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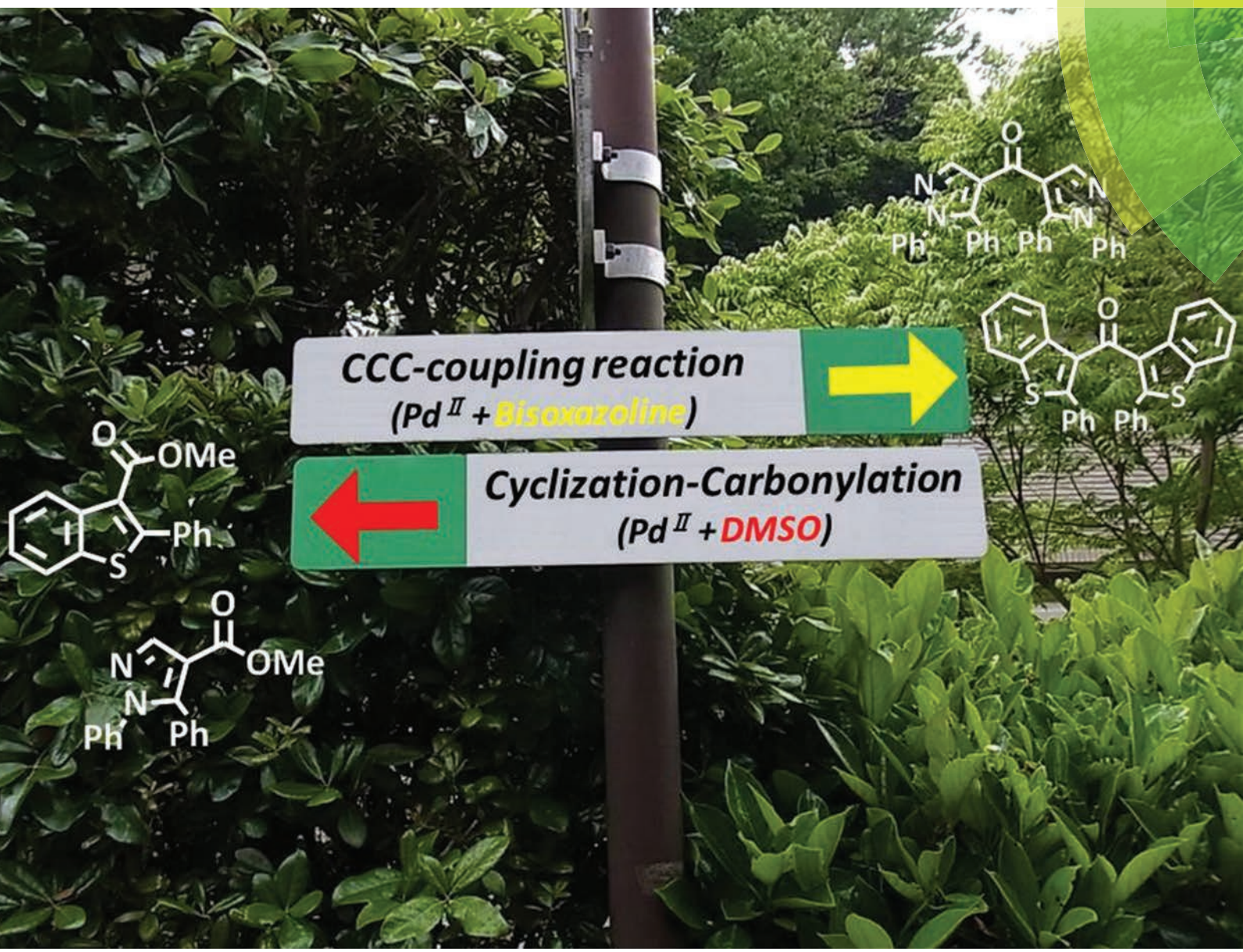

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Pd(II)-catalyzed ligand controlled synthesis of pyrazole-4-carboxylates and benzo[*b*]thiophene-3-carboxylates†

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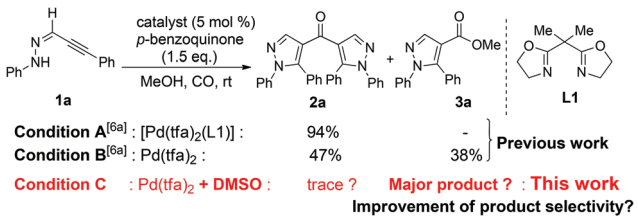
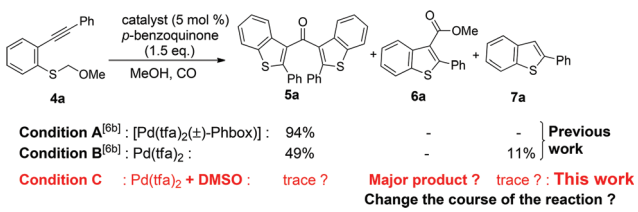
Cyclization–carbonylation of α,β-alkynic hydrazones and (*o*-alkynylphenyl) (methoxymethyl) sulfides with $Pd(tfa)_2$ in DMSO/MeOH afforded methyl pyrazole-4-carboxylates and benzo[*b*]thiophene-3-carboxylates, respectively, in good yields. A simple change of the ligand (solvent) allowed controlled, effective switching between cyclization–carbonylation–cyclization-coupling (CCC-coupling) reactions and cyclization–carbonylation reactions.

Introduction

Pyrazoles and benzo[*b*]thiophenes are important classes of N- and S-heterocycles in pharmaceutical science.[1] They are found in a variety of drugs, pesticides and biologically active compounds, such as razaxaban (anticoagulant), zometapine (antidepressant), celecoxib (anti-inflammatory), fomepizole (an antidote for methanol poisoning), cyenopyrafen (acaricide), raloxifene (a selective estrogen receptor modulator used for treatment of osteoporosis) and penthiopyrad (fungicide).[2] Pyrazole-4-carboxylates also possess antitumor, antimicrobial and analgesic activities.[3] They can be synthesized by several methods: (i) thermal cycloaddition of sydnones with acetylenic esters,[4a] (ii) 1,3-dipolar cycloaddition of nitrile imines,[3a] (iii) condensation of β-enaminoketoesters or cyano ketene dithioacetals with hydrazines[4b,c] and (iv) Vilsmeier cyclization of hydrazones.[4d] Although α,β-alkynic hydrazones are good precursors for the synthesis of pyrazoles,[5] there is only one example of cyclization–carbonylation reaction of α,β-alkynic hydrazones (Scheme 1, condition B).[6a] Recently, we reported that the cyclization–carbonylation–cyclization-coupling reaction (CCC-coupling reaction) of α,β-alkynic hydrazones **1** and (*o*-alkynylphenyl) (methoxymethyl) sulfides **4** catalyzed by palladium(II)-bisoxazoline (box) complexes afforded bis(pyrazol-3-yl)methanones **2** and bis(benzothiophen-3-yl)methanones **5**, respectively, in good yields (condition A in Schemes 1 and 2).[6a,b] In the absence of a box ligand (condition B in Schemes 1 and 2), dimeric ketones **2a** and **5a** were obtained in 47–49% yields along with low yields of pyrazole-4-carboxylate **3a** (38%) and benzo[*b*]thiophene **7a** (11%). In the case of condition B in Scheme 2, benzo[*b*]thiophene-3-carboxylate **6a** was not obtained. The course of the reaction can be switched by a simple change of the ligand (or the solvent) to afford pyrazole-4-carboxylate **3a** and benzo[*b*]thiophene-3-carboxylate **6a** selectively. Very recently, we reported[6c] palladium(II)-catalyzed ligand controlled synthesis of indole-3-carboxylates **10** and bis(indol-3-yl)methanones **9**; the box complex gave bis(indol-3-yl)methanone **9a** in good yield (condition A in Scheme 3). In the absence of a ligand (condition B in Scheme 3), indole-3-car-



Scheme 1 CCC-coupling (previous work)[6a] *versus* cyclization–carbonylation (this work).



Scheme 2 CCC-coupling (previous work)[6b] *versus* cyclization–carbonylation (this work).

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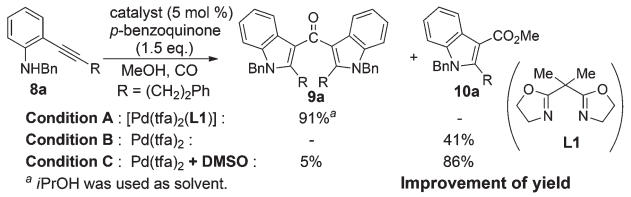
† Electronic supplementary information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/c4ob01576b



Scheme 3 Previous work.[6c]

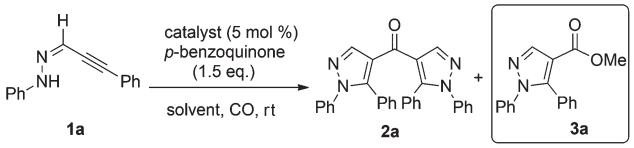
boxylate was obtained in 41% yield. Addition of DMSO (mixed solvent; DMSO–MeOH) improved the yield of indole-3-carboxylates. To investigate the generality of the effect of DMSO, we re-examined the Pd(II)-catalyzed carbonylation of α,β-alkynic hydrazones **1** and (*o*-alkynylphenyl) (methoxymethyl) sulfides **4** using mixed solvents. Consequently, we would like to report here a new method for the synthesis of pyrazole-4-carboxylate **3** and benzo[*b*]thiophene-3-carboxylates **6** (condition C in Schemes 1 and 2).

Results and discussion

Initially, we selected **1a** as a standard substrate to search for potential catalysts and solvents (Table 1). The results of entries 1–5 in Table 1 have been reported previously.[6a] The reaction of **1a** with $Pd(tfa)_2$ (5 mol%) and *p*-benzoquinone (1.5 equiv.) in methanol under a carbon monoxide atmosphere (balloon) generated the bis(pyrazolyl)ketone **2a** in 47% yield along with 38% yield of pyrazole-4-carboxylate **3a** (Table 1, entry 1). These products were easily separated by silica gel chromatography. The use of $[PdCl_2(PPh_3)_2]$ and a (2,2′-bipyridine)dichloro-palladium(II) complex also gave a mixture of the two products in low yields (Table 1, entries 2 and 3). The palladium(0) complex $Pd(PPh_3)_4$ was ineffective, affording **3a** in low yield (Table 1, entry 4). The use of $PdCl_2(CH_3CN)_2$ afforded **2a** as the sole product in increased yield (Table 1, entry 5). Next, we investigated the reaction in mixed solvents containing MeOH according to our previous findings.[6c] Although DMF–MeOH, THF–MeOH and toluene–MeOH were not suitable as solvents, the use of DMSO strikingly changed the course of the reaction, affording pyrazole-4-carboxylate **3a** as the major product (Table 1, entries 6–12). A large amount of DMSO (DMSO–MeOH = 5/1) led to decreased product yield, and the use of a small amount of DMSO (DMSO–MeOH = 1/5) gave almost the same result as that of entry 1 (Table 1, entries 10 and 11). Eventually, the best result was obtained using a 2.5/3 ratio of DMSO–MeOH, affording **3a** in 91% yield (Table 1, entry 12). In addition, $PdCl_2$ and $Pd(OAc)_2$ were not suitable catalysts (Table 1, entries 13 and 14), and the use of $CuCl_2$ instead of *p*-benzoquinone afforded **2a** in 30% yield along with recovery of substrate **1a** (34%).

Having elucidated the optimum conditions for the reaction, we then employed several α,β-alkynic hydrazone derivatives in the cyclization–carbonylation reaction (Table 2). First, the reaction of substrates derived from α,β-alkynic aldehydes and $PhNHNH_2$ (R^1 = H, Ar = Ph) was investigated (Table 2, entries 1–7). The substrates **1b–1d**, bearing electron-donating substituents (R^2 = 4-MePh, 4-MeOPh) and a thiophene ring, gave good results which were similar to that of the parent substrate **1a** (Table 2, entries 1–4). Replacement of the aryl groups at the alkyne terminus with an alkyl group afforded a slightly lower yield (76%) of **3e** (Table 2, entry 5). Both a Br substituent on the Ar moiety (Ar = 4-BrPh) and an electron-withdrawing group (R^2 = 4-CF_3Ph) were tolerated (Table 2, entries 6 and 7). Next, the reactions of substrates derived from α,β-alkynic ketones (R^1 = alkyl) and $ArNHNH_2$ were investigated (Table 2, entries

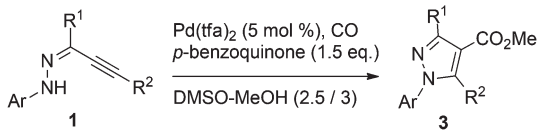
Table 1 Optimization of the reaction[a] (synthesis of **3a**)



Entry	Catalyst	Solvent	Time (h)	Yield of **2a** (%)	Yield of **3a** (%)
1	$Pd(tfa)_2$	MeOH	46	47	38
2	$[PdCl_2(PPh_2)_2]$	MeOH	24	28	31
3	$[PdCl_2(2,2'\text{-bipy})]$	MeOH	24	36	6
4	$Pd(PPh_3)_4$	MeOH	24	—	19
5	$[PdCl_2(CH_3CN)_2]$	MeOH	21	76	—
6	$Pd(tfa)_2$	DMF–MeOH (1/1)	24	15	28
7	$Pd(tfa)_2$	THF–MeOH (1/1)	24	18	37
8	$Pd(tfa)_2$	Toluene–MeOH (1/1)	24	22	22
9[b]	$Pd(tfa)_2$	DMSO–MeOH (1/1)	73	5	79
10[b]	$Pd(tfa)_2$	DMSO–MeOH (1/5)	49	41	54
11[b]	$Pd(tfa)_2$	DMSO–MeOH (5/1)	49	32	3
12[b]	$Pd(tfa)_2$	DMSO–MeOH (2.5/3)	72	Trace	91
13[c]	$PdCl_2$	DMSO–MeOH (2.5/3)	72	12	—
14[d]	$Pd(OAc)_2$	DMSO–MeOH (2.5/3)	72	—	—

[a] The results of entries 1–5 have been reported in ref. 6*a*. [b] 0 °C. [c] Recovery 34%. [d] Recovery 99%.

Table 2 Synthesis of pyrazole-4-carboxylates **3** *via* cyclization–carbonylation

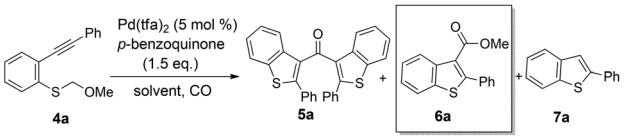


Entry	R^1	R^2	Ar	Temp (°C) Time (h)	Yield of **3** (%)
1	H	Ph	Ph	0 °C, 71 h	**3a:** 91
2	H	4-MePh	Ph	0 °C, 72 h	**3b:** 82
3	H	4-MeOPh	Ph	0 °C, 24 h	**3c:** 80
4	H	3-Thienyl	Ph	0 °C, 21 h	**3d:** 82
5	H	Octyl	Ph	0 °C, 72 h	**3e:** 76
6	H	Ph	4-BrPh	40 °C, 22 h	**3f:** 86
7	H	Ph	4-CF_3Ph	40 °C, 72 h	**3g:** 85
8	Me	Ph	Ph	−10 °C, 23 h	**3h:** 81
9	Phenethyl	Ph	Ph	0 °C, 20 h	**3i:** 83
10	Me	Ph	4-BrPh	0 °C, 24 h	**3j:** 87
11	Me	Ph	4-CF_3Ph	0 °C, 17 h	**3k:** 98
12	Me	Ph	4-NO_2Ph	0 °C, 17 h	**3l:** 90
13	Phenethyl	*n*-Hexyl	Ph	0 °C, 18 h	**3m:** 90
14	i-Pr	*n*-Butyl	Ph	0 °C, 6 h	**3n:** 93
15	Me	TMS	Ph	0 °C, 47 h	**3o:** 93

8–15). For substrates **1h–l**, bearing a Ph group at the alkyne terminus, the reaction proceeded well (Table 2, entries 8–12). A Br substituent on an Ar moiety (Ar = 4-BrPh) was also tolerated (Table 2, entry 10). The substrates **1k** and **1l**, bearing electron-withdrawing groups on the Ar moiety (Ar = 4-CF_3Ph, 4-NO_2Ph), were transformed in 98% and 90% yields, respectively (Table 2, entries 11 and 12). Replacement of the Ph group at the alkyne terminus with alkyl groups also led to the desired **3m** and **3n** in good yields (Table 2, entries 13 and 14). It is noteworthy that the presence of a TMS group at the alkyne terminus was tolerated under the reaction conditions (Table 2, entry 15).

Next, we re-investigated the carbonylation of (*o*-alkynylphenyl) (methoxymethyl) sulfides **4a** using mixed solvents (Table 3). As reported recently, the reaction in MeOH without ligands afforded bis(benzothiophen-3-yl)methanone **5a** in 49% yield along with the cyclized product **7a**, while the ester product **6a** was not detected (Table 3, entry 1).[6b] When the reaction was performed in a mixed-solvent, *e.g.*, DMF–MeOH (2/1) and CH_2Cl_2–MeOH (2/1), **7a** was obtained as the major product (Table 3, entries 2 and 3). As in the case of Tables 1 and 2, the use of DMSO strikingly changed the course of the reaction, affording benzo[*b*]thiophene-3-carboxylate **6a** as the major product (Table 3, entry 4). Although an increased amount of MeOH led to decreased product selectivity, the best result was obtained in DMSO–MeOH (7/1) (Table 3, entries 5, 6 and 9). $PdCl_2$ and $Pd(NO_3)_2$ were not suitable for this reaction (Table 3, entries 7 and 8). Having elucidated the optimum conditions for the reaction, we then employed a variety of (*o*-alkynylphenyl) (methoxymethyl) sulfides **4** in the cyclization–carbonylation reaction (Table 4). The substrates **1b–e**, bearing three kinds of halogen substituents (F, Cl, Br) and a methyl group on the phenyl ring, were tolerated under the reaction

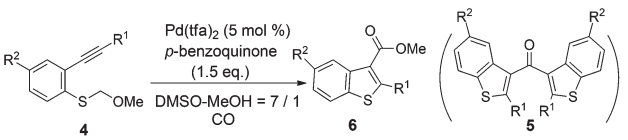
Table 3 Optimization of the reaction[a] (Synthesis of **6a**)



Entry	Solvent	Temp (°C) Time (h)	Yield of **5a** (%)	Yield of **6a** (%)	Yield of **7a** (%)
1[a]	MeOH	−20 to −10, 45	49	—	11
2	DMF–MeOH (2/1)	rt, 24	2	8	71
3	CH_2Cl_2–MeOH (2/1)	rt, 24	1	9	76
4	DMSO–MeOH (2/1)	rt, 24	9	74	—
5	DMSO–MeOH (1/1)	5, 28	45	37	—
6	DMSO–MeOH (5/1)	rt, 16	13	76	—
7[b]	DMSO–MeOH (5/1)	rt, 48	65	26	—
8[c]	DMSO–MeOH (5/1)	rt, 22	21	56	—
9	DMSO–MeOH (7/1)	5, 17	8	80	—

[a] The result was reported in ref. 6*b*. [b] $PdCl_2$ was employed. [c] $Pd(NO_3)_2$ was employed.

Table 4 Synthesis of benzo[*b*]thiophene-3-carboxylate **6** *via* cyclization–carbonylation

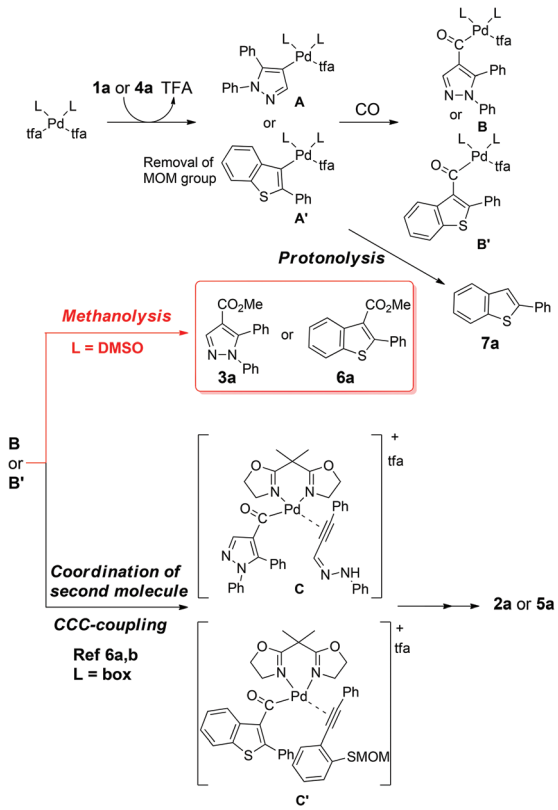


Entry	R^1	R^2	Temp (°C) Time (h)	Yield %
1	Ph	H	5, 17	**6a:** 80
2	4-BrPh	H	5, 48	**6b:** 81
3	4-ClPh	H	5, 18	**6c:** 83
4	4-FPh	H	5, 17	**6d:** 82
5	4-MePh	H	0, 48	**6e:** 82
6	TMS	H	5, 96	**6f:** 86
7[a]	Ph	MeO	−20, 24	**6g:** 80
8	Phenethyl	H	0, 48	**6h:** 82

[a] DMSO–MeOH (2/1).

conditions: **6b–e** were obtained in similar yields as that of the parent substrate **4a** (Table 4, entries 2–5). Replacement of the aryl groups at the alkyne terminus with a TMS group and an alkyl group also led to the desired **6f** and **6h**, respectively, in good yields (Table 4, entries 6 and 8). For substrate **4g**, bearing a methoxy group on an aromatic moiety, the reaction proceeded well (Table 4, entry 7).

A plausible mechanism for the reaction of **1a** and **4a** is shown in Scheme 4. Nucleophilic attack by the nitrogen atom of **1a** at the electrophilically activated triple bond produces the pyrazol-3-yl palladium intermediate **A**. In the case of **4a**, a similar intermediate **A′** is produced, accompanied by removal of the methoxymethyl group.[8] Insertion of carbon monoxide into intermediates **A** and **A′** leads to acyl palladium intermediates **B** and **B′**, while protonolysis of intermediate **A′** generates **7a**. As reported previously, we believe that the box ligand



Scheme 4 A plausible mechanism for the cyclization–carbonylation reaction **1a** and **4a**.

enhances the π-electrophilicity of palladium(II),[7] and thus promotes coordination of the second triple bond to the acyl palladium intermediates (**C** and **C′**), leading to a dimerization reaction. On the other hand, methanolysis of the acyl palladium intermediates **B** and **B′** gave the ester products **3a** and **6a** as a result of cyclization–carbonylation. Under condition C (Schemes 1–3), DMSO acts as a neutral ligand instead of the box (condition A) or MeOH (condition B),[6c] and it plays important roles in the production of esters **3a** and **6a**, namely, (1) stabilizing intermediates **A** and **A′** to prevent protonolysis, suppressing the formation of **7a**; (2) facilitating the methanolysis of the acyl palladium intermediates **B** and **B′**; and (3) impeding coordination of the second triple bond to the acyl palladium intermediates **B** and **B′**, suppressing the formation of dimeric ketones **2a** and **5a**. Consequently, the ester products **3a** and **6a** should be produced smoothly in the presence of DMSO as a mixed solvent.

Conclusions

In conclusion, we investigated the carbonylation reactions of α,β-alkynic hydrazones **1** and (*o*-alkynylphenyl) (methoxymethyl) sulfides **4** with $Pd(tfa)_2$ in a mixed solvent, and found that DMSO–MeOH was very effective for controlling the reaction pathway. An effective switching between cyclization–carbonylation and cyclization–carbonylation–cyclization-coupling (CCC-coupling) reactions was achieved. At the same time a new method for the synthesis of pyrazole-4-carboxylates **3** and benzo[*b*]thiophene-3-carboxylates **6** was developed. These reactions were general for a wide range of substrates. We are currently investigating additional reactions based on this DMSO–MeOH strategy for cyclization–carbonylation in the synthesis of other types of heterocycles–carboxylates.

Experimental section

General information

All melting points were determined on a microscopic melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz (^{1}H NMR) and 100 MHz (^{13}C NMR) spectrometer using $CDCl_3$ as the solvent and TMS as the internal standard. Coupling constants (*J*) are reported in hertz (Hz), and spin multiplicities are presented by the following symbols: s (singlet), br-s (broad singlet), d (doublet), br-d (broad doublet), t (triplet), q (quartet), and m (multiplet). High-resolution mass spectra were obtained using high-resolution EI or ESI-TOF mass spectrometers. Infrared spectra (IR) were recorded on a FT-IR spectrophotometer and are reported as wavelength numbers (cm^{-1}). All evaporations were performed under reduced pressure. For column chromatography, silica gel (63–200 mm) was employed. See ESI† for ^{1}H NMR and ^{13}C NMR spectra of all new compounds.

Preparation of substrates 1 and 4

The α,β-alkynic hydrazones **1** were prepared by condensation of the corresponding α,β-alkynic aldehydes or ketones with $ArNHNH_2$ according to known literature procedures.[5c,d,6a] The (*o*-alkynylphenyl) (methoxymethyl) sulfides **4** were prepared from known *o*-iodoanilines by the published procedure.[6b] All substrates were known compounds except **1k** and **4f**.

(*Z*)-1-(4-Nitrophenyl)-2-(4-phenylbut-3-yn-2-ylidene)-hydrazine (1l). Yellow solid; mp 137–138 °C; ^{1}H NMR ($CDCl_3$): δ = 2.82 (3H, s), 7.08–7.12 (2H, m), 7.40–7.48 (3H, m), 7.54–7.57 (2H, m), 8.15–8.18 (2H, m), 8.63 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 22.4, 79.9, 102.4, 112.0, 120.7, 126.1, 128.6, 128.7, 130.0, 131.9, 140.5, 148.8; IR (KBr): 3306, 2173, 1596, 1499, 1478, 1330, 1272, 1144, 1114, 835, 752, 688 cm^{-1}; HRMS-EI: *m*/*z* [M^+] calcd for $C_{16}H_{13}N_3O_2$: 279.1008; found: 279.1008.

Methoxymethyl 2-(trimethylsilylethynyl)phenyl sulfide (4f). Brown oil; ^{1}H NMR ($CDCl_3$): δ = 0.27 (9H, s), 3.43 (3H, s), 5.04 (2H, s), 7.10–7.14 (1H, m), 7.23–7.27 (1H, m), 7.43 (1H, br-d, *J* = 8.0 Hz), 7.56 (1H, br-d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 0.07 (3C), 56.2, 76.3, 100.6, 102.6, 123.2, 125.8, 128.4, 129.1, 132.9, 139.4; IR (KBr): 2945, 1697, 1681, 1456, 1354, 1225, 1010, 822, 755 cm^{-1}; HRMS-EI: *m*/*z* [M^+] calcd for $C_{13}H_{18}O_2SSi$: 250.0848; found: 250.0859.

General procedure for the cyclization–carbonylation reaction of α,β-alkynic hydrazones 1

A 30 mL two-necked round-bottom flask containing a magnetic stirring bar, substrate **1** (0.5 mmol), *p*-benzoquinone (81.1 mg, 0.75 mmol), DMSO (2 mL) and MeOH (6 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling *via* the three-way stopcock. A DMSO (1 mL) solution of $Pd(tfa)_2$ (8.3 mg, 0.025 mmol) was added to the stirred solution *via* a syringe at the appropriate temperature. The remaining catalyst was washed in DMSO (1 mL) twice, and stirred for a set period of time. The reaction mixture was diluted with CH_2Cl_2 (60 mL), water (40 mL) and 5% NaOH (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane–EtOAc (25/1–10/1) afforded pyrazole-4-carboxylate **3**, and that eluted with hexane–EtOAc (3/1–2/1) afforded a small amount of bis(pyrazol-3-yl)methanones **2**.

Bis(1,5-diphenyl-1*H*-pyrazol-4-yl)methanone (2a),[6a] methyl 1,5-diphenyl-1*H*-pyrazole-4-carboxylate (3a)[6a] and methyl 1-phenyl-5-(*p*-tolyl)-1*H*-pyrazole-4-carboxylate (3b). Pale yellow solid; mp 116–117 °C; ^{1}H NMR ($CDCl_3$): δ = 2.35 (3H, s), 3.75 (3H, s), 7.12–7.31 (9H, m), 8.16 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 21.4, 51.2, 113.2, 125.3, 125.5, 127.8, 128.8, 130.3, 139.2, 139.3, 142.4, 145.7, 163.4; IR (KBr): 3035, 1718, 1563, 1504, 1445, 1382, 1293, 1225, 1130, 773, 693 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{18}H_{16}N_2O_2$ [M^+]: 292.1212; found: 292.1212.

Methyl 5-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carboxylate (3c). Colorless solid; mp 125–126 °C; ^{1}H NMR ($CDCl_3$): δ = 3.76 (3H, s), 3.80 (3H, s), 6.83–6.87 (2H, m), 7.19–7.30 (7H, m), 8.16 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 51.2, 55.2, 113.0, 113.5, 120.6, 125.3, 127.8, 128.8, 131.8, 139.3, 142.4, 145.5, 160.2, 163.5; IR (KBr): 3054, 1717, 1506, 1447, 1226, 1130, 775 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{18}H_{16}N_2O_3$ [M^+]: 308.1161; found: 308.1159.

Methyl 1-phenyl-5-(thiophen-3-yl)-1*H*-pyrazole-4-carboxylate (3d). Colorless solid; mp 97–98 °C; ^{1}H NMR ($CDCl_3$): δ = 3.79 (3H, s), 6.96 (1H, dd, *J* = 5.2 Hz, *J* = 1.2 Hz), 7.22–7.27 (3H, m), 7.32–7.35 (3H, m), 7.39 (1H, dd, *J* = 2.8 Hz, *J* = 1.2 Hz), 8.15 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 51.3, 113.2, 125.0, 125.3, 127.9, 128.0, 128.2, 128.9, 128.9, 139.3, 140.7, 142.5, 163.3; IR (KBr): 3100, 1719, 1594, 1496, 1277, 1230, 1129, 1037, 973, 762, 690 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{15}H_{12}N_2O_2S$ [M^+]: 284.0619; found: 284.0621.

Methyl 5-octyl-1-phenyl-1*H*-pyrazole-4-carboxylate (3e). Pale yellow oil; mp 99–100 °C; ^{1}H NMR ($CDCl_3$): δ = 0.85 (3H, s), 1.17–1.27 (10H, m), 1.47–1.55 (2H, m), 2.90–2.94 (2H, m), 3.85 (3H, s), 7.38–7.40 (2H, m), 7.46–7.52 (3H, m), 8.01 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 14.0, 22.5, 24.9, 28.9, 28.9, 29.0, 29.2, 31.7, 51.1, 111.8, 125.9, 128.8, 129.2, 139.0, 141.9, 148.5, 163.9; IR (KBr): 2928, 2857, 1717, 1595, 1553, 1502, 1460, 1252, 1091, 978, 772, 696 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{19}H_{26}N_2O_2$ [M^+]: 314.1994; found: 314.1995.

Methyl 1-(4-bromophenyl)-5-phenyl-1*H*-pyrazole-4-carboxylate (3f). Pale yellow solid; mp 112–113 °C; ^{1}H NMR ($CDCl_3$): δ = 3.75 (3H, s), 7.05–7.09 (2H, m), 7.26–7.28 (2H, m), 7.34–7.42 (5H, m), 8.17 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 51.3, 113.8, 121.7, 126.6, 128.2, 128.4, 129.4, 130.3, 132.0, 138.2, 142.6, 145.5, 163.1; IR (KBr): 3056, 1722, 1551, 1498, 1291, 1223, 1130, 1068, 1014, 770, 697 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{17}H_{13}BrN_2O_2$ [M^+]: 356.0160; found: 356.0156.

Methyl 5-phenyl-1-((4-trifluoromethyl)phenyl)-1*H*-pyrazole-4-carboxylate (3g). Pale yellow solid; mp 100–101 °C; ^{1}H NMR ($CDCl_3$): δ = 3.75 (3H, s), 7.20–7.40 (7H, m), 7.48–7.55 (2H, m), 8.20 (1H, s); ^{13}C NMR ($CDCl_3$): δ = 51.4, 114.2, 123.6 (q, J_{C-F} = 270.8 Hz), 125.1, 126.0 (q, J_{C-F} = 2.9 Hz), 128.3, 128.4, 129.6, 129.7 (q, J_{C-F} = 32.4 Hz), 130.3, 141.9, 142.9, 145.7, 163.0; IR (KBr): 3056, 1727, 1612, 1553, 1448, 1386, 1324, 1226, 1123, 1064, 846 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{18}H_{13}F_3N_2O_2$ [M^+]: 346.0929; found: 346.0929.

Methyl 3-methyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (3h). Colorless solid; mp 122–123 °C; ^{1}H NMR ($CDCl_3$): δ = 2.58 (3H, s), 3.69 (3H, s), 7.15–7.17 (2H, m), 7.22–7.37 (8H, m); ^{13}C NMR ($CDCl_3$): δ = 14.3, 51.0, 111.6, 125.3, 127.6, 127.9, 128.7, 128.9, 129.7, 130.3, 139.1, 146.4, 151.7, 164.3; IR (KBr): 2946, 1712, 1595, 1548, 1502, 1311, 1238, 1101, 1091, 793, 693 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{18}H_{16}N_2O_2$ [M^+]: 292.1212; found: 292.1212.

Methyl 3-phenethyl-1,5-diphenyl-1*H*-pyrazole-4-carboxylate (3i). Pale yellow solid; mp 113–114 °C; ^{1}H NMR ($CDCl_3$): δ = 3.01–3.05 (2H, m), 3.20–3.24 (2H, m), 3.62 (3H, s), 7.08–7.28 (15H, m); ^{13}C NMR ($CDCl_3$): δ = 30.6, 35.5, 51.0, 111.1, 125.3, 125.8, 127.6, 127.9, 128.3, 128.5, 128.7, 128.8, 129.7, 130.3, 139.1, 142.4, 146.5, 154.8, 164.0; IR (KBr): 3025, 2941, 1698, 1596, 1487, 1384, 1322, 1237, 1182, 1100 760, 696 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{25}H_{22}N_2O_2$ [M^+]: 382.1681; found: 382.1680.

Methyl 1-(4-bromophenyl)-3-methyl-5-phenyl-1*H*-pyrazole-4-carboxylate (3j). Pale yellow solid; mp 99–100 °C; ^{1}H NMR ($CDCl_3$): δ = 2.57 (3H, s), 3.68 (3H, s), 7.02–7.05 (2H, m), 7.21–7.24 (2H, m), 7.32–7.40 (5H, m); ^{13}C NMR ($CDCl_3$): δ = 14.3, 51.0, 112.0, 121.3, 126.5, 128.1, 129.1, 129.4, 130.3, 131.9, 138.1, 146.4, 152.0, 164.1; IR (KBr): 3060, 1711, 1547, 1497, 1430, 1321, 1246, 1182, 1100, 1010, 700 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{18}H_{15}BrN_2O_2$ [M^+]: 370.0317; found: 370.319.

Methyl 3-methyl-5-phenyl-1-(4-(trifluoromethyl)phenyl)-1*H*-pyrazol-4-carboxylate (3k). Pale yellow solid; mp 113–114 °C; ^{1}H NMR ($CDCl_3$): δ = 2.58 (3H, s), 3.69 (3H, s), 7.24–7.30 (4H, m), 7.34–7.43 (3H, m), 7.49–7.52 (2H, m); ^{13}C NMR ($CDCl_3$): δ = 14.3, 51.1, 112.5, 122.3, 125.0, 125.9 (q, J_{C-F} = 30.4 Hz), 128.2, 129.36, 130.3 (q, J_{C-F} = 263.2 Hz), 130.2, 141.9, 146.6, 152.4, 164.0; IR (KBr): 2944, 1712, 1615, 1429, 1388, 1325, 1240, 1103, 844, 760, 697 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{19}H_{15}F_3N_2O_2$ [M^+]: 360.1086; found: 360.1086.

Methyl 3-methyl-1-(4-nitrophenyl)-5-phenyl-1*H*-pyrazol-4-carboxylate (3l). Pale yellow solid; mp 127–128 °C; ^{1}H NMR ($CDCl_3$): δ = 2.59 (3H, s), 3.70 (3H, s), 7.24–7.27 (2H, m),

7.32–7.44 (5H, m), 8.09–8.13 (2H, m); ^{13}C NMR ($CDCl_3$): δ = 14.3, 51.2, 113.2, 124.3, 124.9, 128.5, 129.2, 129.6, 130.1, 144.0, 146.0, 146.8, 152.9, 163.8; IR (KBr): 2949, 1715, 1597, 1523, 1505, 1321, 1249, 1105, 763, 700 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{18}H_{15}N_3O_4$ [M^+]: 337.1063; found: 337.1064.

Methyl 5-hexyl-3-phenethyl-1-phenyl-1*H*-pyrazole-4-carboxylate (3m). Pale yellow solid; mp 38 °C; ^{1}H NMR ($CDCl_3$): δ = 0.84 (3H, t, *J* = 7.2 Hz), 1.14–1.28 (6H, m), 1.50–1.57 (2H, m), 2.85–2.90 (2H, m), 3.0–3.04 (2H, m), 3.19–3.23 (2H, m), 3.88 (3H, s), 7.18–7.22 (1H, m), 7.28–7.32 (4H, m), 7.35–7.39 (2H, m), 7.42–7.52 (3H, m); ^{13}C NMR ($CDCl_3$): δ = 13.9, 22.4, 25.5, 29.1, 29.1, 30.7, 31.1, 35.6, 50.9, 109.2, 125.8, 126.2, 128.2, 128.5, 128.7, 129.2, 139.0, 142.2, 149.7, 154.5, 164.5; IR (KBr): 2942, 2854, 1710, 1595, 1541, 1460, 1267, 1108, 758, 696 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{25}H_{30}N_2O_2$ [M^+]: 390.2307; found: 390.2308.

Methyl 5-butyl-3-isopropyl-1-phenyl-1*H*-pyrazole-4-carboxylate (3n). Pale yellow solid; mp 45–46 °C; ^{1}H NMR ($CDCl_3$): δ = 0.81 (3H, t, *J* = 7.2 Hz), 1.20–1.31 (2H, m), 1.32 (6H, d, *J* = 6.8 Hz), 1.46–1.54 (2H, m), 2.88–2.86 (2H, m), 3.52–3.62 (1H, m), 3.85 (3H, s), 7.36–7.49 (5H, m); ^{13}C NMR ($CDCl_3$): δ = 13.5, 21.9 (2C), 22.5, 25.4, 27.2, 31.4, 50.8, 108.5, 126.2, 128.6, 129.1, 139.2, 149.3, 160.4, 164.8; IR (KBr): 2967, 2870, 1698, 1539, 1448, 1281, 1174, 1106, 795, 697 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{18}H_{24}N_2O_2$ [M^+]: 300.1836; found: 300.1838.

Methyl 3-methyl-1-phenyl-5-trimethylsilyl-1*H*-pyrazole-4-carboxylate (3o). Colorless solid; mp 63–64 °C; ^{1}H NMR ($CDCl_3$): δ = 0.05 (9H, s), 2.49 (3H, s), 3.85 (3H, s), 7.32–7.37 (2H, m), 7.42–7.45 (3H, m); ^{13}C NMR ($CDCl_3$): δ = 0.0 (3C), 13.7, 51.2, 121.1, 127.1, 129.1, 129.3, 142.3, 149.3, 151.5, 165.5; IR (KBr): 2996, 1705, 1596, 1501, 1261, 1110, 1008, 848, 774, 699 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{15}H_{20}N_2O_2Si$ [M^+]: 288.1294; found: 288.1292.

General procedure for the cyclization–carbonylation reaction of (*o*-alkynylphenyl) (methoxymethyl) sulfides 4

A 30 mL two-necked round-bottom flask containing a magnetic stirring bar, substrate **1** (0.4 mmol), *p*-benzoquinone (65 mg, 0.6 mmol) and mixed solvent (5 mL) was fitted with a rubber septum and a three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pump-filling *via* the three-way stopcock. A mixed solvent (1 mL) solution of $Pd(tfa)_2$ (6.7 mg, 0.02 mmol) was added to the stirred solution *via* a syringe at the appropriate temperature. The remaining catalyst was washed in the mixed solvent (1 mL) twice, and stirred for a set period of time. The reaction mixture was diluted with CH_2Cl_2 (60 mL), water (40 mL) and 5% NaOH (10 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (25 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel. The fraction eluted with hexane–Et_2O (200/1) afforded benzo[*b*]thiophene-3-carboxylate **6** and a small amount of bis(benzothiophen-3-yl) methanone **5**. In the case of entries 2 and 4 in Table 4, a small amount of ketone **5** contaminated ester **6**. Pure esters **6b** and **6d** were obtained in 81–82% yields after recrystallization (hexane).

Bis(2-phenylbenzo[*b*]thiophen-3-yl)methanone (5a)[6b]
Methyl 2-phenylbenzo[*b*]thiophen-3-carboxylate (6a)[9]
2-phenylbenzo[*b*]thiophene (7a)[10]

Methyl 2-(4-bromophenyl)benzo[*b*]thiophen-3-carboxylate (6b) Orange solid; mp 80–81 °C; ^{1}H NMR ($CDCl_3$): δ = 3.79 (3H, s), 7.37–7.43 (3H, m), 7.46–7.51 (1H, m), 7.55–7.59 (2H, m), 7.82 (1H, br-d, *J* = 8.0 Hz), 8.36 (1H, br-d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 51.6, 121.7, 123.1, 123.3, 124.7, 125.1, 125.5, 131.0, 131.3, 132.9, 138.3, 138.4, 150.4, 164.1; IR (KBr): 2945, 1697, 1681, 1456, 1354, 1225, 1010, 822, 755 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{16}H_{11}BrO_2S$ [M^+]: 345.9663; found: 345.9693.

Methyl 2-(4-chlorophenyl)benzo[*b*]thiophen-3-carboxylate (6c). Orange solid; mp 64–65 °C; ^{1}H NMR ($CDCl_3$): δ = 3.79 (3H, s), 7.39–7.51 (6H, m), 7.82 (1H, br-d, *J* = 8.0 Hz), 8.38 (1H, br-d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 51.6, 121.7, 123.1, 124.7, 125.1, 125.5, 128.3, 130.7, 132.4, 135.0, 138.3, 138.4, 150.4, 164.1; IR (KBr): 2946, 1698, 1429, 1355, 1224, 1091, 1018, 824, 768 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{16}H_{11}ClO_2S$ [M^+]: 302.0168; found: 302.0169.

Methyl 2-(4-fluorophenyl)benzo[*b*]thiophen-3-carboxylate (6d). Orange solid; mp 78–80 °C; ^{1}H NMR ($CDCl_3$): δ = 3.79 (3H, s), 7.46–7.52 (3H, m), 7.38–7.42 (1H, m), 7.14–7.16 (2H, m), 8.35 (1H, br-d, *J* = 8.4 Hz), 7.82 (1H, br-d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 51.6, 115.2 (d, J_{C-F} = 21.9 Hz), 121.7, 123.0, 124.7, 125.1, 125.5, 129.9 (d, J_{C-F} = 3.8 H), 131.2 (d, J_{C-F} = 8.6 Hz), 138.3, 138.4, 150.8, 163.1 (d, J_{C-F} = 248 Hz), 164.2; IR (KBr): 2924, 1715, 1701, 1457, 1203, 1159, 750 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{16}H_{11}FO_2S$ [M^+]: 286.0464; found: 286.0466.

Methyl 2-(4-methylphenyl)benzo[*b*]thiophen-3-carboxylate (6e). Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 2.40 (3H, s), 3.77 (3H, s), 7.22–7.24 (2H, m), 7.34–7.47 (4H, m), 7.79 (1H, br-d, *J* = 8.4 Hz), 8.31 (1H, br-d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ = 21.3, 51.5, 121.6, 122.5, 124.4, 124.8, 125.3, 128.9, 129.2, 130.9, 138.4, 138.5, 138.9, 152.1, 164.5; IR (KBr): 2944, 1497, 1350, 1159, 1019, 818, 740 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{17}H_{14}O_2S$ [M^+]: 282.0715; found: 282.0714.

Methyl 2-(4-trimethylsilyl)phenylbenzo[*b*]thiophen-3-carboxylate (6f). Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 0.44 (9H, s), 3.98 (3H, s), 7.35–7.39 (1H, m), 7.43–7.47 (1H, m), 7.86 (1H, br-d, *J* = 8.4 Hz), 8.54 (1H, br-d, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ = 0.18 (3C), 51.5, 121.9, 124.8, 124.8, 125.3, 132.5, 139.6, 142.8, 154.6, 164.5; IR (KBr): 2946, 1693, 1414, 1262, 1186, 1045, 965, 762 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{13}H_{16}O_2SSi$ [M^+]: 264.0640; found: 264.0641.

Methyl 5-methoxy-2-phenylbenzo[*b*]thiophen-3-carboxylate (6g). White solid; mp 100–110 °C; ^{1}H NMR ($CDCl_3$): δ = 3.76 (3H, s), 3.89 (3H, s), 7.08 (1H, dd, *J* = 8.8 Hz, *J* = 2.4 Hz), 7.27 (1H, d, *J* = 2.4 Hz), 7.40–7.46 (3H, m), 7.47–7.52 (2H, m), 8.23 (1H, br-d, *J* = 9.2 Hz); ^{13}C NMR ($CDCl_3$): δ = 51.5, 55.5, 104.0, 115.3, 122.3, 125.3, 128.1, 128.6, 129.4, 132.4, 134.0, 139.9, 149.3, 157.6, 164.4; IR (KBr): 2943, 1701, 1435, 1205, 1065, 827, 769 cm^{-1}; HRMS-EI: *m*/*z* calcd for $C_{17}H_{14}O_3S$ [M^+]: 298.0664; found: 298.0663.

Methyl 2-phenethylbenzo[*b*]thiophen-3-carboxylate (6h). Yellow oil; ^{1}H NMR ($CDCl_3$): δ = 3.03–3.07 (2H, m), 3.53–3.57 (2H, m), 3.94 (3H, s), 7.18–7.33 (6H, m), 7.38–7.43 (1H, m), 7.72 (1H, br-d, J = 8.4 Hz), 8.39 (1H, br-d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$): δ = 32.7, 37.5, 51.4, 121.7, 122.2, 124.4, 124.5, 125.1, 126.2, 128.4, 128.5, 137.1, 138.3, 140.7, 156.7, 164; IR (KBr): 2940, 1497, 1275, 1236, 1180, 759 cm^{-1}; HRMS-EI: m/z calcd for $C_{18}H_{16}O_2S$ [M^+]: 296.0871; found: 296.0871.

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References

1 (*a*) H. H. Seltzman, *Drug Dev. Res.*, 2009, **70**, 601; (*b*) I. I. Gerus, R. X. Mironetz, I. S. Kondratov, A. V. Bezdudny, Y. V. Dmytriv, O. V. Shishkin, V. S. Starova, O. A. Zaporozhets, A. A. Tolmachev and P. K. Mykhailiuk, *J. Org. Chem.*, 2012, **77**, 47; (*c*) C. Wasylyk, H. Zheng, C. Castell, L. Debussche, M.-C. Multon and B. Wasylyk, *Cancer Res.*, 2008, **68**, 1275; (*d*) S. Kiyonaka, K. Kato, M. Nishida, K. Mio, T. Numaga, Y. Sawaguchi, T. Yoshida, M. Wakamori, E. Mori, T. Numata, M. Ishii, H. Takemoto, A. Ojida, K. Watanabe, A. Uemura, H. Kurose, T. Morii, T. Kobayashi, Y. Sato, C. Sato, I. Hamachi and Y. Mori, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 5400; (*e*) C.-H. Cho, B. Neuenswander, G. H. Lushington and R. C. Larock, *J. Comb. Chem.*, 2009, **11**, 900; (*f*) C.-H. Cho, B. Neuenswander and R. C. Larock, *J. Comb. Chem.*, 2010, **12**, 278; (*g*) L. Berrade, B. Aisa, M. J. Ramirez, S. Galiano, S. Guccione, L. R. Moltzau, F. O. Levy, F. Nicoletti, G. Battaglia, G. Molinaro, I. Aldana, A. Monge and S. Perez-Silanes, *J. Med. Chem.*, 2011, **54**, 3086; (*h*) H. F. Guo, H. Y. Shao, Z. Y. Yang, S. T. Xue, X. Li, Z. Y. Liu, X. B. He, J. D. Jiang, Y. Q. Zhang, S. Y. Si and Z. R. Li, *J. Med. Chem.*, 2010, **53**, 1819.

2 (*a*) T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogier, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang and P. C. Isakson, *J. Med. Chem.*, 1997, **40**, 1347; (*b*) S. R. Cox, S. Liao, M. Payne-Johnson, R. J. Zielinski and M. R. Stegemann, *J. Vet. Pharmacol. Ther.*, 2011, **34**, 1; (*c*) D. Zhang, N. Raghavan, S.-Y. Chen, H. Zhang, M. Quan, L. Lecureux, L. M. Patrone, P. Y. S. Lam, S. J. Bonacorsi, R. M. Knabb, G. L. Skiles and K. He, *Drug Metab. Dispos.*, 2008, **36**, 303; (*d*) H. A. De Wald, S. Lobbestael and B. P. H. Poschel, *J. Med. Chem.*, 1981, **24**, 982; (*e*) M. J. Casavant, *Pediatrics*, 2001, **107**, 170; (*f*) H. Murakami, S. Masuzawa, S. Takii and T. Ito, *Patent*, JP2003201280, 2003, p. 38; (*g*) A. K. Culbreath, T. B. Brenneman, R. C. Kemerait Jr. and G. G. Hammes, *Pestic. Manag. Sci.*, 2009, **65**, 66; (*h*) I. Jarak, M. Kralj, L. Suman, G. Pavlovic, J. Dogan, I. Piantanida, M. Zinic, K. Pavelic and G. Karminski-Zamola, *J. Med. Chem.*, 2005, **48**, 2346; (*i*) N. J. Hrib, J. G. Jurcak, D. E. Bregna, R. W. Dunn, H. M. Geyer, H. B. Hartman, J. R. Roehr, K. L. Rogers, D. K. Rush, A. M. zczepanik, M. R. Szewczak, C. A. Wilmot and P. G. Conway, *J. Med. Chem.*, 1992, **35**, 2712; (*j*) D. H. Boschelli, J. B. Kramer, S. S. Khatana, R. J. Sorenson, D. T. Connor, M. A. Ferin, C. D. Wright, M. E. Lesch, K. Imre, G. C. Okonkwo, D. J. Schrier, M. C. Conroy, E. Ferguson, J. Woelle and U. Saxena, *J. Med. Chem.*, 1995, **38**, 4597; (*k*) D. H. Boschelli, J. B. Kramer, S. S. Khatana, R. J. Sorenson, D. T. Connor, M. A. Ferin, C. D. Wright, M. E. Lesch, K. Imre, G. C. Okonkwo, D. J. Schrier, M. C. Conroy, E. Ferguson, J. Woelle and U. Saxena, *J. Med. Chem.*, 1992, **35**, 958; (*l*) M.-J. R. P. Queiroz, I. C. F. R. Ferreira, Y. D. Gaetano, G. Kirsch, R. C. Calhelha and L. M. Estevinho, *Bioorg. Med. Chem.*, 2006, **14**, 6827; (*m*) K. G. Pinney, A. D. Bounds, K. M. Dingeman, V. P. Mocharla, G. R. Pettit, R. Bai and E. Hamel, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1081.

3 (*a*) H. Sekkak, E. M. Rakib, M.-A. Abdelouahid, A. Hafid and A. E. Malki, *Int. J. Org. Chem.*, 2013, **3**, 37; (*b*) A. S. Shawali, T. A. Farghaly and A. R. Al-Dahshoury, *ARKIVOC*, 2009, **14**, 88; (*c*) B. Chandrakantha, A. M. Isloor, P. Shetty, S. Isloor, S. Malladi and H. K. Fun, *Med. Chem. Res.*, 2012, **21**, 2702; (*d*) R. Sridhar, P. T. Perumal, S. Etti, G. Shanmugam, M. N. Ponnuswamy, V. R. Prabavathyc and N. Mathivanan, *Bioorg. Med. Chem. Lett.*, 2004, **14**, 6035.

4 (*a*) H. Gotthardt and F. Reiter, *Chem. Ber.*, 1979, **112**, 1193; (*b*) Y. O. Ko, Y. S. Chun, C.-L. Park, Y. Kim, H. Shin, S. Ahn, J. Hong and S. Lee, *Org. Biomol. Chem.*, 2009, **7**, 1132; (*c*) S. K. Abubukkar, S. D. Minhaj and K. G. Baheti, *Asian J. Chem.*, 2012, **24**, 2947; (*d*) R. Sridhar and P. T. Perumal, *Synth. Commun.*, 2003, **33**, 1483.

5 For recent examples, see: (*a*) Y. Suzuki, S. Naoe, S. Oishi, N. Fujii and H. Ohno, *Org. Lett.*, 2012, **14**, 326; (*b*) J. Qian, Y. Liu, J. Zhu, B. Jiang and Z. Xu, *Org. Lett.*, 2011, **13**, 4220; (*c*) M. Zora and A. Kivrak, *J. Org. Chem.*, 2011, **76**, 9379; (*d*) M. Zora, A. Kivrak and C. Yazici, *J. Org. Chem.*, 2011, **76**, 6726; (*e*) B. Willy and T. J. J. Müller, *Org. Lett.*, 2011, **13**, 2082; (*f*) J. P. Waldo, S. Mehta and R. C. Larock, *J. Org. Chem.*, 2008, **73**, 6666; (*g*) M. S. M. Ahmed, K. Kobayashi and A. Mori, *Org. Lett.*, 2005, **7**, 4487.

6 (*a*) T. Kusakabe, H. Sagae and K. Kato, *Org. Biomol. Chem.*, 2013, **11**, 4943; (*b*) Y. Jiang, T. Kusakabe, K. Takahashi and K. Kato, *Org. Biomol. Chem.*, 2014, **12**, 3380; (*c*) R. Shen, T. Kusakabe, K. Takahashi and K. Kato, *Org. Biomol. Chem.*, 2014, **12**, 4533.

7 (*a*) K. Kato, S. Motodate, T. Mochida, T. Kobayashi and H. Akita, *Angew. Chem.*, 2009, **121**, 3376, (*Angew. Chem. Int. Ed.*, 2009, **48**, 3326); (*b*) S. Motodate, T. Kobayashi, M. Fujii, T. Mochida, T. Kusakabe, S. Katoh, H. Akita and K. Kato, *Chem. – Asian J.*, 2010, **5**, 2221; (*c*) K. Kato, R. Teraguchi,

S. Yamamura, T. Mochida, H. Akita, T. A. Peganova, N. V. Vologdin and O. V. Gusev, *Synlett*, 2007, 638; (*d*) K. Kato, R. Teraguchi, S. Motodate, A. Uchida, T. Mochida, T. A. Peganova, N. V. Vologdin and H. Akita, *Chem. Commun.*, 2008, 3687.

8 The methoxymethyl group may be removed by acetal exchange (or hydrolysis) after cyclization.

9 K. Liu, F. Jia, H. Xi, Y. Li, X. Zheng, Q. Guo, B. Shen and Z. Li, *Org. Lett.*, 2013, **15**, 2026.

10 A. B. Biro and A. Kotschy, *Eur. J. Org. Chem.*, 2007, 1364.