investigated other reaction parameters, such as palladium catalyst, ligand, base, and solvent (Table 2). To our delight, screeing of solvents (Table 2, entries 1–13) revealed that mono-coupled product **4a** was generated in 92% yield when toluene/water (v/v: 2/1) was used as the co-solvent in the presence of $Pd_2(dba)_3$, JohnPhos, and KF (Table 2, entries 13), and no formation of 4-position coupled product was observed. Reactions employing other palladium catalysts such as $Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and Pd/C gave rise to the corresponding product **4a** in lower yields (Table 2, 14–17). Inferior results were displayed when other ligands such as PPh_3, Josiphos, Xantphos, DPPF, and DIPF were examined (Table 2, entries 18–23). No better results were obtained when different bases (Na_2CO_3, K_2CO_3, Cs_2CO_3, $NaHCO_3$, $K_3PO_4{\cdot}3H_2O$, $K_2HPO_4{\cdot}3H_2O$, and Et_3N) were used in the reaction (Table 2, entries 24–30).

With this promising result in hands, we investigated the cross-coupling reactions between 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** and various arylboronic acids under optimized reaction conditions [$Pd_2(dba)_3$ (2.5 mol%), JohnPhos (5 mol%), KF (3.0 equiv.), toluene/H_2O = 2/1, 60 °C]. The results indicated that arylboronic acids containing electron-donating or -withdrawing groups could be successfully employed in the reaction, leading to the corresponding 2-pyrone derivatives in good to excellent isolated yields (Scheme 2). For instance, 4-methylphenyl-boronic acid reacted with compound **3**, giving rise to the desired product **4b** in 83% yield. It is noteworthy that the ester group could be tolerated under the standard conditions, and compound **4g** was isolated in 95% yield.

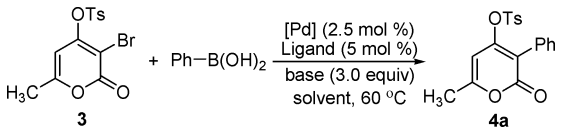
To further diversify the monocoupled 2-pyrones, we then explored the reactivity of the remaining tosyloxy group at the C4



Scheme 2 Synthesis of 3-aryl-4-tosyloxy-2-pyrone **4**.

position. Our investigation began with the reaction of 6-methyl-3-phenyl-4-tosyloxy-2-pyrone **4a** with phenylboronic acid under the above optimized reaction conditions. The expected product **5a** was generated only in 28% yield. After screening of different conditions, the best result (89% yield) was obtained when the reaction was catalyzed by 5 mol% of $Pd(OAc)_2$ and 10 mol% of PCy_3 in the presence of 3.0 equiv. of $K_2HPO_4{\cdot}3H_2O$ in MeOH at 90 °C. To test the effectiveness of the 4-position couplings of 6-methyl-3-aryl-4-tosyloxy-2-pyrone **4**, a range of arylboronic acids were examined under the optimized reaction conditions (Table 3). As shown, various arylboronic acids bearing electron-withdrawing as well as electron-donating substituents underwent the 4-position cross-coupling reactions, providing 3,4-diarlyated 2-pyrones in fair to excellent yields. For example, 6-methyl-3-phenyl-4-tosyloxy-2-pyrone **4a** coupled with 4-tolylboronic acid gave the desired product **5b** in 95% yield (Table 3, entry 2). Reaction of compound **4c** with 4-chlorophenylboronic acid afforded the corresponding product **5k** in 80% yield (Table 3, entry 11). Various symmetrical or unsymmetrical 3,4-diarylated 2-pyrones **5** could be generated as well under the standard conditions. Again, when ester-substituted phenylboronic acid was used in the reaction of 6-methyl-3-phenyl-4-tosyloxy-2-pyrone **4a**, the desired product **5l** could be formed with a 66% yield (Table 3, entry 12). However, only a trace

Table 2 Condition screening for palladium-catalyzed reaction of 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** with phenylboronic acid

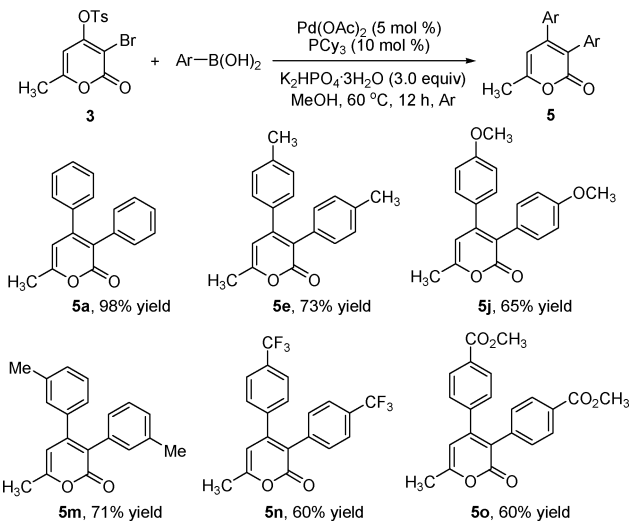


Entry	[Pd]	Ligand	Base	Solvent	Yield[a] (%)
1	$Pd_2(dba)_3$	JohnPhos	KF	Toluene	49
2	$Pd_2(dba)_3$	JohnPhos	KF	THF	5
3	$Pd_2(dba)_3$	JohnPhos	KF	MeCN	27
4	$Pd_2(dba)_3$	JohnPhos	KF	Dioxane	Trace
5	$Pd_2(dba)_3$	JohnPhos	KF	DCE	41
6	$Pd_2(dba)_3$	JohnPhos	KF	DMF	nr
7	$Pd_2(dba)_3$	JohnPhos	KF	NMP	nr
8	$Pd_2(dba)_3$	JohnPhos	KF	DMSO	nr
9	$Pd_2(dba)_3$	JohnPhos	KF	Acetone	19
10	$Pd_2(dba)_3$	JohnPhos	KF	MeOH	21
11	$Pd_2(dba)_3$	JohnPhos	KF	^{t}BuOH	Trace
12	$Pd_2(dba)_3$	JohnPhos	KF	H_2O	nr
13	$Pd_2(dba)_3$	JohnPhos	KF	Toluene/H_2O	92
14	$Pd(OAc)_2$	JohnPhos	KF	Toluene/H_2O	49
15	$Pd(PPh_3)_4$	JohnPhos	KF	Toluene/H_2O	58
16	$Pd(PPh_3)_2Cl_2$	JohnPhos	KF	Toluene/H_2O	64
17	Pd/C	JohnPhos	KF	Toluene/H_2O	24
18	$Pd_2(dba)_3$	—	KF	Toluene/H_2O	44
19	$Pd_2(dba)_3$	PPh_3	KF	Toluene/H_2O	45
20	$Pd_2(dba)_3$	Josiphos	KF	Toluene/H_2O	52
21	$Pd_2(dba)_3$	Xantphos	KF	Toluene/H_2O	33
22	$Pd_2(dba)_3$	DPPF	KF	Toluene/H_2O	42
23	$Pd_2(dba)_3$	DIPF	KF	Toluene/H_2O	51
24	$Pd_2(dba)_3$	JohnPhos	Na_2CO_3	Toluene/H_2O	43
25	$Pd_2(dba)_3$	JohnPhos	K_2CO_3	Toluene/H_2O	33
26	$Pd_2(dba)_3$	JohnPhos	Cs_2CO_3	Toluene/H_2O	45
27	$Pd_2(dba)_3$	JohnPhos	$NaHCO_3$	Toluene/H_2O	66
28	$Pd_2(dba)_3$	JohnPhos	$K_3PO_4{\cdot}3H_2O$	Toluene/H_2O	38
29	$Pd_2(dba)_3$	JohnPhos	$K_2HPO_4{\cdot}3H_2O$	Toluene/H_2O	49
30	$Pd_2(dba)_3$	JohnPhos	Et_3N	Toluene/H_2O	56

[a] Isolated yield based on 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3**.

amount of product was observed when compound **4** with electron-withdrawing group attached to the aromatic ring in the 3-position was used (Table 3, entries 13–15).

We also tried the one-pot synthesis of symmetrical 3,4-diarylated 2-pyrone derivatives from 3-bromo-6-methyl-4-tosyloxy-2-pyrone **3** under the conditions shown in Table 2 (Scheme 3). Good yields were observed for the transformation when arylboronic acids bearing eletron-donating or -withdrawing substituents were used, by increasing the amount of arylboronic acid to 3.0 equiv. compared to substrate **3**. For instance, reaction of compound **3** with 4-methylphenylboronic acid led to 2-pyrone **5e** in 73% yield. Trifluoromethyl- or ester-substituted phenylboronic acid was a good partner as well in the conversion.



Scheme 3 One-pot synthesis of symmetrical 3,4-diarylated 2-pyrones **5**.

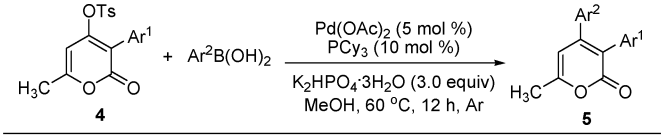
Conclusions

In summary, we have developed an efficient synthetic method for the synthesis of 3,4-disubstituted 2-pyrones *via* a sequential site-selective Pd-catalyzed Suzuki cross-coupling reactions of 3-bromo-6-methyl-4-tosyloxy-2-pyrone. This approach has the potential for the rapid synthesis of bioactive substituted 2-pyrone derivatives. Further studies for generation of diverse 2-pyrones are currently underway in our laboratory.

Experimental Section

Unless otherwise stated, all commercial reagents and solvents were used without additional purification. All solvents were dried

Table 3 Palladium-catalyzed cross-coupling reactions of compound **4** with arylboronic acids[a]



Entry	**4**/Ar^1	Ar^2	Product **5**	Yield (%)[b]
1	**4a**/C_6H_5	C_6H_5	**5a**	89
2	**4a**/C_6H_5	4-MeC_6H_4	**5b**	95
3	**4a**/C_6H_5	4-$MeOC_6H_4$	**5c**	94
4	**4a**/C_6H_5	4-ClC_6H_4	**5d**	73
5	**4b**/4-MeC_6H_4	4-MeC_6H_5	**5e**	82
6	**4b**/4-MeC_6H_4	4-$MeOC_6H_4$	**5f**	70
7	**4b**/4-MeC_6H_4	4-ClC_6H_4	**5g**	64
8	**4c**/4-$MeOC_6H_4$	C_6H_5	**5h**	55
9	**4c**/4-$MeOC_6H_4$	4-MeC_6H_4	**5i**	67
10	**4c**/4-$MeOC_6H_4$	4-$MeOC_6H_4$	**5j**	80
11	**4c**/4-$MeOC_6H_4$	4-ClC_6H_4	**5k**	80
12	**4a**/C_6H_5	4-$MeO_2CC_6H_4$	**5l**	66
13	**4d**/4-ClC_6H_4	4-$MeOC_6H_4$	—	Trace
14	**4d**/4-ClC_6H_4	4-ClC_6H_4	—	Trace
15	**4g**/4-$MeO_2CC_6H_4$	4-$MeOC_6H_4$	—	Trace

[a] Reaction conditions: substrate **4** (0.30 mmol), arylboronic acid (1.5 equiv.), $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%), $K_2HPO_4·3H_2O$ (3.0 equiv.), methanol (2.0 mL), 60 °C, 12 h, Ar. [b] Isolated yield based on compound **4**.

and distilled according to standard procedures. All reactions were performed in reaction tubes under Ar. The flash column chromatography was performed using silica gel (60-Å pore size, 32–63 μm, standard grade). Analytical thin–layer chromatography was performed using glass plates pre-coated with 0.25 mm 230–400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Thin layer chromatography plates were visualized by exposure to ultraviolet light. Organic solutions were concentrated on rotary evaporators at ~20 Torr (house vacuum) at 25–35 °C. Nuclear magnetic resonance (NMR) spectra are recorded in parts per million from internal tetramethylsilane (TMS) on the δ scale.

General procedure for the synthesis of compound **4** through palladium-catalyzed reaction of compound **3** with arylboronic acids: A mixture of compound **3** (0.3 mmol), arylboronic acid (1.5 equiv.), $Pd_2(dba)_3$ (2.5 mol%), JohnPhos (5 mol%), and KF (3.0 equiv.) in 3.0 mL of toluene/H_2O (v/v:2/1) was stirred at 60 °C for 24 h. After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to produce the corresponding product **4**.

6-Methyl-4-(4-methylbenzenesulfonyloxy)-3-phenyl-2-pyrone **4a**. White solid (92% yield), mp: 125.7–127.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 7.2 Hz, 2H), 7.26–7.18 (m, 3H), 7.08–7.05 (m, J = 8 Hz, 4 Hz, 4H), 6.45 (s, 1H), 2.39 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.2, 161.8, 156.4, 145.8, 131.5, 130.0, 129.7, 128.5, 128.1, 127.9, 127.7, 116.1, 102.3, 21.69, 20.1; HRMS (ESI) Calcd for $C_{19}H_{16}O_5SNa$ (M+Na^+), 379.0616; Found, 379.0622.

6-Methyl-4-(4-methylbenzenesulfonyloxy)-3-(4-methylphenyl)-2-pyrone **4b**. Yellow oil (83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.0 Hz, 2H), 7.06–6.96 (m, 6H), 6.42 (s, 1H), 2.39 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.4, 161.5, 156.2, 145.8, 138.1, 131.6, 129.9, 129.5, 128.4, 127.9, 126.0, 116.2, 102.4, 21.74, 21.34, 20.09; HRMS (ESI) Calcd for $C_{20}H_{18}O_5SH$ (M+H^+) 371.0953; Found, 371.0951.

3-(4-Methoxylphenyl)-6-methyl-4-(4-methylbenzenesulfonyloxy)-2-pyrone **4c**. Yellow oil (62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 7.04 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.4 Hz, 2H), 6.43 (s, 1H), 3.81 (s, 3H), 2.39 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.2, 161.2, 159.4, 155.9, 145.7, 131.3, 129.6, 127.9, 121.1, 115.1, 113.2, 102.5, 55.2, 21.7, 20.0; HRMS (ESI) Calcd for $C_{20}H_{18}O_6SNa$ (M+Na^+) 409.0722; Found, 409.0714.

3-(4-Chlorophenyl)-6-methyl-4-(4-methylbenzenesulfonyloxy)-2-pyrone **4d**. Yellow solid (59% yield), mp: 108.1–109.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 6.43 (s, 1H), 2.34 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.0, 162.3, 156.8, 146.2, 134.3, 131.5, 129.7, 127.9, 127.8, 127.5, 114.9, 102.7, 21.7, 20.2; HRMS (ESI) Calcd for $C_{19}H_{15}ClO_5Na$ (M+Na), 413.0226; Found, 413.0219.

3-(2-Methoxyphenyl)-6-methyl-2-oxo-2*H*-pyran-4-yl 4-methylbenzenesulfonate **4e**. Yellow solid (66% yield), mp: 134.9–136.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 12.0 Hz, 1H), 7.13 (d, J = 8.0 Hz, 2H), 6.84 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 8.0 Hz, 2H), 6.44 (s, 1H), 3.65 (s, 3H), 2.42 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.8, 161.8, 157.1, 157.0, 145.5, 132.0, 131.3, 130.3, 130.0, 129.7, 128.4, 127.9, 120.1, 118.3, 113.5, 110.8, 101.8, 55.4, 21.7, 20.1; HRMS (ESI) Calcd for $C_{20}H_{18}NaO_6S$ (M+Na), 409.0722; Found, 409.0710.

6-Methyl-2-oxo-3-*m*-tolyl-2*H*-pyran-4-yl 4-methylbenzenesulfonate **4f**. Yellow oil (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.0 Hz, 2H), 7.12–7.04 (m, 4H), 6.91 (d, J = 4.0 Hz, 1H), 6.81 (s, 1H), 6.45 (s, 1H), 2.39 (s, 3H), 2.33 (s, 3H), 2.24 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.3, 161.7, 156.3, 145.7, 137.3, 131.6, 130.4, 129.6, 128.9, 128.5, 127.9, 127.7, 127.2, 116.3, 102.4, 21.7, 21.3, 20.1; HRMS (ESI) Calcd for $C_{20}H_{19}O_5S$ (M+H), 371.0953; Found, 371.0958.

Methyl 4-(6-methyl-2-oxo-4-(tosyloxy)-2*H*-pyran-3-yl)benzoate **4g**. Yellow solid (95% yield), mp: 152.1–153.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.47 (s, 1H), 3.94 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.6, 162.8, 162.7, 157.1, 146.2, 133.9, 131.3, 130.1, 129.8, 129.6, 128.8, 127.8, 115.0, 102.5, 52.2, 21.6, 20.2; HRMS (ESI) Calcd for $C_{21}H_{18}NaO_7S$ (M+Na), 437.0671; Found, 437.0678.

General procedure for the generation of 3,4-disubstituted 2-pyrones **5** through palladium-catalyzed reaction of compound **4** with arylboronic acids: A mixture of substrate **4** (0.3 mmol), arylboronic acid (1.5 equiv.), $Pd(OAc)_2$ (5 mol%), PCy_3 (10 mol%), and $K_2HPO_4·3H_2O$ (3.0 equiv.) in methanol (2.0 mL) was stirred at 60 °C for 12 h. After completion of the reaction as indicated by TLC, the solvent was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to produce the corresponding product **5**.

3,4-Diphenyl-6-methyl-2-pyrone **5a**. Yellow solid (89% yield), mp: 130.1–130.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.20 (m, 6H), 7.14–7.12 (m, 2H), 7.09–7.07 (m, 2H), 6.17 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 160.1, 152.6, 137.5, 133.8, 130.8, 128.7, 128.6, 128.2, 127.9, 127.5, 122.0, 107.1, 19.9; HRMS (ESI) Calcd for $C_{18}H_{14}NaO_2$ (M+Na) 285.0891; Found, 285.0895.

6-Methyl-4-(4-methylphenyl)-3-phenyl-2-pyrone **5b**. Yellow solid (95% yield), mp: 109.2–110.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22–7.15 (m, 3H), 7.15–7.13 (m, 2H), 7.02–6.96 (m, 4H), 6.16 (s, 1H), 2.31 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.7, 159.9, 152.7, 138.8, 134.5, 134.2, 130.8, 128.9, 128.7, 128.0, 127.4, 121.6, 107.2, 21.3, 19.9; HRMS (ESI) Calcd for $C_{19}H_{16}O_2Na$ (M+Na$^+$) 299.1048; Found, 299.1044.

4-(4-Methoxylphenyl)-6-methyl-3-phenyl-2-pyrone **5c**. Yellow solid (94% yield), mp: 109.3–110.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.22 (m, 3H), 7.16 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 6.17 (s, 1H), 3.75 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.7, 159.9, 152.2, 134.3, 130.9, 130.4, 129.5, 128.1, 127.5, 121.1, 113.7, 107.1, 55.2, 19.9; HRMS (ESI) Calcd for $C_{19}H_{16}O_3Na$ (M+Na) 315.0997; Found, 315.0997.

4-(4-Chlorophenyl)-6-methyl-3-phenyl-2-pyrone **5d**. Yellow solid (73% yield), mp: 120.9–122.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.11 (m, 8H), 7.03–7.01 (m, 1H), 6.13 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.1, 160.4, 151.4, 135.9, 134.8, 133.5, 130.8, 130.1, 128.6, 128.2, 127.8, 122.2, 106.7, 19.9; HRMS (ESI) Calcd for $C_{18}H_{13}ClO_2Na$ (M+Na$^+$) 319.0502; Found, 319.0495.

3,4-Di(4-methylphenyl)-6-methyl-2-pyrone **5e**. Yellow oil (82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03–6.97 (m, 8H), 6.14 (s, 1H), 2.30 (s, 3H), 2.29 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.8, 159.6, 152.3, 138.7, 137.2, 134.7, 131.1, 130.6, 128.9, 128.8, 128.6, 121.6, 107.2, 21.3, 19.9; HRMS (ESI) Calcd for $C_{20}H_{18}NO_2Na$ (M+Na$^+$) 313.1204; Found, 313.1204.

4-(4-Methoxylphenyl)-6-methyl-3-(4-methylphenyl)-2-pyrone **5f**. Yellow solid (70% yield), mp: 135.7–137.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–7.29 (m, 6H), 6.72 (d, J = 8.8 Hz, 2H), 6.15 (s, 1H), 3.76 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.9, 159.8, 159.6, 151.8, 137.1, 131.2, 130.7, 130.3, 129.8, 128.8, 121.2, 113.7, 107.1, 55.2, 21.3, 19.9; HRMS (ESI) Calcd for $C_{20}H_{18}O_3Na$ (M+Na$^+$) 329.1154; Found, 329.1160.

4-(4-Chlorophenyl)-6-methyl-3-(4-methylphenyl)-2-pyrone **5g**. White solid (64% yield), mp: 131.6–132.6 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.4 Hz, 2H), 7.05–7.03 (m, 4H), 7.01(d, J = 8.0 Hz, 2H), 6.11 (s, 1H), 2.32 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.5, 160.1, 150.9, 137.6, 136.1, 134.7, 130.6, 130.4, 130.1, 128.9, 128.6, 122.2, 106.7, 21.3, 19.9; HRMS (ESI) Calcd for $C_{19}H_{15}ClO_2Na$ (M+Na$^+$) 333.0658; Found, 333.0664.

3-(4-Methoxylphenyl)-6-methyl-4-phenyl-2-pyrone **5h**. Yellow oil (55% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24–7.22 (m, 3H), 7.11–7.05 (m, 4H), 6.75 (d, J = 8.8 Hz, 2H), 6.15 (s, 1H), 3.75 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.8, 159.6, 158.8, 152.1, 137.8, 132.0, 128.6, 128.5, 128.3, 125.9, 113.5, 107.1, 55.1, 19.8; HRMS (ESI) Calcd for $C_{19}H_{17}O_3$ (M+H$^+$) 293.1178; Found, 293.1170.

3-(4-Methoxylphenyl)-6-methyl-4-(4-methylphenyl)-2-pyrone **5i**. Yellow oil (67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08–6.98 (m, 6H), 6.76 (d, J = 8.4 Hz, 2H), 6.13 (s, 1H), 3.76 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.9, 159.4, 158.8, 152.1, 138.6, 134.8, 132.0, 129.0, 128.6, 126.2, 121.2, 113.5, 107.2, 55.1, 21.2, 19.8; HRMS (ESI) Calcd for $C_{20}H_{19}O_3$ (M+H$^+$) 307.1334; Found, 307.1329.

3,4-Di(4-methoxylphenyl)-6-methyl-2-pyrone **5j**. Yellow oil (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 6.75 (d, J = 8.8 Hz, 2H) 6.30 (s, 1H), 3.77 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.7, 161.8, 158.7, 151.70, 132.0, 130.3, 128.2, 126.4, 120.8, 114.6, 113.7, 107.1, 103.2, 55.5, 55.2, 19.9. HRMS (ESI) Calcd for $C_{20}H_{18}O_4Na$ (M+Na$^+$), 345.1103; Found, 345.1088.

4-(4-Chlorophenyl)-3-(4-methoxylphenyl)-6-methyl-2-pyrone **5k**. Yellow oil (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.8 Hz, 2H), 7.06–7.03 (m, 4H), 6.78 (d, J = 8.8 Hz, 2H), 6.10 (s, 1H), 3.76 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.6, 159.9, 159.0, 150.8, 136.2, 134.6, 132.0, 130.1, 128.6, 125.6, 121.8, 113.7, 106.7, 55.2, 19.9; HRMS (ESI) Calcd for $C_{19}H_{15}ClO_3Na$ (M+Na$^+$) 349.0607; Found, 349.0601.

Methyl 4-(6-methyl-2-oxo-3-phenyl-2*H*-pyran-4-yl)benzoate **5l**. Yellow solid (66% yield), mp: 195.0–196.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 2H), 7.22 (t, J = 4.0 Hz, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 4.0 Hz, 2H), 6.17 (s, 1H), 3.89 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.4, 163.2, 160.5, 151.5, 142.1, 133.3, 130.7, 130.1, 129.5, 128.7, 128.1, 127.8, 122.6, 106.5, 52.2, 19.9; HRMS (ESI) Calcd for $C_{20}H_{16}NaO_4$ (M+Na$^+$) 343.0946; Found, 343.0931.

6-Methyl-3,4-di*m*-tolyl-2*H*-pyran-2-one **5m**. Yellow oil (71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07–7.00 (m, 5H), 6.93 (s, 1H), 6.88–6.82 (m, 2H), 6.16 (s, 1H), 2.31 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 163.7, 159.8, 152.7, 137.8, 137.4, 137.3, 133.8, 131.3, 129.3, 129.2, 128.3, 128.0, 127.9, 127.8, 125.8, 122.0, 107.1, 21.4, 21.3, 19.9; HRMS (ESI) Calcd for $C_{20}H_{18}NaO_2$ (M+Na$^+$) 313.1204; Found, 313.1215.

6-Methyl-3,4-bis(4-(trifluoromethyl)phenyl)-2*H*-pyran-2-one **5n**. White crystal (60% yield), mp: 125.8-126.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54–7.49 (m, 4H), 7.25 (d, J = 8.0 Hz, 2H), 7.22 (d, J = 8.0 Hz, 2H), 6.18 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 162.6, 161.6, 152.0, 140.6, 137.0, 131.5, 130.9, 129.7, 128.9, 125.6 (dd), 125.2 (dd), 122.5, 122.2, 121.2, 106.6, 20.0; HRMS (ESI) Calcd for $C_{20}H_{12}F_6NaO_2$ (M+Na$^+$) 421.0639; Found, 421.0651.

6-Methyl-2-pyrone **5o**. Yellow solid (60% yield), mp: 54.9–55.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.87 (m, 4H), 7.22 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 6.20 (s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 166.6, 166.2, 162.6, 161.3, 152.4, 141.5, 138.3, 130.9, 130.4, 129.6, 129.3, 129.2, 128.6, 121.5, 106.6, 52.2, 52.1, 20.0; HRMS (ESI) Calcd for $C_{22}H_{18}NaO_6$ (M+Na$^+$) 401.1001; Found, 401.1012.

Acknowledgements

Financial support from the National Natural Science Foundation of China (Nos. 20862009 and 20962010) and the Natural Science Foundation of Jiangxi Province (No. 2008GQH0026) is gratefully acknowledged.

Notes and references

1 (*a*) G. Schlingmann, L. Milne and G. T. Carter, *Tetrahedron*, 1998, **54**, 13013; (*b*) X. Shi, W. S. Leal, Z. Liu, E. Schrader and J. Meinwald, *Tetrahedron Lett.*, 1995, **36**, 71.

2 (*a*) R. W. Spencer, L. J. Copp and J. R. Pfister, *J. Med. Chem.*, 1985, **28**, 1828; (*b*) J. V. N. Vara Prasad, K. S. Para, E. A. Lunney, D. F. Ortwine, J. B. Dunbar, D. Ferguson, P. J. Tummino, D. Hupe, B. D. Tait, J. M. Domagala, C. Humblet, T. N. Bhat, B. Liu, D. A. M. Guerin, E. T. Baldwin, J. W. Erickson and T. K. Sawyer, *J. Am. Chem. Soc.*, 1994, **116**, 6989; (*c*) P. N. P. Rao, M. J. Uddin and E. E. Knaus, *J. Med. Chem.*,

2004, **47**, 3972; (*d*) P. N. P. Rao, M. Amini, H. Li, A. G. Habeeb and E. E. Knaus, *J. Med. Chem.*, 2003, **46**, 4872; (*e*) L. R. Marrison, J. M. Dickinsona and I. J. S. Fairlamb, *Bioorg. Med. Chem. Lett.*, 2002, **12**, 3509.

3 (*a*) G. H. Posner, C. G. Cho, T. E. N. Anjeh, N. Johnson, R. L. Horst, T. Kobayashi, T. Okano and N. Tsugawa, *J. Org. Chem.*, 1995, **60**, 4617; (*b*) L. Li, J. A. Bender and F. G. West, *Tetrahedron Lett.*, 2009, **50**, 1188; (*c*) N. T. Tam and C. G. Cho, *Org. Lett.*, 2008, **10**, 601; (*d*) L. Li, C. E. Chaseband and F. G. West, *Chem. Commun.*, 2008, 4025; (*e*) R. Sagar, J. Park, M. Koh and S. B. Park, *J. Org. Chem.*, 2009, **74**, 2171.

4 (*a*) N. H. Tam, E. J. Jung and C. G. Cho, *Org. Lett.*, 2010, **12**, 2012; (*b*) N. H. Tam and C. G. Cho, *Org. Lett.*, 2007, **9**, 3391; (*c*) G. H. Posner, T. D. Nelson, C. M. Kinter and J. N. Johnson, *J. Org. Chem.*, 1992, **57**, 4083; (*d*) C. J. Moody and K. F. Rahimtoola, *J. Chem. Soc., Perkin Trans. 1*, 1990, 673.

5 (*a*) M. Rueping, E. Merino and A. Ugionoa, *Adv. Synth. Catal.*, 2008, **350**, 2127; (*b*) H. Miyauchia, C. Ikematsu, T. Shimazakib, S. Kato, T. Shinmyozu, T. Shimo and K. Somekawa, *Tetrahedron*, 2008, **64**, 4108.

6 (*a*) S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2009, **74**, 6295; (*b*) Y. Kuninobu, A. Kawata, M. Nishi, H. Takata and K. Takai, *Chem. Commun.*, 2008, 6360; (*c*) T. Yao and R. C. Larock, *J. Org. Chem.*, 2003, **68**, 5936; (*d*) S. Rousset, M. Abarbri, J. Thibonnet, J. L. Parrainb and A. Duchenea, *Tetrahedron Lett.*, 2003, **44**, 7633; (*e*) R. C. Larock, M. J. Doty and X. Han, *J. Org. Chem.*, 1999, **64**, 8770; (*f*) R. C. Larock, X. Han and M. J. Doty, *Tetrahedron Lett.*, 1998, **39**, 5713; (*g*) W. Henry and R. P. Hughes, *J. Am. Chem. Soc.*, 1986, **108**, 7862.

7 (*a*) L. R. Marrison, J. M. Dickinsona and I. J. S. Fairlamb, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2667; (*b*) S. Cerezo, M. M. Manas and R. Pleixats, *Tetrahedron*, 1998, **54**, 7813.

8 (*a*) I. J. S. Fairlamb, L. R. Marrison, J. M. Dickinson, F. J. Lua and I. J. S. Schmidt, *Bioorg. Med. Chem.*, 2004, **12**, 4285; (*b*) I. J. S. Fairlamb, A. F. Lee, F. E. M. Loe-Mie, E. H. Niemela, C. T. O'Brien and A. C. Whitwood, *Tetrahedron*, 2005, **61**, 9827; (*c*) J. H. Lee, J. S. Park and C. G. Cho, *Org. Lett.*, 2002, **4**, 1171; (*d*) L. R. Marrison, J. M. Dickinsona, R. Ahmeda and I. J. S. Fairlamb, *Tetrahedron Lett.*, 2002, **43**, 8853; (*e*) E. H. Niemela, A. F. Lee and I. J. S. Fairlamb, *Tetrahedron Lett.*, 2004, **45**, 3593; (*f*) I. J. S. Fairlamb, C. T. O'Brien, Z. Linb and K. C. Lam, *Org. Biomol. Chem.*, 2006, **4**, 1213.

9 W. S. Kim, H. J. Kim and C. G. Cho, *J. Am. Chem. Soc.*, 2003, **125**, 14288.

10 J. H. Lee and C. G. Cho, *Tetrahedron Lett.*, 2003, **44**, 65.

11 (*a*) J. H. Lee, W. S. Kim, Y. Y. Leeb and C. G. Cho, *Tetrahedron Lett.*, 2002, **43**, 5779; (*b*) Z. Liu and J. Meinwald, *J. Org. Chem.*, 1996, **61**, 6693.

12 (*a*) E. C. Gravett, P. J. Hilton, K. Jones and F. Romero, *Tetrahedron Lett.*, 2001, **42**, 9081; (*b*) E. C. Gravett, P. J. Hilton, K. Jones and J. M. Peron, *Synlett*, 2003, 253.

13 (*a*) F. Bellina, M. Biagetti, A. Carpita and R. Rossi, *Tetrahedron Lett.*, 2001, **42**, 2859; (*b*) B. Danieli, G. Lesma, M. Martinelli, D. Passarella, I. Peretto and A. Silvani, *Tetrahedron*, 1998, **54**, 14081.

14 G. H. Posner, W. Harrison and D. G. Wettlaufer, *J. Org. Chem.*, 1985, **50**, 5041.

15 (*a*) S. Schröter, C. Stock and T. Bach, *Tetrahedron*, 2005, **61**, 2245; (*b*) P. Zezschwitz, F. Petry and A. Meijere, *Chem.–Eur. J.*, 2001, **7**, 4035; (*c*) K. Voigt, P. Zezschwitz, K. Rosauer, A. Lansky, A. Adams, O. Reiser and A. Meijere, *Eur. J. Org. Chem.*, 1998, 1521; (*d*) S. T. Handy and J. J. Sabatini, *Org. Lett.*, 2006, **8**, 1537; (*e*) X.-F. Duan, X.-H. Li, F.-Y. Li and C.-H. Huang, *Synthesis*, 2004, 2614; (*f*) I. Kaswasaki, M. Yamashita and S. Ohta, *J. Chem. Soc., Chem. Commun.*, 1994, 2085; (*g*) F. Bellina, A. Anselmi, F. Martina and R. Rossi, *Eur. J. Org. Chem.*, 2003, 2290; (*h*) F. Bellina, E. Falchi and R. Rossi, *Tetrahedron*, 2003, **59**, 9091; (*i*) I. C. Christoforou and P. A. Koutentis, *Org. Biomol. Chem.*, 2007, **5**, 1381; (*j*) I. Cerna, R. Pohl, B. Klepetarova and M. Hocek, *Org. Lett.*, 2006, **8**, 5389; (*k*) R. Pereira, A. Furst, B. Iglesias, P. Germain, H. Gronemeyerb and A. R. Lera, *Org. Biomol. Chem.*, 2006, **4**, 4514; (*l*) J. X. Araujo-Junior, M. Schmitt, P. Benderittera and J. Bourguignon, *Tetrahedron Lett.*, 2006, **47**, 6125; (*m*) T. T. Dang, N. Rasool, H. Reinkea and P. Langer, *Tetrahedron Lett.*, 2007, **48**, 845.

16 (*a*) I. J. S. Fairlamb, *Chem. Soc. Rev.*, 2007, **36**, 1036; (*b*) F. Bellinaa and R. Rossi, *Adv. Synth. Catal.*, 2010, **352**, 1223; (*c*) N. T. Hung, M. Hussain, I. Malik, A. Villinger and P. Langer, *Tetrahedron Lett.*, 2010, **51**, 2420; (*d*) J. H. Chang, H. U. Kang, I. K. Jung and C. G. Cho, *Org. Lett.*, 2010, **12**, 2016; (*e*) X. Zhang, W. Xie and W. Chen, *Tetrahedron*, 2010, **66**, 1188; (*f*) L. Zhang, T. Meng, R. Fan and J. Wu, *J. Org. Chem.*, 2007, **72**, 7279; (*g*) D. Conreaux, E. Bossharth, N. Monteiro, P. Desbordes, J. Vors and G. Balme, *Org. Lett.*, 2007, **9**, 271; (*h*) K. Ryu, Y. S. Cho, S. I. Jung and C. G. Cho, *Org. Lett.*, 2006, **8**, 3343; (*i*) W. S. Kim, H. J. Kim and C. G. Cho, *J. Am. Chem. Soc.*, 2003, **125**, 14288; (*j*) F. Bellina, C. Anselmi, S. Viel, L. Mannina and R. Rossi, *Tetrahedron*, 2001, **57**, 9997.

17 For selected examples, see: (*a*) D. Alonso, I. P. Beletskaya and M. Yus, *Tetrahedron*, 2008, **64**, 3047; (*b*) A. Suzuki, *Proc. Jpn. Acad., Ser. B, Phys. Biol. Sci.*, 2004, **80**, 359; (*c*) S. Kotha, K. Lahiri and D. Kashinath, *Tetrahedron*, 2002, **58**, 9633; (*d*) Y. Peng, J. Liu, X. Lei and Z. Yin, *Green Chem.*, 2010, **12**, 1072; (*e*) C. M. So, C. P. Lau, A. S. C. Chan and F. Y. Kwong, *J. Org. Chem.*, 2008, **73**, 7731.

