Cobalt-Catalyzed Alkenylation of Thiazoles with Alkynes via C–H Bond Functionalization

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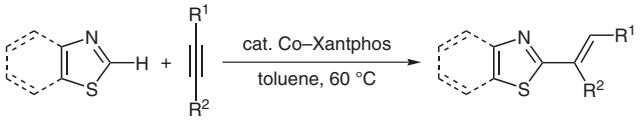
Received 15 March 2011

Abstract: A cobalt–Xantphos catalyst has been developed for the *syn* addition of (benzo)thiazoles to internal alkynes via C–H bond functionalization. The reaction affords C2-alkenylated (benzo)thiazoles with high regio- and stereoselectivities under mild conditions.

Key words: cobalt, C–H activation, heterocycles, hydroarylation, alkynes

The prevalence of aromatic heterocycles in functional molecules as well as increasing interest in C–H bond functionalization as a viable synthetic strategy have driven chemists to develop a variety of metal-catalyzed direct functionalization reactions of heteroaromatic C–H bonds.[1] Among such transformations, insertion of an unsaturated molecule into the C–H bond is particularly attractive due to the intrinsically atom-economical process. We recently reported a cobalt-catalyzed alkenylation reaction of the C2 position of a (benz)oxazole derivative with an internal alkyne that occurs at room temperature.[2–4] This reaction represents a rare example of cobalt-catalyzed heteroaromatic C–H bond functionalization, and features the low cost of the cobalt catalyst[5] and mild reaction conditions. We report here an extension of this chemistry to (benzo)thiazole derivatives. Thus, a cobalt–Xantphos catalyst has been developed for the C2-alkenylation of a (benzo)thiazole with an internal alkyne with high regio- and stereoselectivities (Scheme 1).[6,7] The reported reaction adds to the rapidly expanding repertoire of cobalt catalysis for C–H bond functionalization.[8–10]



Scheme 1 Co–Xantphos-catalyzed addition of (benzo)thiazole to alkyne

We chose 4,5-dimethylthiazole (**1a**) and oct-2-yne (**2a**) as model reactants, and screened reaction conditions (Table 1). The cobalt–DPEphos catalyst, which was generated from cobalt(II) bromide (10 mol%), DPEphos (10 mol%), and (trimethylsilyl)methylmagnesium chloride (50 mol%) and was effective for the addition of (benz)oxazole derivatives,[2] poorly promoted the reaction (entry 1). Throughout the screening of other ligands, Xantphos emerged as the ligand of choice, allowing the reaction to proceed smoothly at 60 °C in tetrahydrofuran to afford the alkenylation product **3a** in 75% yield with exclusive *syn* selectivity (entry 2). Note that Xantphos was a rather poor ligand for the reaction of (benz)oxazole derivatives.[2] Other bidentate phosphine ligands such as dppe, dppp, dppb, and dppf were less effective (entries 3–6). The use of other Grignard reagents such as methylmagnesium chloride and 2,2-dimethylpropylmagnesium bromide resulted in lower yields (entries 7 and 8). The reaction did not take place at all when the amount of (trimethylsilyl)methylmagnesium chloride was reduced to 30 mol%. The product yield was further improved to 90% when toluene was used as the solvent instead of tetrahydrofuran (entry 9).

The optimized reaction conditions allowed C2-alkenylation of a variety of thiazole derivatives with oct-4-yne in good yield with high *syn* stereoselectivity (Figure 1). 4-Methylthiazole served as an excellent substrate, affording the corresponding alkenylation product **3b** in 85% yield, while the reaction of unsubstituted thiazole was rather

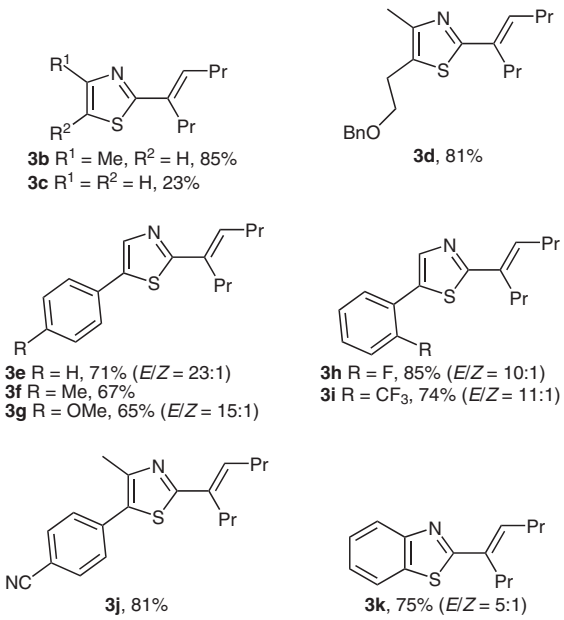
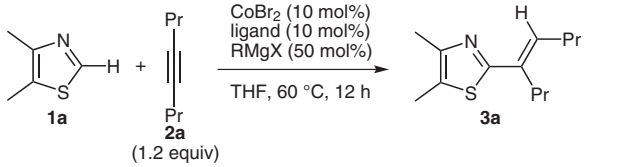
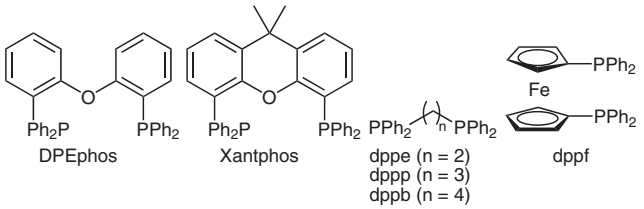


Figure 1 Scope of thiazoles. Unless otherwise noted, the reaction was performed under the conditions described in Table 1, entry 9, and the *E*/*Z* ratio was >99:1. The yield of **3c** was determined by GC.

SYNTHESIS 2011, No. 16, pp 2561–2566
Advanced online publication: 17.06.2011
DOI: 10.1055/s-0030-1260077; Art ID: C29411SS

Table 1 Optimization of Reaction Conditions[a]





Entry	Ligand	RMgX	Yield[b] (%)
1	DPEphos	Me_3SiCH_2MgCl	2
2	Xantphos	Me_3SiCH_2MgCl	75
3	dppe	Me_3SiCH_2MgCl	12
4	dppp	Me_3SiCH_2MgCl	64
5	dppb	Me_3SiCH_2MgCl	34
6	dppf	Me_3SiCH_2MgCl	29
7	Xantphos	MeMgCl	51
8	Xantphos	*t*-$BuCH_2MgBr$	58
9	Xantphos	Me_3SiCH_2MgCl	90[c]

[a] Reaction was performed on a 0.3-mmol scale at 0.2 M concentration.
[b] GC yield.
[c] Toluene was used as the solvent. Isolated yield.

sluggish (**3c**). A related thiazole substrate bearing a benzyloxy group also afforded the corresponding alkenylation product **3d** in good yield. 5-Arylthiazole derivatives, which could be readily synthesized by direct C5-arylation of thiazole with the corresponding aryl bromides or iodides,[11] also participated in the reaction to afford the alkenylation products **3e–j** in moderate to good yields with high stereoselectivities. The aryl group on the thiazole ring could be either electron-rich (**3f**, **3g**) or electron-withdrawing (**3h**, **3i**). The cobalt–Xantphos catalyst tolerated the presence of a cyano group (**3j**), as did the cobalt–DPEphos catalyst in the alkenylation of oxazole derivatives.[2] Benzothiazole also participated in the reaction (**3k**).

Next, the scope of alkynes was studied (Figure 2). Aliphatic alkynes afforded the alkenylation products **3l–n** in moderate to good yields. Unsymmetrical alkynes such as hex-2-yne and 4-methylpent-2-yne underwent C–C bond formation preferentially at the less-hindered positions, while the regioselectivity was modest (2:1) for the former alkyne. The reactions of aromatic alkynes were sluggish and required heating at 80 °C, affording the products **3o** and **3p** in modest yields. For 1-phenylprop-1-yne, C–C bond formation took place exclusively at the position proximal to the methyl group. Note that the regioselectivity trend observed for the unsymmetrical alkynes (**3m**, **3n**, and **3o**) is the same as observed for the reaction of oxazoles catalyzed by Co–DPEphos.[2] Terminal alkynes failed to participate in the reaction.

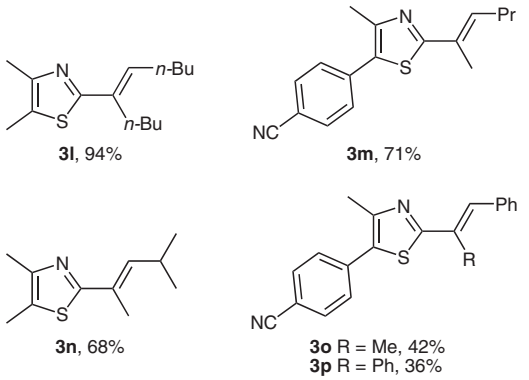
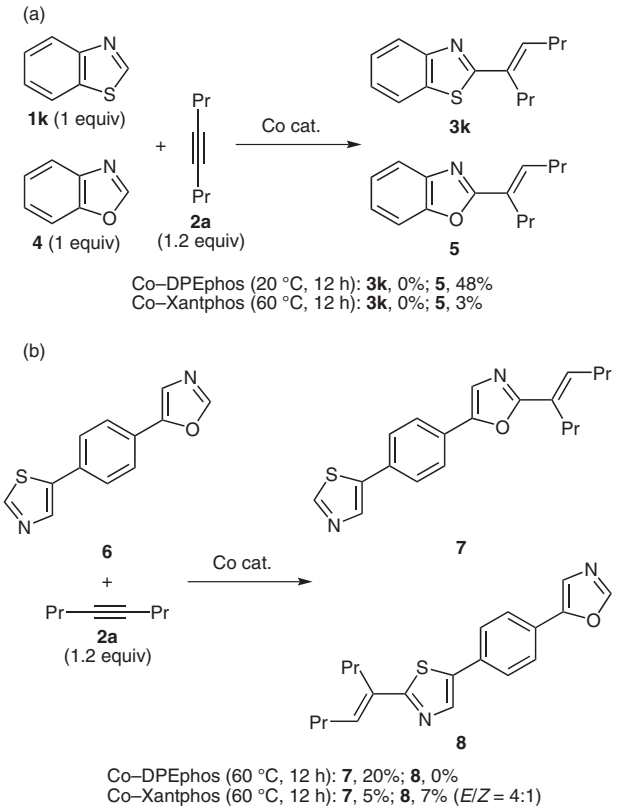


Figure 2 Scope of alkynes. Unless otherwise noted, the reaction was performed under the conditions described in Table 1, entry 2, and the *E*/*Z* ratio was > 99:1. **3m** is the major regioisomer (regioselectivity was 2:1). For **3o** and **3p**, the reaction was performed at 80 °C.

Because the optimum catalytic systems for the alkenylation of (benz)oxazoles and (benzo)thiazoles are different, we became interested in the chemoselectivity of each systems. First, we performed competition experiments using benzothiazole **1k** and benzoxazole **4** [Scheme 2 (a)]. The reaction of an equimolar mixture of **1k** and **4** with oct-4-yne (**2a**) in the presence of the Co–DPEphos catalyst expectedly resulted in exclusive formation of a benzoxazole adduct **5** in 48% yield. On the other hand, it was rather unexpected that the Co–Xantphos catalyst did not promote the alkenylation of **1k**, but afforded only a small amount (3%) of **5**. Apparently, benzoxazole seems to have inhibited the reaction of benzothiazole, while the reason for the inhibition is not clear at this stage.

Next, a substrate **6** bearing both oxazole and thiazole moieties was subjected to the Co–DPEphos and Co–Xantphos catalytic systems [Scheme 2 (b)]. While the reaction was rather sluggish with both of the catalytic systems, we noted a difference in the chemoselectivity. While the oxazole moiety was exclusively alkenylated with the Co–DPEphos system, the Co–Xantphos system afforded a mixture of products **7** and **8** resulting from activation of the oxazolyl and thiazolyl C–H bonds, respectively. The origin of this chemoselectivity difference is elusive at this moment, while we consider that the Co–Xantphos- and Co–DPEphos-catalyzed reactions share essentially the same catalytic cycle consisting of (1) oxidative addition of the C2–H bond to the cobalt center, (2) insertion of the alkyne into the Co–H bond, and (3) reductive elimination of the resulting diorganocobalt intermediate.[2]

In summary, we have developed a cobalt–Xantphos catalyst for activation of a (benzo)thiazole C2–H bond followed by insertion of an internal alkyne, which affords the



Scheme 2 Competition of benzothiazole and benzoxazole in cobalt-catalyzed reaction with oct-4-yne. Co–DPEphos: $CoBr_2$ (10 mol%), DPEphos (10 mol%), Me_3SiCH_2MgCl (50 mol%), pyridine (80 mol%), THF; Co–Xantphos: $CoBr_2$ (10 mol%), Xantphos (10 mol%), Me_3SiCH_2MgCl (50 mol%), toluene.

corresponding alkenylation product in moderate to good yield with high *syn* stereoselectivity. The present catalytic system adds to the repertoire of direct C–H functionalization of aromatic heterocycles. The different reactivities of the Co–Xantphos and Co–DPEphos catalysts toward thiazole and oxazole derivatives deserve further synthetic and mechanistic investigations.

Melting points were determined using a capillary melting point apparatus and are uncorrected. Column chromatography was performed on silica gel 60 (Merck). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AV-400 (400 MHz) or Jeol ECX-400 (400 MHz) spectrometers using TMS (δ = 0) and $CHCl_3$ (δ = 77.0) as internal standards, respectively. Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a capillary column, DB-5 (Agilent J&W, 0.25 mm i.d. × 30 m, 0.25 mm film thickness). HRMS were obtained with a Q-Tof Premier LC HR mass spectrometer. Unless otherwise noted, chemicals were commercial grade and were used as received. Toluene was distilled over CaH_2. Grignard reagents except MeMgCl were prepared from the corresponding halides and Mg turnings and titrated before use. The following thiazole derivatives were prepared according to the literature procedure, and their spectral data showed good agreement with the reported data: 5-[2-(benzyloxy)ethyl]-4-methylthiazole,[12] 5-phenylthiazole,[11c] 5-(4-tolyl)thiazole,[11c] 5-(4-methoxyphenyl)thiazole,[11c] and 4-(4-methylthiazol-5-yl)benzonitrile.[11a]

5-[2-(Trifluoromethyl)phenyl]thiazole; Typical Procedure

2-Iodobenzotrifluoride (0.70 mL, 5 mmol), thiazole (0.42 mL, 6 mmol), KOAc (0.59 g, 6 mmol), and $Pd(OAc)_2$ (11.2 mg, 0.05 mmol) were dissolved in *N*,*N*-dimethylacetamide (15 mL), stirred at 130 °C for 18 h, and then quenched with H_2O (10 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and purified by chromatography (silica gel, hexane–EtOAc, 10:1) to afford the product as a colorless oil; yield: 70%; R_f = 0.13 (hexane–EtOAc, 10:1).

IR (NaCl): 3072, 1605, 1578, 1527, 1446, 1396, 1315, 1267, 1174, 1130, 1066, 1035, 869, 767 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.88 (s, 1 H), 7.88 (s, 1 H), 7.80–7.78 (m, 1 H), 7.61–7.51 (m, 2 H), 7.48–7.46 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.6, 142.9 (q, $^4J_{C\text{-}F}$ = 2.0 Hz), 134.0, 133.4, 131.6, 129.6 (q, $^2J_{C\text{-}F}$ = 30.0 Hz), 129.5, 128.9, 126.5 (q, $^3J_{C\text{-}F}$ = 5.3 Hz), 123.6 (q, $^1J_{C\text{-}F}$ = 272 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{10}H_7NSF_3$: 230.0251; found: 230.0248.

5-(2-Fluorophenyl)thiazole

Following the typical procedure; yellow oil; yield: 75%; R_f = 0.52 (hexane–EtOAc, 3:1).

IR (NaCl): 3080, 1718, 1577, 1523, 1483, 1473, 1450, 1390, 1247, 1222, 1122, 1103, 873, 812, 754 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.84 (s, 1 H), 8.25 (s, 1 H), 7.63–7.59 (m, 1 H), 7.35–7.30 (m, 1 H), 7.22–7.16 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.7 (d, $^1J_{C\text{-}F}$ = 249 Hz), 152.8 (d, $^4J_{C\text{-}F}$ = 4.0 Hz), 141.4 (d, $^3J_{C\text{-}F}$ = 7.0 Hz), 131.8 (d, $^3J_{C\text{-}F}$ = 5.0 Hz), 129.5 (d, $^3J_{C\text{-}F}$ = 9.0 Hz), 129.0 (d, $^4J_{C\text{-}F}$ = 3.0 Hz), 124.5 (d, $^4J_{C\text{-}F}$ = 4.0 Hz), 118.9 (d, $^2J_{C\text{-}F}$ = 14.0 Hz), 116.2 (d, $^2J_{C\text{-}F}$ = 12.0 Hz).

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for C_9H_7NSF: 180.0283; found: 180.0286.

(*E*)-4,5-Dimethyl-2-(oct-4-en-4-yl)thiazole (3a); Typical Procedure

To a Schlenk tube were added $CoBr_2$ (6.6 mg, 0.03 mmol), Xantphos (17.9 mg, 0.03 mmol), and toluene (1.3 mL); to the resulting soln was added Me_3SiCH_2MgCl (0.89 M in THF, 0.17 mL, 0.15 mmol) at 0 °C. After stirring for 30 min at this temperature, 4,5-dimethylthiazole (34 mg, 0.30 mmol) and oct-4-yne (53 μL, 0.36 mmol) were added sequentially. The mixture was stirred at 60 °C for 12 h, and then quenched with sat. aq NH_4Cl soln (1.5 mL) at r.t. The resulting mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), concentrated under reduced pressure, and purified by chromatography (silica gel, hexane–EtOAc, 100:1) to afford **3a** (60 mg, 90%) as a yellow oil. The spectral data showed good agreement with the literature data.[3a] Spectral data for **3k** has been reported previously.[2]

(*E*)-4-Methyl-2-(oct-4-en-4-yl)thiazole (3b)

Yellow oil; yield: 85%; R_f = 0.50 (hexane–EtOAc, 10:1).

IR (NaCl): 2958, 2927, 2870, 1519, 1452, 1375, 1301, 1103, 977, 893 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.69 (s, 1 H), 6.38 (t, *J* = 7.5 Hz, 1 H), 2.55 (t, *J* = 7.6 Hz, 2 H), 2.42 (s, 3 H), 2.23–2.17 (m, 2 H), 1.56–1.47 (m, 4 H), 0.96 (t, *J* = 7.4 Hz, 3 H), 0.94 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 152.8, 134.5, 132.9, 111.7, 31.5, 30.5, 22.5, 22.3, 17.4, 14.02, 13.99.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{20}NS$: 210.1316; found: 210.1317.

(*E*)-5-[2-(Benzyloxy)ethyl]-4-methyl-2-(oct-4-en-4-yl)thiazole (3d)
Yellow oil; yield: 81%; R_f = 0.46 (hexane–EtOAc, 10:1).

IR (NaCl): 3028, 2958, 2927, 2868, 1722, 1680, 1544, 1454, 1377, 1359, 1269, 1103, 1028, 904, 734, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 5 H), 6.31 (t, *J* = 7.4 Hz, 1 H), 4.53 (s, 2 H), 3.63 (t, *J* = 6.8 Hz, 2 H), 2.99 (t, *J* = 6.8 Hz, 2 H), 2.54–2.50 (m, 2 H), 2.32 (s, 3 H), 2.21–2.16 (m, 2 H), 1.56–1.44 (m, 4 H), 0.95 (t, *J* = 7.3 Hz, 3 H), 0.94 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 148.5, 138.0, 134.5, 132.1, 128.3, 127.58, 127.57, 126.3, 73.0, 70.3, 31.3, 30.5, 27.2, 22.6, 22.3, 15.1, 14.0, 13.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{30}NOS$: 344.2048; found: 344.2052.

(*E*)-2-(Oct-4-en-4-yl)-5-phenylthiazole (3e)
Colorless oil; yield: 71%; R_f = 0.45 (hexane–EtOAc, 10:1).

IR (NaCl): 3076, 3061, 3024, 2958, 2929, 2870, 1598, 1523, 1483, 1448, 1429, 1377, 1163, 1103, 1074, 756, 688 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.88 (s, 1 H), 7.56–7.54 (m, 2 H), 7.40–7.36 (m, 2 H), 7.32–7.29 (m, 1 H), 6.41 (t, *J* = 7.4 Hz, 1 H), 2.60 (t, *J* = 7.7 Hz, 2 H), 2.27–2.22 (m, 2 H), 1.61–1.49 (m, 4 H), 0.99 (t, *J* = 7.4 Hz, 3 H), 0.98 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.5, 138.2, 137.4, 134.9, 133.8, 131.7, 129.0, 127.9, 126.5, 31.1, 30.6, 22.6, 22.3, 14.1, 14.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{22}NS$: 272.1473; found: 272.1476.

(*E*)-2-(Oct-4-en-4-yl)-5-(4-tolyl)thiazole (3f)
Yellow solid; yield: 67%; mp 42–43 °C; R_f = 0.62 (hexane–EtOAc, 10:1).

IR (NaCl): 3022, 2727, 1890, 1494, 1301, 1234, 1163, 1105, 1066, 968, 891, 852, 812, 746 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1 H), 7.47–7.42 (m, 2 H), 7.22–7.17 (m, 2 H), 6.39 (t, *J* = 7.4 Hz, 1 H), 2.61–2.57 (m, 2 H), 2.36 (s, 3 H), 2.27–2.21 (m, 2 H), 1.63–1.49 (m, 4 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 137.9, 137.8, 137.5, 135.0, 133.6, 129.6, 128.8, 126.4, 31.1, 30.6, 22.6, 22.3, 21.2, 14.1, 14.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}NS$: 286.1629; found: 286.1634.

(*E*)-5-(4-Methoxyphenyl)-2-(oct-4-en-4-yl)thiazole (3g)
White solid; yield: 65%; mp 44–45 °C; R_f = 0.28 (hexane–EtOAc, 10:1).

IR (NaCl): 1610, 1533, 1494, 1253, 1178, 1041, 827 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (s, 1 H), 7.51–7.45 (m, 2 H), 6.93–6.89 (m, 2 H), 6.37 (t, *J* = 7.4 Hz, 1 H), 3.82 (s, 3 H), 2.59 (t, *J* = 7.6 Hz, 2 H), 2.27–2.21 (m, 2 H), 1.60–1.47 (m, 4 H), 0.98 (t, *J* = 7.3 Hz, 3 H), 0.97 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.6, 159.5, 137.27, 137.22, 135.0 133.4, 127.8, 124.3, 114.4, 55.3, 31.1, 30.6, 22.6, 22.3, 14.1, 13.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{24}NOS$: 302.1579; found: 302.1578.

(*E*)-5-(2-Fluorophenyl)-2-(oct-4-en-4-yl)thiazole (3j)
Yellow oil; yield: 85%; R_f = 0.51 (hexane–EtOAc, 10:1).

IR (NaCl): 3020, 2956, 2927, 2870, 1629, 1575, 1521, 1475, 1452, 1402, 1377, 1257, 1219, 1168, 1105, 1076, 1037, 974, 935, 893, 864, 812, 752 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.05 (s, 1 H), 7.59–7.55 (m, 1 H), 7.30–7.24 (m, 1 H), 7.19–7.12 (m, 2 H), 6.44 (t, *J* = 7.4 Hz, 1 H), 2.61 (t, *J* = 7.6 Hz, 2 H), 2.28–2.22 (m, 2 H), 1.64–1.50 (m, 4 H), 0.99 (t, *J* = 7.4 Hz, 3 H), 0.98 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (d, $^5J_{C-F}$ = 3.0 Hz), 158.9 (d, $^1J_{C-F}$ = 248 Hz), 141.2 (d, $^4J_{C-F}$ = 8.0 Hz), 134.8, 134.1, 130.2 (d, $^3J_{C-F}$ = 5.0 Hz), 129.2 (d, $^3J_{C-F}$ = 11.0 Hz), 129.0 (d, $^3J_{C-F}$ = 4.0 Hz), 124.5 (d, $^4J_{C-F}$ = 4.0 Hz), 119.7 (d, $^2J_{C-F}$ = 13.0 Hz), 116.2 (d, $^2J_{C-F}$ = 22.0 Hz), 31.1, 30.6, 22.5, 22.3, 14.1, 14.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{21}NFS$: 290.1379; found: 290.1384.

(*E*)-2-(Oct-4-en-4-yl)-5-[2-(trifluoromethyl)phenyl]thiazole (3i)
Yellow oil; yield: 74%; R_f = 0.42 (hexane–EtOAc, 10:1).

IR (NaCl): 2960, 2931, 2872, 1604, 1575, 1448, 1315, 1263, 1172, 1130, 1109, 1066, 1035, 765, 746 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.78–7.76 (m, 1 H), 7.66 (s, 1 H), 7.58–7.554 (m, 1 H), 7.51–7.47 (m, 2 H), 6.43 (t, *J* = 7.4 Hz, 1 H), 2.60 (t, *J* = 7.8 Hz, 2 H), 2.28–2.22 (m, 2 H), 1.65–1.48 (m, 4 H), 0.99 (t, *J* = 7.4 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 142.1, 134.7, 134.1, 133.3, 132.2, 131.5, 130.2, 129.4 (q, $^2J_{C-F}$ = 30.0 Hz), 128.5, 126.5 (q, $^3J_{C-F}$ = 5.3 Hz), 123.8 (q, $^1J_{C-F}$ = 272 Hz), 31.3, 30.6, 22.5, 22.2, 14.1, 14.0.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{21}NF_3S$: 340.1347; found: 340.1349.

(*E*)-4-[4-Methyl-2-(oct-4-en-4-yl)thiazol-5-yl]benzonitrile (3j)
White solid; yield: 81%; mp 86–87 °C; R_f = 0.43 (hexane–EtOAc, 10:1).

IR (NaCl): 3057, 2725, 2227, 1624, 1593, 1554, 1537, 1494, 1328, 1309, 1078, 1035, 983, 898, 844 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.67 (m, 2 H), 7.55–7.53 (m, 2 H), 6.44 (t, *J* = 7.5 Hz, 1 H), 2.56 (t, *J* = 7.6 Hz, 2 H), 2.51 (s, 3 H), 2.26–2.21 (m, 2 H), 1.62–1.49 (m, 4 H), 0.98 (t, *J* = 7.4 Hz, 3 H), 0.97 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.5, 149.4, 137.4, 134.4, 134.1, 132.3, 129.3, 128.4, 118.6, 110.7, 31.2, 30.6, 22.5, 22.3, 16.7, 14.0, 13.9.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{23}N_2S$: 311.1582; found: 311.1578.

(*E*)-2-(Dec-5-en-5-yl)-4,5-dimethylthiazole (3l)
Yellow oil; yield: 94%; R_f = 0.64 (hexane–EtOAc, 10:1).

IR (NaCl): 2956, 2926, 2858, 1552, 1454, 1377, 1259, 1095, 1020, 800, 665 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.25 (t, *J* = 7.5 Hz, 1 H), 2.53–2.50 (m, 2 H), 2.31 (s, 3 H), 2.30 (s, 3 H), 2.22–2.17 (m, 2 H), 1.47–1.32 (m, 8 H), 0.91 (t, *J* = 7.2 Hz, 3 H), 0.90 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.5, 148.1, 134.6, 131.8, 124.5, 31.5, 31.4, 29.2, 28.1, 22.7, 22.5, 14.8, 13.97, 13.96, 11.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{26}NS$: 252.1786; found: 252.1792.

(*E*)-4-[2-(Hex-2-en-2-yl)-4-methylthiazol-5-yl]benzonitrile (3m) and (*E*)-4-[2-(Hex-2-en-3-yl)-4-methylthiazol-5-yl]benzonitrile (3m′)
Yellow solid; yield: 71%; mp 60–61 °C; R_f = 0.36 (hexane–EtOAc, 10:1).

IR (NaCl): 3055, 2725, 2229, 1602, 1527, 1492, 1305, 1180, 1074, 1041, 979, 850, 833 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.4 Hz, 2 H, **3m** and **3m′**), 7.54 (d, *J* = 8.4 Hz, 2 H, **3m** and **3m′**), 6.54 (q, *J* = 7.1 Hz, 1 H, **3m′**), 6.48 (t, *J* = 7.4 Hz, 1 H, **3m**), 2.59–2.55 (m, 2 H, **3m′**), 2.51 (s, 3 H, **3m** and **3m′**), 2.27–2.21 (m, 2 H, **3m**), 2.13 (s, 3 H, **3m**), 1.86 (d, *J* = 7.2 Hz, 3 H, **3m′**), 1.60–1.49 (m, 2 H, **3m** and **3m′**), 0.97 (t, *J* = 7.3 Hz, 3 H, **3m** and **3m′**).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 169.4, 149.38, 149.34, 137.4, 137.3, 135.2, 133.8, 132.3, 129.7, 129.3, 129.25, 129.24, 128.42, 128.39, 128.34, 118.58, 118.56, 110.7, 110.6, 30.8, 30.7, 22.2, 22.0, 16.67, 16.64, 14.7, 14.2, 13.92, 13.85.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{17}H_{19}N_2S$: 283.1269; found: 283.1266.

(*E*)-4,5-Dimethyl-2-(4-methylpent-2-en-2-yl)thiazole (3n)
Colorless oil; yield: 68%; R_f = 0.47 (hexane–EtOAc, 10:1).

IR (NaCl): 2960, 2924, 2866, 1635, 1519, 1454, 1402, 1375, 1361, 1301, 1244, 1232, 1222, 1176, 1132, 1049, 1024, 977, 858 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.12 (d, *J* = 9.3 Hz, 1 H), 2.74–2.65 (m, 1 H), 2.31 (s, 3 H), 2.30 (s, 3 H), 2.08 (s, 3 H), 1.05 (d, *J* = 6.7 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.11, 148.09, 138.59, 127.78, 124.62, 27.81, 22.53, 14.82, 14.72, 11.35.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{11}H_{18}NS$: 196.1160; found: 196.1165.

(*E*)-4-[4-Methyl-2-(1-phenylprop-1-en-2-yl)thiazol-5-yl]benzonitrile (3o)
Yellow solid; yield: 42%; mp 136–138 °C; R_f = 0.11 (hexane–EtOAc, 10:1).

IR (NaCl): 2225, 1602, 1521, 1490, 1305, 1045, 835 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.70 (m, 2 H), 7.59–7.57 (m, 2 H), 7.50 (s, 1 H), 7.45–7.38 (m, 4 H), 7.32–7.30 (m, 1 H), 2.56 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 149.9, 137.2, 136.5, 132.5, 131.2, 130.8, 129.5, 129.4, 128.4, 127.6, 118.6, 111.0, 16.7, 16.5.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}N_2S$: 317.1112; found: 317.1114.

(*E*)-4-[2-(1,2-Diphenylvinyl)-4-methylthiazol-5-yl]benzonitrile (3p)
Yellow solid; yield: 36%; mp 174–175 °C; R_f = 0.10 (hexane–EtOAc, 10:1).

IR (NaCl): 2225, 1602, 1490, 1305, 835, 665 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.85 (s, 1 H), 7.66–7.64 (m, 2 H), 7.51–7.49 (m, 2 H), 7.46–7.45 (m, 3 H), 7.39–7.37 (m, 2 H), 7.16–7.14 (m, 3 H), 7.08–7.06 (m, 2 H), 2.59 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 150.5, 138.3, 137.3, 135.5, 134.0, 132.4, 131.3, 130.2, 130.1, 130.0, 129.3, 129.2, 128.7, 128.2, 128.0, 118.5, 111.0, 16.8.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{25}H_{19}N_2S$: 379.1269; found: 379.1272.

5-[4-(Thiazol-5-yl)phenyl]oxazole (6)
White solid; yield: 74%; mp 152–153 °C; R_f = 0.18 (hexane–EtOAc, 3:1).

IR (NaCl): 2725, 1525, 1269, 1105, 1047, 966, 941, 871, 831 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.79 (s, 1 H), 8.14 (s, 1 H), 7.95 (s, 1 H), 7.72–7.69 (m, 2 H), 7.66–7.64 (m, 2 H), 7.41 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.4, 150.9, 150.7, 139.4, 131.3, 127.7, 127.4, 125.0 (2 peaks are overlapped), 122.1.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{12}H_9N_2OS$: 229.0436; found: 229.0437.

(*E*)-2-(Oct-4-en-4-yl)-5-[4-(thiazol-5-yl)phenyl]oxazole (7)
Yellow solid; yield: 20%; mp 183–184 °C; R_f = 0.20 (hexane–EtOAc, 3:1).

IR (NaCl): 2725, 2360, 2341, 1724, 1683, 1525, 1269, 1105, 1047, 966, 941, 871, 831, 721 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.78 (s, 1 H), 8.13 (s, 1 H), 7.70–7.61 (m, 4 H), 7.37 (s, 1 H), 6.67 (t, *J* = 7.6 Hz, 1 H), 2.56 (t, *J* = 7.6 Hz, 2 H), 2.54–2.25 (m, 2 H), 1.62–1.52 (m, 4 H), 1.01 (t, *J* = 7.2 Hz, 3 H), 0.99 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 152.2, 149.5, 145.1, 139.2, 135.4, 130.6, 128.22, 128.18, 127.3, 124.6, 123.6, 30.4, 29.4, 22.54, 22.50, 14.1, 14.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{23}N_2OS$: 339.1531; found: 339.1531.

(*E*)-5-{4-[2-(Oct-4-en-4-yl)thiazol-5-yl]phenyl}oxazole (8)
Yellow solid; yield: 7%; mp 189–190 °C; R_f = 0.22 (hexane–EtOAc, 3:1).

IR (NaCl): 2723, 2669, 1724, 1681, 1303, 1220, 1116, 1062, 964, 948, 877, 831, 721, 665 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1 H), 7.93 (s, 1 H), 7.70–7.60 (m, 4 H), 7.39 (s, 1 H), 6.43 (t, *J* = 6.8 Hz, 1 H), 2.60 (t, *J* = 7.6 Hz, 2 H), 2.29–2.23 (m, 2 H), 1.59–1.50 (m, 4 H), 0.99 (t, *J* = 7.2 Hz, 3 H), 0.98 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.28, 163.25, 152.2, 149.5, 141.4, 139.2, 135.4, 130.7, 128.2, 127.3, 124.6, 123.6, 30.5, 29.4, 22.54, 22.50, 14.1, 14.0.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{20}H_{23}N_2OS$: 339.1531; found: 339.1537.

Acknowledgment

We thank Singapore National Research Foundation (NRF-RF2009-05) and Nanyang Technological University for financial support.

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