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Rhodium-Catalyzed C3-Selective Alkenylation of Substituted Thiophene-2-Carboxylic Acids and Related Compounds

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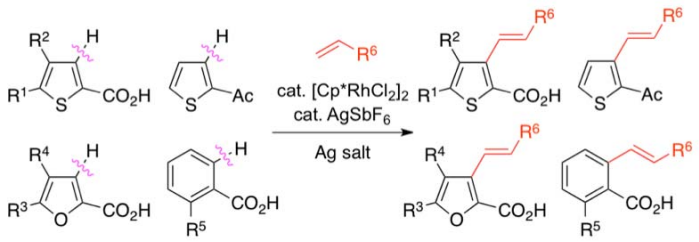


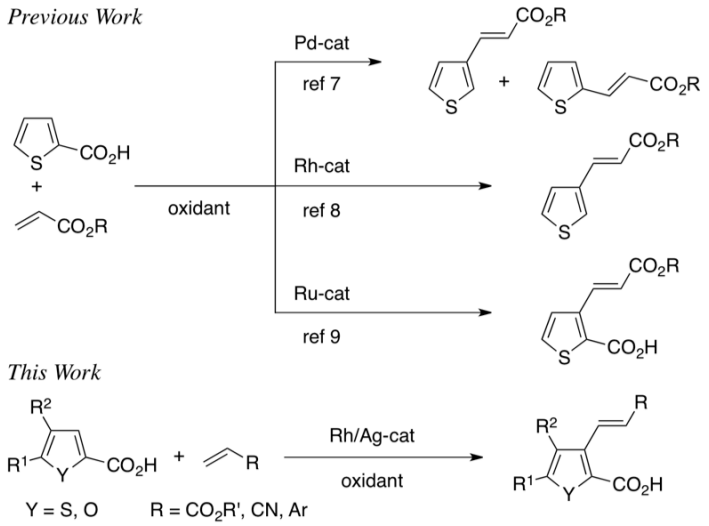
Abstract: The regioselective C3-alkenylation of thiophene-2-carboxylic acids can be achieved effectively via rhodium/silver-catalyzed oxidative coupling with alkenes, unaccompanied by

decarboxylation. A wide range of substrates including brominated thiophenecarboxylic acids and furan-2-carboxylic acids can be employed together with styrenes as well as acrylates. The present catalyst system is also applicable to *ortho*-alkenylation of benzoic acids.

Introduction

Alkenylthiophene and –furan structures can be seen in various organic functional materials and bioactive compounds.[1] As an atom- and step-economical tool for constructing such frameworks, the transition-metal-catalyzed direct alkenylation of thiophenes and furans via C–H bond cleavage have gained considerable attention. This type of reaction is known to usually take place at the electron-rich C2-position on the heterocycles predominantly.[2] Among the most powerful methods for direct functionalization of non-activated C–H bonds is a chelation-assisted version with the aid of directing groups.[3] Although the methodology has been well-developed, its application to thiophene and furan derivatives, especially to their C3-selective alkenylation has been less explored and only few examples utilizing amide groups as directing groups have been reported.[4,5] One of more promising directing groups is a carboxyl function, which is readily removable and substitutable through decarboxylation and decarboxylative coupling, respectively,[6] after the chelation-assisted alkenylation. Recently, we reported the palladium-,[7] rhodium-,[8] and ruthenium-catalyzed[9] C3-alkenylation of thiophene-2-carboxylic acids (Scheme 1). While the palladium-catalyzed version gave a mixture of C2-

Scheme 1. Catalytic C3-Alkenylation of Thiophene- and Furan-2-Carboxylic Acids



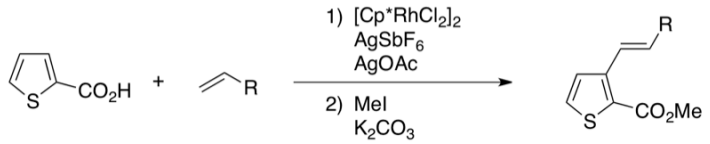
and C3-alkenylated products, the use of a rhodium catalyst allowed exclusive C3-alkenylation. These reactions proceeded accompanied by decarboxylation. In contrast, simple C3-alkenylation retaining the carboxyl group was realized under ruthenium catalysis. The third version is synthetically meaningful because the remained carboxyl group can be utilized for further transformations. However, the substrate scope for the ruthenium catalysis is narrow: only some thiophene-2-carboxylic acids and acrylates undergo the reaction smoothly. During further investigation, we succeeded in finding that the C3-alkenylation of variously substituted thiophene-2-carboxylic acids proceeds efficiently with retaining their carboxyl function in the presence of a rhodium/silver catalyst system. The present catalysis was found to be applicable to the reactions of a wider range of substrates including substituted thiophene- and furan-2-carboxylic acids, 2-substituted benzoic acids, and 1-naphthoic acid. Moreover, various styrenes could be employed as alkenyl sources. The results obtained with respect to these reactions are described herein.

Results and Discussion

In an initial attempt, thiophene-2-carboxylic acid (**1a**) (0.5 mmol) was treated with butyl acrylate (**2a**) (1 mmol) in the presence of $[Cp^*RhCl_2]_2$ (0.005 mmol), $AgSbF_6$ (0.02 mmol), and AgOAc (1 mmol) in dioxane (3 mL) at 120 ºC for 5 h. As a result, the C3-alkenylated product was formed, which was then esterified for quantification to produce **3a** in a moderate yield (entry 1 in Table 1). Even at 120 ºC,

decarboxylation was not observed at all under the Rh/Ag catalysis. The reaction was terminated with remaining unconsumed substrates. At 100 °C, the yield of **3a** was significantly improved (entry 2). Under similar conditions, however, the reaction did not proceed at all in the presence of $Cu(OAc)_2•H_2O$ in place of AgOAc (entry 3). At 80 °C, the reaction proceeded smoothly to produce **3a** quantitatively (entry 4). In the absence of $AgSbF_6$, the reaction was sluggish at 80 °C (entry 5). In the presence of $[Cp^*RhCl_2]_2/AgSbF_6$ as catalyst at 80 °C, **1a** efficiently reacted with various acrylates **2b**-**e** as well as acrylonitrile (**2f**) to selectively produce the corresponding C3-alkenylated products **3b**-**f** in 71-87% yield (entries 6-10).

Table 1. Reaction of Thiophene-2-Carboxylic Acid (1a) with Alkenes 2[a]



1a **2** **3**

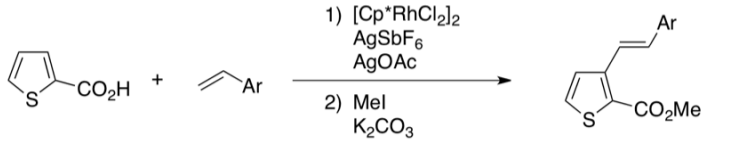
entry	2	R	product, % yield
1[b]	**2a**	CO_2Bu	**3a**, (41)[c]
2[d]	**2a**	CO_2Bu	**3a**, (95)[c]
3[d,e]	**2a**	CO_2Bu	**3a**, (0)[c]
4	**2a**	CO_2Bu	**3a**, 84 (99)[c]
5[f]	**2a**	CO_2Bu	**3a**, (36)[c]
6	**2b**	CO_2Et	**3b**, 87
7	**2c**	CO_2Cy[e]	**3c**, 79
8	**2d**	$CO_2(i\text{-Bu})$	**3d**, 81
9	**2e**	$CO_2(t\text{-Bu})$	**3e**, 76
10	**2f**	CN	**3f**, 71

[a] Reaction conditions: (1) **1a** (0.5 mmol), **2** (1 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $AgSbF_6$ (0.02 mmol), AgOAc (1 mmol), dioxane (3 mL) under N_2 at 80 °C for 8 h; (2) with the addition of MeI (3 mmol), K_2CO_3 (1.5 mmol), and DMF (3 mL) at rt for 3 h. [b] At 120 °C for 5 h. [c] GC yield. [d] At 100 °C for 5 h. [e] $Cu(OAc)_2•H_2O$ (1 mmol) was employed as oxidant in place of AgOAc. [f] Without $AgSbF_6$.

Next, we examined reactions using styrenes as alkenyl sources, which could not be utilized under ruthenium catalysis (Scheme 1).[9] Under the conditions employed for entry 2 in Table 1, **1a** coupled with styrene (**2g**) to form a C3-styrylated product **3g** in a low yield (entry 1 in Table 2). In this case, the reaction proceeded more smoothly at 120 °C to improve the product yield to 56% (entry 2). Increasing

the amount of $[Cp^*RhCl_2]_2$ to 0.01 mmol led to further enhancement of the yield (entry 3). Finally, **3g** was obtained in 74% yield, when the reaction was conducted using 4 equiv of **2g** (entry 4). Under the optimized reaction conditions, **1a** reacted with a number of 4-substitued styrenes **2h**-**l** and 2-vinylnaphthalene (**2m**) in fair to good yields (entries 5-10).

Table 2. Reaction of Thiophene-2-Carboxylic Acid (1a) with Styrenes 2[a]



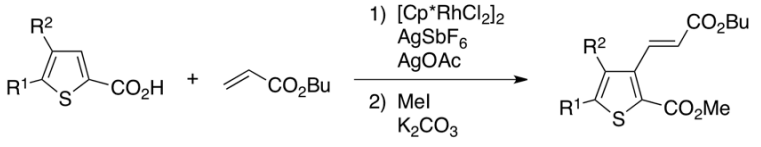
1a **2** **3**

entry	2	Ar	product, % yield
1[b,c,d]	**2g**	Ph	**3g**, (16)[e]
2[b,c]	**2g**	Ph	**3g**, (56)[e]
3[b]	**2g**	Ph	**3g**, (62)[e]
4	**2g**	Ph	**3g**, 74 (74)[e]
5	**2h**	4-MeC_6H_4	**3h**, 76
6	**2i**	4-(*t*-Bu)C_6H_4	**3i**, 84
7	**2j**	4-$MeOC_6H_4$	**3j**, 60
8	**2k**	4-ClC_6H_4	**3k**, 85
9	**2l**	4-$CF_3C_6H_4$	**3l**, 74
10	**2m**	2-naphthyl	**3m**, 82

[a] Reaction conditions: (1) **1a** (0.5 mmol), **2** (2 mmol), $[Cp^*RhCl_2]_2$ (0.01 mmol), $AgSbF_6$ (0.02 mmol), AgOAc (2 mmol), dioxane (3 mL) under N_2 at 120 °C for 8 h; (2) with the addition of MeI (3 mmol), K_2CO_3 (1.5 mmol), and DMF (3 mL) at rt for 3 h. [b] With $[Cp^*RhCl_2]_2$ (0.005 mmol). [c] With **2g** (1 mmol). [d] At 80 °C. [e] GC yield.

A series of 4- and/or 5-substituted thiophene-2-carboxylic acids **1b-f** also underwent C3-alkenylation upon treatment with **2a** (Table 3). It should be noted that each of the C–Br bond in **1d**-**f** was tolerated. The retained bromine atom, as well as a carboxyl function, are utilizable for further transformation (*vide infra*). In contrast, the ruthenium-catalyzed reaction of **1d** gave a mixture of **3p** and a debrominated product in a moderate yield. Similar debromination was also observed in the palladium-catalyzed alkenylation of 2-bromothiophene.[2a,9]

Table 3. Reaction of Thiophene-2-Carboxylic Acids 1 with Butyl Acrylate (2a)[a]



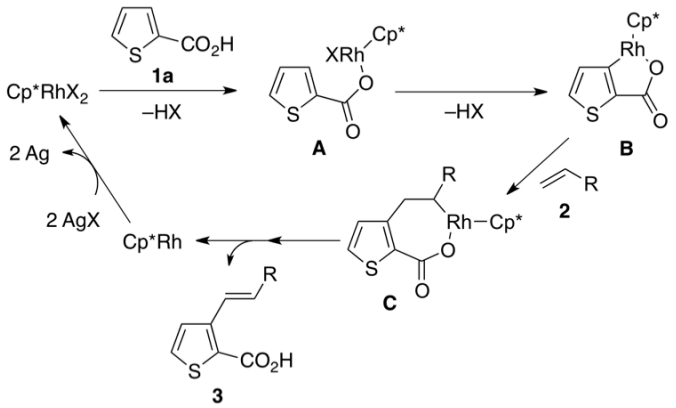
1 2a 3

entry	1	R^1	R^2	product, % yield
1	**1b**	Me	H	**3n**, 84
2	**1c**	Cl	H	**3o**, 80
3	**1d**	Br	H	**3p**, 91
4	**1e**	H	Br	**3q**, 93
5	**1f**	Br	Br	**3r**, 89

[a] Reaction conditions: (1) **1** (0.5 mmol), **2a** (1 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $AgSbF_6$ (0.02 mmol), AgOAc (1 mmol), dioxane (3 mL) under N_2 at 80 ºC for 8 h; (2) with the addition of MeI (3 mmol), K_2CO_3 (1.5 mmol), and DMF (3 mL) at rt for 3 h.

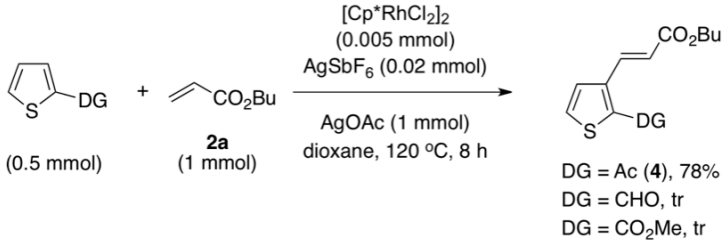
A possible mechanism for the C3-alkenylation of **1a** with **2** is illustrated in Scheme 2, in which neutral ligands are omitted. Coordination of the carboxyl oxygen of **1a** to a $Cp^*Rh(III)X_2$ species gives a rhodium(III) carboxylate **A**. Subsequent cyclorhodation to form a rhodacycle **B**, alkene insertion, and β-hydrogen elimination take place to produce the corresponding C3-alkenylated product. After liberation of **3**, the resulting Cp*Rh(I) species may be oxidized in the presence of AgOAc to regenerate $Cp^*Rh(III)X_2$. To conduct the reaction efficiently under relatively mild conditions, the addition of $AgSbF_6$ as a cocatalyst was essential. Therefore, a cationic rhodium species may be generated in situ and catalyze the reaction.

Scheme 2. Possible Mechanism for the Reaction of 1a with 2



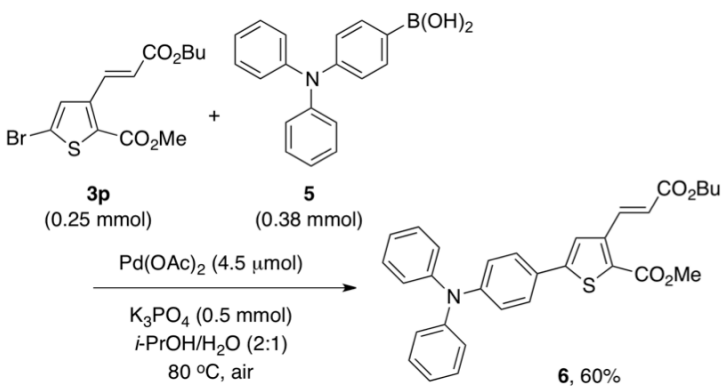
Under the conditions using $[Cp^*RhCl_2]_2/AgSbF_6$ and AgOAc as catalyst and oxidant, respectively, 2-acetylthiophene also underwent C3-alkenylation via acetyl-directed C–H bond cleavage[10] (Scheme 3). Thus, (*E*)-butyl 3-(2-acetylthiophene-3-yl)acrylate (**4**) was obtained in 78% yield. However, the corresponding aldehyde and ester were found to be inefficient substrates.

Scheme 3. Reaction of 2-Substituted Thiophenes with 2a

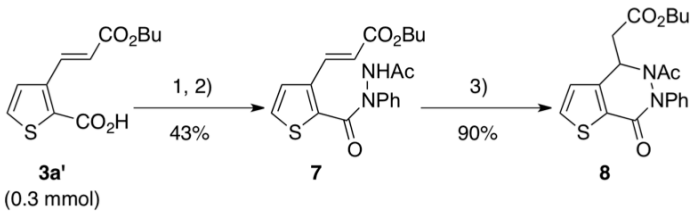


Further derivatization of C3-alkenylated thiophenes was then examined. Treatment of **3p** with boronic acid **5** under Suzuki-Miyaura coupling conditions[11] gave 3-alkenyl-5-arylthiophene-2-carboxylic acid derivative **6** (Scheme 4). This kind of push-pull molecule has attracted much attention due to their optical, electronic, and biological properties.[12] Meanwhile, a thienopyridazinone framework can be seen in a range of bioactive compounds.[13] The fused heterocyclic structure could be readily constructed in a few steps from (*E*)-3-(3-butoxy-3-oxoprop-1-en-1-yl)thiophene-2-carboxylic acid (**3a'**) (Scheme 5).[14]

Scheme 4. Transformation of C3-Alkenylated Thiophene 3p



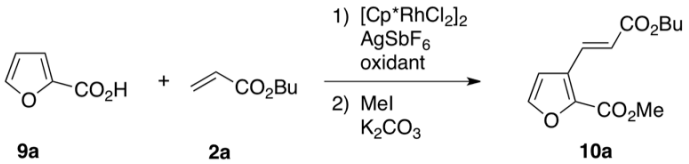
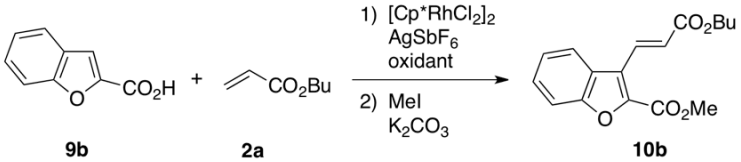
Scheme 5. Transformation of C3-Alkenylated Thiophene 3a'



1) $SOCl_2$ (0.5 mL), toluene (1.5 mL), rt, over night.
2) NHPhNHAc (1.2 equiv), pyridine (1.2 equiv), DCM, 0 ºC to rt, over night.
3) DBU (1.2 equiv), DMSO, rt, 2 h.

Besides thienyl substrates **1**, furan-2-carboxylic acid (**9a**) also underwent C3-alkenylation under standard conditions (entry 2 in Table 1) to afford the desired product **10a**, albeit with a low yield (entry 1 in Table 4). The use of Ag_2CO_3 (0.5 mmol) in place of AgOAc slightly improved the yield of **10a** (entry 2). Among solvents examined (entries 3-7), diglyme was found to be the solvent of choice (entry 3). At 120 ºC in diglyme, the yield of **10a** was enhanced up to 78% (entry 8). Under similar conditions, benzofuran-2-carboxylic acid (**9b**) also reacted with **2a** smoothly to give the C3-alkenylated product **10b** in 83% yield (entry 10).

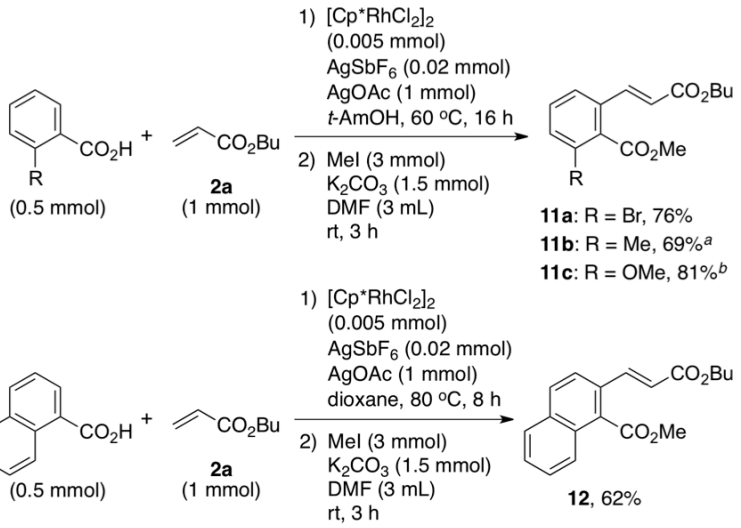
Table 4. Reaction of Furan- and Benzofuran-2-Carboxylic Acids 9 with Butyl Acrylate (2a)[a]

entry	oxidant (mmol)	solvent	temp	product, % yield[b]
				
	9a + **2a**	1) $[Cp^*RhCl_2]_2$, $AgSbF_6$, oxidant; 2) MeI, K_2CO_3		**10a**
1	AgOAc (1)	dioxane	80	(28)
2	Ag_2CO_3 (0.5)	dioxane	80	(36)
3	Ag_2CO_3 (0.5)	diglyme	80	(45)
4	Ag_2CO_3 (0.5)	CPME	80	(0)
5	Ag_2CO_3 (0.5)	THF	80	(8)
6	Ag_2CO_3 (0.5)	*t*-AmOH	80	(28)
7	Ag_2CO_3 (0.5)	DMF	80	(40)
8	Ag_2CO_3 (0.5)	diglyme	120	63 (78)
				
	9b + **2a**	1) $[Cp^*RhCl_2]_2$, $AgSbF_6$, oxidant; 2) MeI, K_2CO_3		**10b**
9	AgOAc (1)	dioxane	80	(26)
10	Ag_2CO_3 (0.5)	diglyme	120	78 (83)

[a] Reaction conditions: (1) **9** (0.5 mmol), **2** (1 mmol), $[Cp^*RhCl_2]_2$ (0.005 mmol), $AgSbF_6$ (0.02 mmol) under N_2 for 8 h; (2) with the addition of MeI (3 mmol), K_2CO_3 (1.5 mmol), and DMF (3 mL) at rt for 3 h. [b] The value in parentheses indicates GC yield.

We next applied the present Rh/Ag catalyst system to the alkenylation of benzoic acids. Under somewhat modified conditions in *t*-AmOH at 60 ºC, *ortho*-alkenylated product **11a** was obtained in 76% yield from 2-bromobenzoic acid, unaccompanied by debromination nor nucleophilic cyclization (Scheme 6). It should be noted that nucleophilically cyclized products were formed under previously reported conditions at an elevated temperature.[15] 2-Methyl- and 2-methoxybenzoic acids also underwent *ortho*-alkenylation under appropriate conditions to afford **11b** and **11c**, respectively. The alkenylation of 1-naphthoic acid took place selectively at the 2-position to give **12** in 62% yield.

Scheme 6. Reaction of *ortho*-Substituted Benzoic Acids and 1-Naphthoic Acids with 2a



[a] In dioxane. [b] At 80 °C for 8 h.

Conclusions

We have demonstrated that the C3-alkenylation of thiophene- and furan-2-carboxylic acids as well as 2-acetylthiophene with acrylates and styrenes can be performed efficiently in the presence of a rhodium/silver catalyst system and a silver salt oxidant. Several 2-substituted benzoic acids and 1-naphthoic acid also undergo regioselective alkenylation. A bromine substituent and a carboxyl directing-group in substrates are retainable during the reaction. These functions can be utilized for further transformation.

Experimental Section

General. H and ^{13}C NMR spectra were recorded at 400 and 100 MHz for $CDCl_3$ solutions. HRMS data were obtained by EI using a double focusing mass spectrometer, unless noted. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m). GC-MS analysis was carried out using a CBP-1 capillary column (i. d. 0.25 mm x 25 m). The structures of all products listed below were unambiguously determined by ^{1}H and ^{13}C NMR with the aid of NOE, COSY, HMQC, and HMBC experiments.

All starting materials and reagents were commercially available.

General Procedure for the Reaction of Thiophene-2-Carboxylic Acids with Alkenes. To a 20 mL two-necked flask with a reflux condenser, a balloon, and a rubber cup were added thiophene-2-carboxylic acid **1** (0.5 mmol), alkene **2** (1 mmol), [(Cp*$RhCl_2$)$_2$] (0.005 mmol, 3 mg), $AgSbF_6$ (0.02 mmol, 6.8 mg), AgOAc (1 mmol, 167 mg), 1-methylnaphthalene (ca. 50 mg) as internal standard, and dioxane (3 mL). Then, the resulting mixture was stirred under nitrogen at 80 ºC for 8 h. After cooling, iodomethane (3 mmol, 423 mg), K_2CO_3 (1.5 mmol, 207 mg), and DMF (3 mL) were added and the resulting mixture was stirred under air at room temperature for 3 h. GC and GC-MS analyses of the mixtures confirmed formation of **3**. Then, the reaction mixture was extracted with ethyl acetate (100 mL). The organic layer was washed by water (100 mL, three times), and dried over Na_2SO_4. After evaporation of the solvent under vacuum, product **3** was isolated by column chromatography on silica gel using hexane-ethyl acetate (10:1, v/v) as eluant.

Procedure for the Reaction of 3p with 5. To a 20 mL two-necked flask with a reflux condenser, a balloon, and a rubber cup were added **3p** (0.25 mmol, 87 mg), **5** (0.38 mmol, 109 mg), $Pd(OAc)_2$ (4.5 μmol, 1.0 mg), K_3PO_4 (0.5 mmol, 106 mg), 1-methylnaphthalne (ca. 50 mg) as internal standard, and *i*-PrOH/H_2O (1.35 mL/0.65 mL). The resulting mixture was stirred under air at 80 ºC for 6 h (Scheme 4). After cooling, the reaction mixture was extracted with ethyl acetate (100 mL). The organic layer was washed by water (100 mL, three times), and dried over Na_2SO_4. After evaporation of the solvent under vacuum, product **6** (76 mg, 60%) was isolated by column chromatography on silica gel using hexane-ethyl acetate (10:1, v/v) as eluant and preparative GPC using chloroform as eluant.

Procedure for Preparation of 7. To a 20 mL two-necked flask were added **3a'** (0.3 mmol, 77 mg), $SOCl_2$ (0.5 mL), and toluene (1.5 mL). Then, the resulting mixture was stirred at room temperature over night. After azeotropic distillation under vaccum with toluene, NHPhNHAc (0.36 mmol, 54 mg), pyridine (0.72 mmol, 57 mg), and dry DCM (3 mL) were added at 0 ºC and the resulting mixture was stirred at room temperature over night. The reaction mixture was washed with water (20 mL) and extracted with ethyl acetate (20 mL, three times). The organic layer was dried over Na_2SO_4/Al_2O_3. After

evaporation of the solvent under vacuum, product **7** (51 mg, 43%) was isolated by column chromatography on silica gel using hexane-ethyl acetate (1:2, v/v) as eluant.

Procedure for Preparation of 8. To a 20 mL two-necked flask were added **7** (0.06 mmol, 23 mg), DBU (0.072 mmol, 11 mg), and DMSO (0.5 mL). Then, the resulting mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with water (3 mL) and ethyl acetate (5 mL). The aqueous layer was extracted with ethyl acetate (5 mL, three times). The combined organic layer was washed with brine (10 mL) and then dried over Na_2SO_4. After evaporation of the solvent under vacuum, product **8** (21 mg, 90%) was isolated by column chromatography on silica gel using hexane-ethyl acetate (2:1, v/v) as eluant.

(*E*)-Methyl 3-(3-Butoxy-3-oxoprop-1-en-1-yl)thiophene-2-carboxylate (3a):[9] oil, 113 mg (84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.40-1.49 (m, 2H), 1.66-1.74 (m, 2H), 3.92 (s, 3H), 4.22 (t, J = 6.6 Hz, 2H), 6.38 (d, J = 16.5 Hz, 1H), 7.36 (d, J = 5.0 Hz, 1H), 7.48 (d, J = 5.0 Hz, 1H), 8.51 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 30.6, 52.2, 64.5, 122.0, 126.6, 130.8, 131.1, 136.4, 141.7, 162.2, 166.7; HRMS *m/z* Calcd for $C_{13}H_{16}O_4S$ (M^+) 268.0769, found 268.0771.

(*E*)-Methyl 3-(3-Ethoxy-3-oxoprop-1-en-1-yl)thiophene-2-carboxylate (3b):[9] mp 65-67 °C (colorless microcrystals), 104 mg (87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.1 Hz, 3H), 3.92 (s, 3H), 4.28 (q, J = 7.2 Hz, 2H), 6.38 (d, J = 16.0 Hz, 1H), 7.35 (d, J = 5.5 Hz, 1H), 7.47 (d, J = 5.5 Hz, 1H), 8.51 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 52.3, 60.6, 122.1, 126.6, 130.8, 131.1, 136.4, 141.8, 162.2, 166.6; HRMS *m/z* Calcd for $C_{11}H_{12}O_4S$ (M^+) 240.0456, found 240.0455.

(*E*)-Methyl 3-[3-(Cyclohexyloxy)-3-oxoprop-1-en-1-yl]thiophene-2-carboxylate (3c):[9] mp 75-76 °C (colorless microcrystals), 116 mg (79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25-1.56 (m, 6H), 1.76-1.83 (m, 2H), 1.90-1.94 (m, 2H), 3.92 (s, 3H), 4.90 (m, 1H), 6.37 (d, J = 16.0 Hz, 1H), 7.35 (d, J = 5.5 Hz, 1H), 7.47 (d, J = 5.5 Hz, 1H), 8.50 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 25.4, 31.6,

52.2, 72.8, 122.7, 126.6, 130.7, 131.0, 136.2, 141.8, 162.2, 166.1; HRMS *m/z* Calcd for $C_{15}H_{18}O_4S$ (M^+) 294.0926, found 294.0927.

(*E*)-Methyl 3-(3-Isobutoxy-3-oxoprop-1-en-1-yl)thiophene-2-carboxylate (3d):[9] oil, 108 mg (81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, J = 6.9 Hz, 6H), 1.98-2.08 (m, 1H), 3.92 (s, 3H), 4.01 (d, J = 6.9 Hz, 2H), 6.39 (d, J = 16.5 Hz, 1H), 7.36 (d, J = 5.5 Hz, 1H), 7.48 (d, J = 6.0 Hz, 1H), 8.52 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 27.8, 52.3, 70.7, 122.0, 126.6, 130.8, 131.2, 136.4, 141.7, 162.2, 166.7; HRMS *m/z* Calcd for $C_{13}H_{16}O_4S$ (M^+) 268.0769, found 268.0772.

(*E*)-Methyl 3-[3-(*tert*-Butoxy)-3-oxoprop-1-en-1-yl]thiophene-2-carboxylate (3e):[9] oil, 102 mg (76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 3.91 (s, 3H), 6.31 (d, J = 16.0 Hz, 1H), 7.34 (d, J = 5.5 Hz, 1H), 7.46 (d, J = 5.0 Hz, 1H), 8.41 (d, J = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 52.3, 80.7, 124.0, 126.7, 130.7, 130.9, 135.6, 142.0, 162.3, 166.0; HRMS *m/z* Calcd for $C_{13}H_{16}O_4S$ (M^+) 268.0769, found 268.0767.

(*E*)-Methyl 3-(2-Cyanovinyl)thiophene-2-carboxylate (3f):[9] mp 125-126 °C (colorless microcrystals), 68 mg (71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 5.86 (d, J = 16.9 Hz, 1H), 7.31 (d, J = 5.0 Hz, 1H), 7.51 (d, J = 5.5 Hz, 1H), 8.34 (d, J = 17.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5, 99.7, 117.8, 125.5, 131.3, 131.5, 140.4, 142.6, 161.9; HRMS *m/z* Calcd for $C_9H_7NO_2S$ (M^+) 193.0197, found 193.0198.

(*E*)-Methyl 3-styrylthiophene-2-carboxylate (3g):[16] mp 83-84 °C (colorless microcrystals), 90.4 mg (74%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.12 (d, J = 16.5 Hz, 1H), 7.26-7.30 (m, 1H), 7.35-7.38 (m, 2H), 7.44-7.47 (m, 2H), 7.56-7.58 (m, 2H), 8.14 (d, J = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 121.9, 126.1, 126.3, 126.9, 128.2, 128.7, 130.5, 132.9, 136.9, 145.6,163.0; HRMS *m/z* Calcd for $C_{14}H_{12}O_2S$ (M^+) 244.0558, found 244.0559.

(*E*)-Methyl 3-(4-Methylstyryl)thiophene-2-carboxylate (3h): mp 116-117 °C (colorless microcrystals), 98 mg (76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.90 (s, 3H), 7.09 (d, J = 16.5 Hz, 1H), 7.17 (d, J = 8.2 Hz, 2H), 7.42-7.47 (m, 4H), 8.09 (d, J = 16.5 Hz, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 21.3, 51.9, 121.0, 125.9, 126.0, 126.9, 129.4, 130.4, 132.9, 134.2, 138.3, 145.9, 163.1; HRMS *m/z* Calcd for $C_{15}H_{14}O_2S$ (M^+) 258.0715, found 258.0715.

(*E*)-Methyl 3-[4-(*tert*-Butyl)styryl]thiophene-2-carboxylate (3i): oil, 122 mg (84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 9H), 3.90 (s, 3H), 7.10 (d, *J* = 16.5 Hz, 1H), 7.37-7.44 (m, 4H), 7.50 (d, *J* = 8.2 Hz, 2H), 8.09 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.2, 34.7, 51.9, 121.2, 125.6, 125.9, 126.0, 126.7, 130.4, 132.8, 134.2, 145.8, 151.5, 163.0; HRMS *m/z* Calcd for $C_{18}H_{20}O_2S$ (M^+) 300.1184, found 300.1181.

(*E*)-Methyl 3-(4-Methoxystyryl)thiophene-2-carboxylate (3j): mp 126-127 ºC (colorless needle crystals), 83 mg (60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.89 (s, 3H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 16.5 Hz, 1H), 7.40-7.43 (m, 2H), 7.48-7.52 (m, 2H), 8.01 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 55.3, 114.1, 119.9, 125.4, 125.9, 128.2, 129.7, 130.4, 132.5, 146.0, 159.8, 163.1; HRMS *m/z* Calcd for $C_{15}H_{14}O_3S$ (M^+) 274.0664, found 274.0665.

(*E*)-Methyl 3-(4-Chlorostyryl)thiophene-2-carboxylate (3k): m.p. 117-118 ºC (pale yellow microcrystals), 118 mg (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 3H), 7.04 (d, *J* = 16.5 Hz, 1H), 7.30-7.34 (m, 2H), 7.42-7.50 (m, 4H), 8.11 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.0, 122.5, 125.9, 126.5, 128.1, 128.9, 130.6, 131.5, 133.8, 135.5, 145.2, 163.0; HRMS *m/z* Calcd for $C_{14}H_{11}ClO_2S$ (M^+) 278.0168, found 278.0165.

(*E*)-Methyl 3-[4-(Trifluoromethyl)styryl]thiophene-2-carboxylate (3l): mp 88-90 ºC (pale yellow microcrystals), 112 mg (74%); ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.09 (d, *J* = 16.4 Hz, 1H), 7.44-7.46 (m, 2H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.63 (d, *J* = 8.5 Hz, 2H), 8.20 (d, *J* = 16.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 52.0, 124.13 (q, *J* = 271.7 Hz), 124.2, 125.6 (q, *J* = 3.8 Hz), 125.9, 126.9, 127.2, 129.7 (q, *J* = 32.2 Hz), 130.6, 131.1, 140.4, 144.8, 162.8; HRMS *m/z* Calcd for $C_{15}H_{11}F_3O_2S$ (M^+) 312.0432, found 312.0428.

(*E*)-Methyl 3-[2-(Naphthalen-2-yl)vinyl]thiophene-2-carboxylate (3m): mp 131-132 ºC (pale yellow needle crystal), 119 mg (82%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.91 (s, 3H), 7.26 (d, *J* = 16.5 Hz,

1H), 7.43-7.49 (m, 4H), 7.78-7.83 (m, 4H), 7.87 (s, 1H), 8.26 (d, J = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.0, 122.2, 123.7, 126.0, 126.18, 126,22, 126.4, 127.4, 127.7, 128.1, 128.4, 130.5, 133.1, 133.4, 133.6, 134.5, 145.7, 163.1; HRMS m/z Calcd for $C_{18}H_{14}O_2S$ (M^+) 294.0715, found 294.0716.

(*E*)-Methyl 3-(3-Butoxy-3-oxoprop-1-en-1-yl)-5-methylthiophene-2-carboxylate (3n): oil, 118 mg (84%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.6 Hz, 3H), 1.39-1.48 (m, 2H), 1.66-1.73 (m, 2H), 2.49 (s, 3H), 3.88 (s, 3H), 4.21 (t, J = 6.9 Hz, 2H), 6.31 (d, J = 16.5 Hz, 1H), 7.03 (s, 1H), 8.45 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 15.6, 19.1, 30.7, 52.1, 64.5, 121.8, 125.0, 129.0, 136.6, 142.0, 145.8, 162.2, 166.8; HRMS m/z Calcd for $C_{14}H_{18}O_4S$ (M^+) 282.0926, found 282.0924.

***(E)*-Methyl 3-(3-Butoxy-3-oxoprop-1-en-1-yl)-5-chlorothiophene-2-carboxylate (3o)**: mp 45-46 °C (pale yellow microcrystals), 120 mg (80%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.39-1.48 (m, 2H), 1.66-1.73 (m, 2H), 3.90 (s, 3H), 4.21 (t, J = 6.6 Hz, 2H), 6.30 (d, J = 16.0 Hz, 1H), 7.18 (s, 1H), 8.40 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 30.6, 52.4, 64.6, 123.0, 125.7, 129.3, 135.4, 136.4, 141.5, 161.2, 166.4; HRMS m/z Calcd for $C_{13}H_{15}ClO_4S$ (M^+) 302.0380, found 302.0383.

(*E*)-Methyl 5-Bromo-3-(3-butoxy-3-oxoprop-1-en-1-yl)thiophene-2-carboxylate (3p):[9] mp 34-36 °C (colorless microcrystals), 158 mg (91%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.39-1.48 (m, 2H), 1.66-1.73 (m, 2H), 3.90 (s, 3H), 4.21 (t, J = 6.9 Hz, 2H), 6.31 (d, J = 16.5 Hz, 1H), 7.32 (s, 1H), 8.40 (d, J = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.1, 30.6, 52.4, 64.6, 119.5, 122.9, 129.4, 132.0, 135.1, 142.2, 161.0, 166.3; HRMS m/z Calcd for $C_{13}H_{15}BrO_4S$ (M^+) 345.9874, found 345.9873.

(*E*)-Methyl 4-Bromo-3-(3-butoxy-3-oxoprop-1-en-1-yl)thiophene-2-carboxylate (3q): mp 43-45 °C (colorless microcrystals), 162 mg (93%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.40-1.49 (m, 2H), 1.67-1.74 (m, 2H), 3.91 (s, 3H), 4.23 (t, J = 6.6 Hz, 2H), 6.80 (d, J = 16.5 Hz, 1H), 7.52 (s, 1H), 8.18 (d, J = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 30.6, 52.6, 64.6, 112.3, 124.9,

129.4, 131.2, 135.2, 139.4, 161.2, 166.5; HRMS *m/z* Calcd for $C_{13}H_{15}BrO_4S$ (M^+) 345.9874, found 345.9872.

(*E*)-Methyl 4,5-Dibromo-3-(3-butoxy-3-oxoprop-1-en-1-yl)thiophene-2-carboxylate (3r): mp 76-78 °C (colorless needle crystals), 190 mg (89%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.42-1.49 (m, 2H), 1.67-1.74 (m, 2H), 3.90 (s, 3H), 4.23 (t, J = 6.9 Hz, 2H), 6.76 (d, J = 16.5 Hz, 1H), 8.13 (d, J = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.2, 30.7, 52.8, 64.8, 116.6, 119.6, 125.6, 131.2, 135.2, 140.1, 160.6, 166.3; HRMS *m/z* Calcd for $C_{13}H_{14}Br_2O_4S$ (M^+) 423.8980, found 423.8980.

(*E*)-Butyl 3-(2-Acetylthiophen-3-yl)acrylate (4): mp 50-51 °C (colorless needle crystals), 98 mg (78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.40-1.50 (m, 2H), 1.66-1.73 (m, 2H), 2.59 (s, 3H), 4.22 (t, J = 6.6 Hz, 2H), 6.38 (d, J = 16.5 Hz, 1H), 7.38 (d, J = 5.0 Hz, 1H), 7.48 (d, J = 5.0 Hz, 1H), 8.46 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 30.0, 30.6, 64.6, 122.7, 127.6, 130.1, 137.2, 139.1, 140.8, 166.7, 190.8; HRMS *m/z* Calcd for $C_{13}H_{16}O_3S$ (M^+) 252.0820, found 252.0821.

(*E*)-Methyl 3-(3-Butoxy-3-oxoprop-1-en-1yl)-5-(4-(diphenylamino)phenyl)thiophene-2-carboxylate (6): oil, 76 mg (60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.6Hz, 3H), 1.40-1.49 (m, 2H), 1.67-1.74 (m, 2H), 3.91 (s, 3H), 4.22 (t, J = 6.6 Hz, 2H), 6.41 (d, J = 16.5 Hz, 1H), 7.04-7.14 (m, 8H), 7.25-7.31 (m, 4H), 7.41 (s, 1H), 7.44-7.48 (m, 2H), 8.49 (d, J = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.2, 30.7, 52.2, 64.5, 120.9, 122.1, 122.6, 123.7, 125.0, 125.9, 126.9, 128.6, 129.4, 136.7, 142.6, 147.0, 148.9, 149.1, 162.3, 166.8; HRMS *m/z* Calcd for $C_{31}H_{29}NO_4S$ (M^+) 511.1817, found 511.1814.

(*E*)-Butyl 3-(2-(2-Acetyl-1-phenylhydrazinecarbonyl)thiophen-3-yl)acrylate (7): mp 113-115 °C (colorless microcrystals), 51 mg (43%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4Hz, 3H), 1.38-1.45 (m, 2H), 1.62-1.69 (m, 2H), 2.02 (s, 3H), 4.16 (t, J = 6.7 Hz, 2H), 6.17 (d, J = 15.2 Hz, 1H), 7.12 (d, J = 5.2 Hz, 1H), 7.16-7.29 (m, 6H), 8.06 (d, J = 16.0 Hz, 1H), 8.97 (s, 1H); ^{13}C NMR (100 MHz,

$CDCl_3$) δ 13.7, 19.1, 20.7, 30.6, 64.5, 120.4, 125.2, 126.2, 127.6, 128.8, 129.0, 134.3, 136.7, 139.5, 141.7, 163.2, 166.9, 169.6; HRMS *m/z* Calcd for $C_{20}H_{22}N_2O_4S$ (M^+) 386.1300, found 386.1301.

Butyl 2-(5-Acetyl-7-oxo-6-phenyl-4,5,6,7-tetrahydrothieno[2,3-d]pyridazin-4-yl)acetate (8): mp 102-103 ºC (colorless microcrystals), 21 mg (90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 7.3Hz, 3H), 1.28-1.37 (m, 2H), 1.54-1.61 (m, 2H), 1.98 (s, 3H), 2.69 (dd, *J* = 7.1 Hz, 16.0 Hz, 1H), 2.90 (dd, *J* = 7.5 Hz, 16.5 Hz, 1H), 4.11 (t, *J* = 6.6 Hz, 2H), 6.55 (t, *J* = 7.1 Hz, 1H), 7.07 (d, *J* = 5.0 Hz, 1H), 7.20 (t, *J* = 7.34 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 5.0 Hz, 1H), 7.83 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 19.0, 21.9, 30.5, 37.5, 49.5, 65.1, 118.9, 125.2, 125.4, 129.3, 130.6, 134.1, 141.3, 149.4, 158.9, 169.5, 175.3; HRMS *m/z* Calcd for $C_{20}H_{22}N_2O_4S$ (M^+) 386.1300, found 386.1298.

(*E*)-Methyl 3-(3-Butoxy-3-oxoprop-1-en-1-yl)furan-2-carboxylate (10a): mp 32-33 ºC (pale yellow microcrystals), 77 mg (63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.39-1.49 (m, 2H), 1.66-1.73 (m, 2H), 3.97 (s, 3H), 4.22 (t, *J* = 6.6 Hz, 2H), 6.34 (d, *J* = 16.0 Hz, 1H), 6.73 (d, *J* = 1.38 Hz, 1H), 7.53 (d, *J* = 1.83 Hz, 1H), 8.19 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.2, 30.7, 52.2, 64.6, 109.7, 122.8, 128.6, 133.8, 142.0, 145.8, 159.1, 166.4; HRMS *m/z* Calcd for $C_{13}H_{16}O_5$ (M^+) 252.0998, found 252.0999.

(*E*)-Methyl 3-(3-Butoxy-3-oxoprop-1-en-1-yl)benzofuran-2-carboxylate (10b):[9] mp 63-65 ºC (pale yellow microcrystals), 118 mg (78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, *J* = 7.3 Hz, 3H), 1.43-1.52 (m, 2H), 1.70-1.77 (m, 2H), 4.04 (s, 3H), 4.26 (t, *J* = 6.6 Hz, 2H), 6.77 (d, *J* = 16.5 Hz, 1H), 7.40 (m, 1H), 7.52 (m, 1H), 7.62 (d, *J* = 8.3 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 8.46 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.2, 30.7, 52.7, 64.7, 112.7, 122.4, 123.0, 123.5, 124.6, 125.1, 128.3, 134.2, 143.3, 154.8, 159.9, 166.5; HRMS *m/z* Calcd for $C_{17}H_{18}O_5$ (M^+) 302.1154, found 302.1151.

(*E*)-Methyl 2-Bromo-6-(3-butoxy-3-oxoprop-1-en-1-yl)benzoate (11a): oil, 131 mg (76%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.38-1.47 (m, 2H), 1.64-1.72 (m, 2H), 3.99 (s, 3H), 4.20 (t, *J* = 6.9 Hz, 2H), 6.40 (d, *J* = 15.6 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.56-7.60 (m, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 13.7, 19.1, 30.6, 52.9, 64.7, 120.0, 122.3, 125.2, 130.8, 133.7, 133.9, 136.0, 139.9, 166.0, 167.3; HRMS *m/z* Calcd for $C_{15}H_{17}BrO_4$ (M^+) 340.0310, found 340.0310.

(*E*)-Methyl 2-(3-Butoxy-3-oxoprop-1-en-1-yl)-6-methylbenzoate (11b): oil, 95 mg (69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.38-1.48 (m, 2H), 1.64-1.71 (m, 2H), 2.35 (s, 3H), 3.95 (s, 3H), 4.20 (t, *J* = 6.6 Hz, 2H), 6.37 (d, *J* = 15.6 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 7.70 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.2, 19.7, 30.7, 52.3, 64.5, 120.8, 124.0, 129.7, 131.7, 132.3, 134.1, 135.9, 141.6, 166.6, 169.3; HRMS *m/z* Calcd for $C_{16}H_{20}O_4$ (M^+) 276.1362, found 276.1363.

(*E*)-Methyl 2-(3-Butoxy-3-oxoprop-1-en-1-yl)-6-methoxybenzoate (11c): oil, 118 mg (81%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.3 Hz, 3H), 1.38-1.47 (m, 2H), 1.64-1.71 (m, 2H), 3.85 (s, 3H), 3.95 (s, 3H), 4.19 (t, *J* = 6.6 Hz, 2H), 6.40 (d, *J* = 15.6 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.1, 30.7, 52.6, 56.1, 64.5, 112.2, 118.5, 121.4, 124.0, 130.8, 133.3, 140.8, 156.6, 166.4, 167.6; HRMS *m/z* Calcd for $C_{16}H_{20}O_5$ (M^+) 292.1311, found 292.1313.

(*E*)-Methyl 2-(3-Butoxy-3-oxoprop-1-en-1-yl)-1-naphthoate (12): oil, 97 mg (62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.41-1.50 (m, 2H), 1.65-1.74 (m, 2H), 4.09 (s, 3H), 4.23 (t, *J* = 6.6 Hz, 2H), 6.54 (d, *J* = 15.5 Hz, 1H), 7.52-7.58 (m, 2H), 7.70 (d, *J* = 9.2 Hz, 1H), 7.83-7.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 19.2, 30.7, 52.7, 64.6, 121.3, 122.5, 125.6, 127.5, 127.7, 128.2, 129.7, 129.8, 130.3, 132.5, 133.7, 141.2, 166.5, 169.0; HRMS *m/z* Calcd for $C_{19}H_{20}O_4$ (M^+) 312.1362, found 312.1363.

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Supporting Information Available: Copies of ^{1}H- and ^{13}C-NMR spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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