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DIRECT β-ALKENYLATION OF THIOPHENES WITH ALKENYL HALIDES CATALYZED BY A DINUCLEAR PALLADIUM COMPLEX

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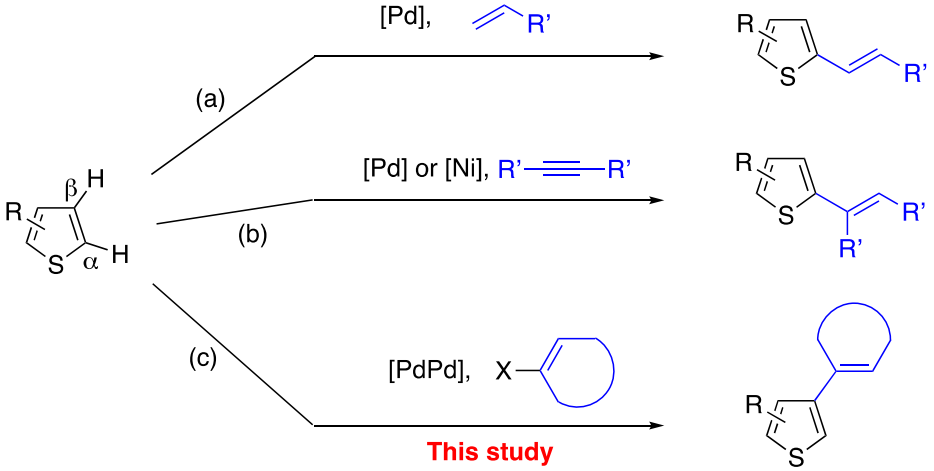
Abstract – Direct alkenylation of thiophenes with iodoalkenes proceeded in the presence of a dinuclear palladium complex formed by a chelate-bridging ligand. In most reactions, β-alkenylthiophenes were obtained with good to high regioselectivity.

Substituted thiophene derivatives are a common motif in natural products,[1] pharmaceuticals,[2] and organic materials.[3] Therefore, efficient ways to introduce substituents into thiophenes have been required. Transition metal-catalyzed reaction is useful for introducing π-extended substituents such as aryl, alkenyl and alkynyl groups. In particular, direct functionalization of C-H bonds of a thiophene ring is valuable because it does not need prehalogenation or premetallation and can minimizing side products in these steps. Along direct arylation[4-6] and alkynylation,[7] several direct alkenylation reactions have been reported.[8,9] Fujiwara-Moritani reaction with terminal alkenes affords alkenylated thiophenes (Scheme 1a).[8] Addition of C-H bonds of thiophene to alkynes is also catalyzed by several transition metals (Scheme 1b).[9] In all of these reactions, α-alkenylated thiophenes are obtained in high regioselectivity. There has been no report for β selective alkenylation of thiophenes.



Scheme 1. Transition metal-catalyzed direct alkenylation of thiophenes

Herein we report a palladium-catalyzed alkenylation of thiophenes with alkenyl halides, giving *β*-alkenylthiophenes as major products (Scheme 1c).

We previously reported that the reaction of thiophenes with iodoarenes in the presence of dinuclear palladium catalysts **1** gave *β*-arylthiophenes with high site-selectivity (Figure 1).[6d] Thus, the application of the complex **1** to the reaction of thiophenes with alkenyl halides was investigated. The reaction of 2-ethylthiophene with iodophenylcyclohexene **3a** in the presence of **1**, Ag_2CO_3 and DMSO gave alkenylthiophenes **4a** and **4b** in 94% yield (Table 1, entry 1). The reaction showed high β selectivity, giving **4a** and **4b** in a ratio of 95:5. The reaction in the presence of palladium acetate and chelate-bridging ligand **2** also gave **4a** selectively although the yield was lower (entry 2). The reaction did not proceed without **1** or **2** (entries **3** and **4**). Although addition of DMSO is not essential for the β selectivity, the yield and selectivity for **4a** became lower without DMSO (entry 5). The use of DMSO as solvent was not effective for both of the yield and selectivity (entry 6). The reaction proceeded at lower temperature with better β selectivity (entry 7).

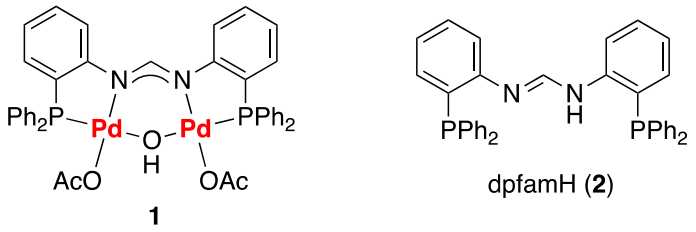
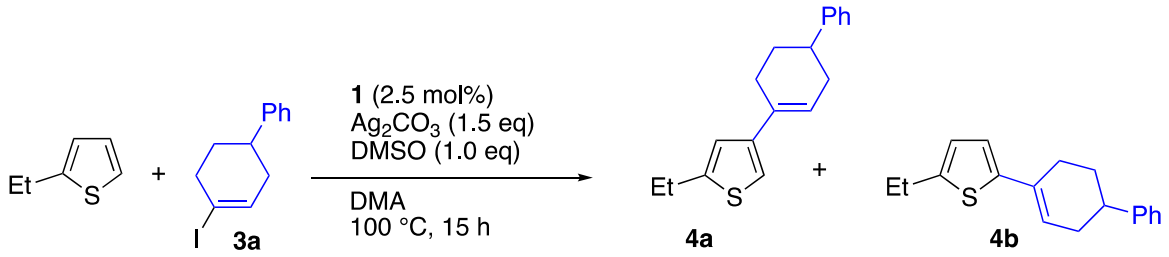


Figure 1. Dinuclear palladium complex **1** and chelate-bridging ligand dpfamH (**2**)

Table 1. Palladium-catalyzed alkenylation of 2-ethylthiophene with iodoalkene **3a**[a]

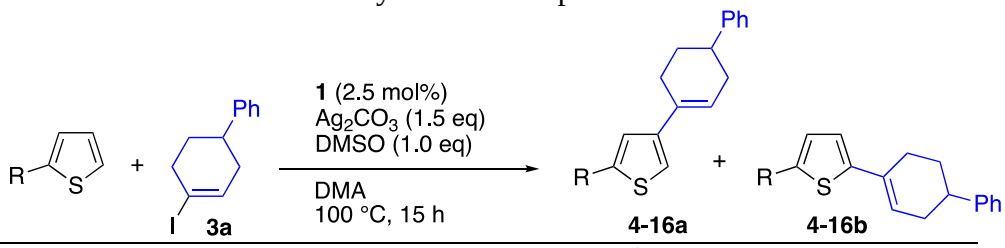


Entry	Changes from "standard conditions"	Yield[b] (%)	**4a**:**4b**[b]
1	—	94	95:5
2	$Pd(OAc)_2$ (5 mol%) and **2** (2.5 mol%) instead of **1**	25	93:7
3	$Pd(OAc)_2$ (5 mol%) and dppe (5 mol%) instead of **1**	3	-
4	$Pd(OAc)_2$ (5 mol%) instead of **1**	3	-
5	without DMSO	73	91:9
6	DMSO instead of DMA	39	78:22
7	80 °C	85	97:3

[a] A mixture of 2-ethylthiophene (0.30 mmol), **3a** (0.30 mmol), Ag_2CO_3 (0.45 mmol), and dimethyl sulfoxide (DMSO, 0.30 mmol) in *N*,*N*-dimethylacetamide (DMA, 1.0 mL) was stirred at 100 °C for 15 h in the presence of **1** (7.5 μmol). [b] Determined by NMR using *p*-xylene as an internal standard.

Table 2 summarizes the results of the reaction of various thiophenes with iodoalkene **3a** in the presence of **1**.[10,11] The reaction of 2-methylthiophene afforded 2-methyl-4-alkenylthiophene **5a** selectively as well as the reaction of 2-ethylthiophene (entries 1 and 2). The reaction tolerates silyl ether, giving *β*-alkenylthiophenes **6a** and **7a** from thiophenes having siloxy substituents with high β selectivity (entries 3 and 4). The reaction also tolerates hydroxy group, giving **8a** and **9a** in similar yields with those of corresponding silyl ethers **6a** and **7a** (entries 5 and 6). Conjugating substituents affect the reaction. While the reaction of 2-phenylthiophene afforded β-alkenylthiophenes **10a** in 69% yield (entry 7), formyl and acetyl groups inhibited the alkenylation (entries 8 and 9). These groups may act as directing groups. Generation of stable metallacycles could stop the catalysis. Although a cyano group is tolerated, the reaction of 2-cyanothiophene afforded only *α*-alkenylthiophene **13b** with high site-selectivity (entry 10). Also in the arylation catalyzed by **1**,[6d,12] electron-withdrawing groups such as nitrile, formyl and acetyl increased α selectivity. One of the most plausible mechanism for the arylation and alkenylation is a Heck-type pathway.[6a] By conjugation with the electron-withdrawing groups, nucleophilic aryl or alkenyl ligands may react with α carbon of thiophene (δ carbon for EWG). The reaction of 2-halothiophenes did not afford any products (entries 12 and 13).

Table 2. Direct alkenylation of thiophenes with iodoalkene **3a**[a]



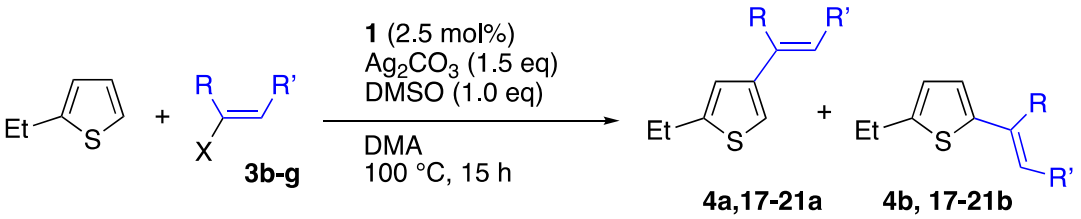
Entry	R	Product	Yield[b] (%)	**a**:**b**[c]
1	Et	**4**	87	95:5
2	Me	**5**	81	94:6
3	CH_2OTBS	**6**	72	92:8
4	CH_2(OTBS)Me	**7**	76	>98:2
5	CH_2OH	**8**	64	93:7
6	CH(OH)Me	**9**	90	>98:2
7	Ph	**10**	69	91:9
8	CHO	**11**	trace	–
9	COMe	**12**	trace	–
10	CN	**13**	55	2:>98
11	OMe	**14**	22	28:72
12	Cl	**15**	trace	–
13	Br	**16**	trace	–

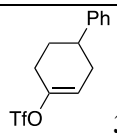
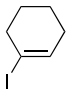
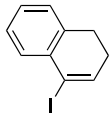
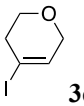
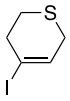
[a] A mixture of a thiophene (0.30 mmol), **3a** (0.30 mmol), DMSO (0.30 mmol), and Ag_2CO_3 (0.45 mmol) in DMA (1.0 mL) was stirred at 100 °C for 15 h in the presence of **1** (7.5 μmol). [b] Isolated yields. [c] Determined by NMR.

Table 3 summarizes the results of the reaction of 2-ethylthiophene with various haloalkenes in the presence of **1**.[13] The reaction of the corresponding triflate **3b** gave **4a** with high selectivity as well as the reaction of the iodide **3a**, although the yield of **4a** was lower (entry 1). Several cyclic alkenyl iodides can be also used for the alkenylation. The reaction 1-iodocyclohexene **3c** gave *β*-alkenylthiophene **17** with high selectivity in 80% yield (entry 2). The reaction of iododihydronaphthalene **3d** afforded *β*-alkenylthiophene **18** with good site-selectivity although the yield was moderate probably due to steric hinderance (entry 3). While *β*-alkenylthiophene **19** was obtained from O-including cyclic iodoalkene **3e**, the reaction of S-including cyclic alkene **3f** gave no product (entries 4 and 5). Acyclic haloalkene **3g** reacted with ethylthiophene, giving alkenylthiophene **21** (entry 6). However, the site-selectivity for **21** was lower than those in the reaction of cyclic haloalkenes.

Using DMSO as a solvent, the site-selectivity for **21** was inverted. The reaction of **3g** in DMSO afforded *α*-alkenylthiophene **21b** selectively.[14] Although several direct α alkenylation reactions of thiophene have already been reported,[8,9] **21b** cannot be synthesized by those reaction. For example, direct alkenylation with styrene affords 2-(*β*-styryl)thiophene **21c** selectively,[8d] not giving its regioisomer, 2-(*α*-styryl)thiophene **21b** (Scheme 2). These are complimentary synthesis methods for styrylthiophenes.

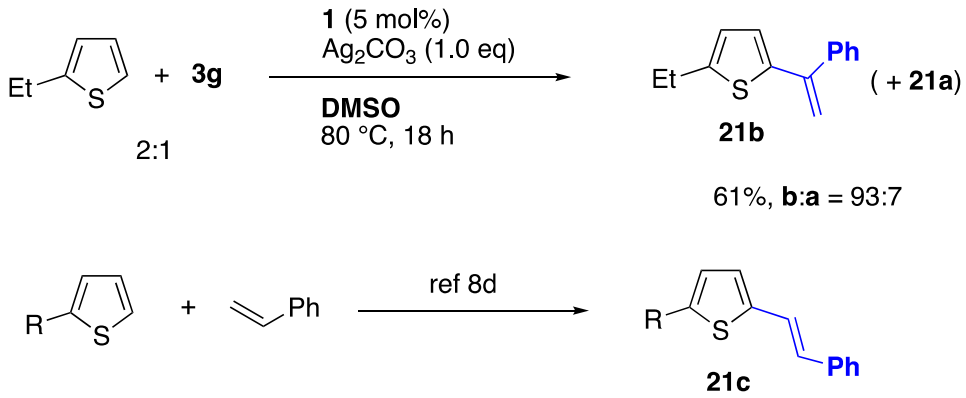
Table 3. Direct alkenylation of 2-ethylthiophene with haloalkenes[a]



Entry	**3**	Product	Yield[b] (%)	**a**:**b**[c]
1	 **3b**	**4**	30	96:4
2	 **3c**	**17**	80	94:6
3	 **3d**	**18**	33	87:13
4	 **3e**	**19**	24	93:7
5	 **3f**	**20**	0	

6	 **3g**	**21**	32	70:30

[a] A mixture of 2-ethylthiophene (0.30 mmol), a haloalkene (0.30 mmol), DMSO (0.30 mmol), and Ag_2CO_3 (0.45 mmol) in DMA (1.0 mL) was stirred at 100 °C for 15 h in the presence of **1** (7.5 μmol). [b] Isolated yields. [c] Determined by NMR.



Scheme 2. Complementary synthesis methods of styrylthiophenes

In summary, we found that the direct alkenylation of thiophenes with iodoalkenes proceeds with good *β*-selectivity by using the dinuclear palladium complex **1**, which formed by the chelate-bridging ligand **2**, as a catalyst. Scope of the alkenylation and applications of the catalytic system to other heteroarenes are in progress.

ACKNOWLEDGEMENTS

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10. General procedure for alkenylation of thiophenes with **3a**. To a mixture of **1** (6.9 mg, 2.5 mol%, 7.5 μmol), **3a** (85 mg, 0.30 mmol) and Ag_2CO_3 (124 mg, 0.45 mmol) were added DMA (1.0 mL), DMSO (21 μL, 0.30 mmol) and then a thiophene (0.30 mmol) in a pressure vial. After stirring at 100 °C for 15

h, the mixture was cooled and then filtered through a short plug of silica gel using EtOAc as an eluent. After evaporation of volatiles in the filtrate, the products were separated from the residue by silica gel column chromatography (*n*-hexane/EtOAc).

11. Spectral data for representative products. **4**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.31 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.97 (m, 1H), 6.89 (d, *J* = 1.4 Hz, 1H), 6.21 (m, 1H), 2.87-2.79 (m, 3H), 2.56-2.46 (m, 3H), 2.33 (m, 1H), 2.08 (m, 1H), 1.89 (m, 1H), 1.31 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 147.27, 146.82, 142.98, 132.06, 128.38, 126.87, 126.06, 122.83, 121.10, 115.84, 39.88, 33.76, 29.92, 27.58, 23.54, 15.87; HRMS (EI): calcd for $C_{18}H_{20}S^{+\bullet}$: 268.1280. Found; 268.1253. **5**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.32 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 6.93 (m, 1H), 6.86 (d, *J* = 1.4 Hz, 1H), 6.18 (m, 1H), 2.85 (m, 1H), 2.56-2.42 (m, 3H), 2.47 (s, 3H), 2.33 (m, 1H), 2.08 (m, 1H), 1.88 (m, 1H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 146.83, 143.23, 139.53, 132.01, 128.39, 126.88, 126.07, 123.04, 122.87, 116.19, 39.87, 33.76, 29.91, 27.57, 15.42; HRMS (EI): calcd for $C_{17}H_{18}S^{+\bullet}$: 254.1124. Found; 254.1084. **6**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.07 (m, 1H), 6.98 (d, *J* = 1.4 Hz, 1H), 6.18 (m, 1H), 4.83 (s, 2H), 2.83 (m, 1H), 2.57-2.43 (m, 3H), 2.31 (m, 1H), 2.07 (m, 1H), 1.87 (m, 1H), 0.93 (s, 9H), 0.11 (s, 6H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 146.80, 145.12, 142.84, 132.00, 128.41, 126.88, 126.09, 122.93, 121.44, 117.50, 60.92, 39.86, 33.76, 29.90, 27.64, 25.89, 18.38, -5.21; HRMS (ESI): calcd for $C_{23}H_{33}OSSi^{+}$ $[M+H]^{+}$: 385.2016. Found; 385.2035. **7**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.02 (m, 1H), 6.94 (d, *J* = 1.4 Hz, 1H), 6.19 (m, 1H), 5.07 (q, *J* = 6.2 Hz, 1H), 2.84 (m, 1H), 2.58-2.44 (m, 3H), 2.32 (m, 1H), 2.07 (m, 1H), 1.87 (m, 1H), 1.51 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 151.53, 146.78, 142.63, 132.05, 128.38, 126.86, 126.06, 122.72, 119.40, 116.59, 67.27, 39.87, 33.77, 29.89, 27.58, 26.95, 25.79, 18.20, -4.79; HRMS (ESI): calcd for $C_{23}H_{33}OSSi^{+}$ $[M+H]^{+}$: 399.2172. Found; 399.2223. **8**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.30 (t, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 7.02 (s, 1H), 6.20 (m, 1H), 4.74 (s, 2H), 2.83 (m, 1H), 2.56-2.44 (m, 3H), 2.31 (m, 1H), 2.25 (br s, 1H), 2.07 (m, 1H), 1.87 (m, 1H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 146.61, 143.81, 143.13, 131.73, 128.34, 126.79, 126.04, 123.27, 123.10, 118.27, 60.12, 39.72, 33.66, 29.78, 27.57; HRMS (ESI): calcd for $C_{17}H_{19}OS^{+}$ $[M+H]^{+}$: 271.1151. Found; 271.1225. **9**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.31 (t, *J* = 7.6 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.6 Hz, 1H), 7.14 (s, 1H), 7.00 (s, 1H), 6.21 (m, 1H), 5.07 (q, *J* = 6.4 Hz, 1H), 2.84 (m, 1H), 2.57-2.44 (m, 3H), 2.32 (m, 1H), 2.20 (br s, 1H), 2.08 (m, 1H), 1.88 (m, 1H), 1.58 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 149.70, 146.69, 143.02, 131.89, 128.41, 126.87, 126.11, 123.27, 120.94, 117.32, 66.44, 39.80, 33.72, 29.86, 27.62, 25.15; HRMS (ESI): calcd for $C_{18}H_{21}OS^{+}$ $[M+H]^{+}$: 285.1308. Found; 285.1287. **10**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.62 (m, 2H), 7.48 (d, *J* = 1.4 Hz, 1H)),

7.38 (t, *J* = 7.6 Hz, 2H)), 7.35-7.26 (m, 5H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.07 (m, 1H), 6.30 (m, 1H), 2.88 (m, 1H), 2.64-2.49 (m, 3H), 2.36 (m, 1H), 2.11 (m, 1H), 1.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 146.69, 144.00, 134.48, 131.85, 128.82, 128.39, 127.48, 126.86, 126.09, 125.90, 125.78, 123.38, 120.76, 117.83, 39.79, 33.75, 29.85, 27.65; HRMS (EI): calcd for $C_{22}H_{20}S^{+\bullet}$: 316.1280. Found; 316.1177. **13**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.48 (d, *J* = 4.1 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.27-7.20 (m, 3H), 6.95 (d, *J* = 4.1 Hz, 1H), 6.41 (m, 1H), 2.87 (m, 1H), 2.65-2.49 (m, 3H), 2.36 (m, 1H), 2.12 (m, 1H), 1.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 153.70, 145.79, 137.87, 130.16, 128.53, 127.80, 126.78, 126.38, 121.56, 114.68, 106.23, 39.33, 33.75, 29.50, 28.01; HRMS (EI): calcd for $C_{17}H_{15}NS^{+\bullet}$: 265.0920. Found; 265.0893.

12. T. Goto, H. Kato, and N. Tsukada, *Heterocycles*, 2017, **94**, 2222.
13. Spectral data for representative products. **17**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.93 (d, *J* = 1.4 Hz, 1H), 6.85 (d, *J* = 1.4 Hz, 1H)), 6.12 (m, 1H), 2.81 (q, *J* = 7.6 Hz, 2H), 2.36 (m, 2H), 2.17 (m, 2H), 1.74 (m, 2H), 1.63 (m, 2H), 1.30 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 147.09, 143.54, 132.16, 123.48, 121.03, 115.41, 26.98, 25.59, 23.54, 22.84, 22.27, 15.89; HRMS (EI): calcd for $C_{12}H_{16}S^{+\bullet}$: 192.0967. Found; 192.0973. **18**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.21-7.12 (m, 4H), 7.00 (d, *J* = 1.4 Hz, 1H), 6.80 (m, 1H), 6.15 (t, *J* = 4.8 Hz, 1H), 2.85 (q, *J* = 7.6 Hz, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.35 (m, 2H), 1.32 (t, *J* = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 146.99, 140.84, 136.74, 135.01, 127.48, 127.16, 127.01, 126.96, 126.23, 125.25, 124.66, 119.56, 28.20, 23.49, 23.27, 15.87; HRMS (EI): calcd for $C_{16}H_{16}S^{+\bullet}$: 240.0967. Found; 240.0925. **19**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.92 (d, *J* = 1.4 Hz, 1H), 6.90 (m, 1H), 6.04 (m, 1H), 4.28 (m, 2H), 3.90 (t, *J* = 5.5 Hz, 2H), 2.82 (q *J* = 7.6 Hz, 2H), 2.47 (m, 2H), 1.31 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 147.69 , 141.68 , 129.86 , 120.96 , 120.64 , 116.43 , 65.53 , 64.29 , 27.02 , 23.52 , 15.84; HRMS (EI): calcd for $C_{11}H_{14}OS^{+\bullet}$: 194.0760. Found; 194.0765. **21**: ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.46-7.30 (m, 5H), 6.69 (d, *J* = 3.4 Hz, 1H), 6.65 (d, *J* = 3.4 Hz, 1H), 5.50 (s, 1H), 5.14 (s, 1H), 2.82 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 147.44, 143.64, 142.02, 141.08, 128.40, 128.09, 127.91, 126.32, 123.60, 112.47, 23.59, 15.82; HRMS (EI): calcd for $C_{14}H_{14}S^{+\bullet}$: 214.0811. Found; 214.0822.
14. Some additives were tested for higher yields of **21b**. Addition of carboxylic acids such as *t*-$BuCO_2H$ and *N*-Boc-valine decreased the yield. Addition of other silver salts such as Ag_2O and AgOAc instead of Ag_2CO_3 decreased the yield. The reaction with other bases such as K_2CO_3 and *t*-BuOK instead of Ag_2CO_3 did not afford **21b**.