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Synthesis of Multisubstituted Enamides via Pd-Catalyzed Chloroallylation of Ynamides

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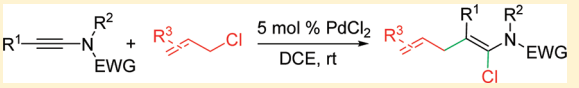
Supporting Information

ABSTRACT: An atom-economic approach to the regio- and stereoselective assembly of highly substituted enamides is described via the Pd-catalyzed chloroallylation of ynamides at room temperature, which offers a simple and practical alternative to the stereodefined multisubstituted enamides.

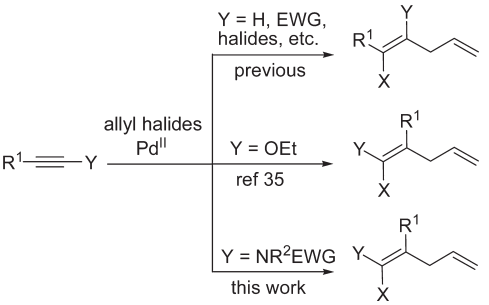


The prevalence of enamides as substrates for asymmetric hydrogenation, heterocycle syntheses and other synthetic useful transformations renders this class of compounds one of the most important building blocks in organic chemistry.[1−3] In addition, the enamide motif appears in a number of pharmaceutically attractive natural products such as salicylihalamides, as well as the antitumor macrolides lobatamides and oximidines.[4] As such, it is of central importance to develop methods allowing the effective synthesis of enamides. Besides the classical method using the condensation of carbonyl compounds,[5] various other strategies including hydroamination of acetylenes,[6] methylenation of amides,[7] and transition-metal-catalyzed amidation of alkenyl halides[8−12] have emerged in the past decades. But nevertheless, the existing methods mainly afford disubstituted enamides and often require rigorous conditions, such as the exclusion of moisture and air, elevated temperature, and utilization of excess strong base. As such, it is highly desirable to develop general and practical methods for the stereoselective preparation of sterically demanding enamides,[13−16] such as tertiary amides-containing tetrasubstituted enamides.

On the other hand, the halopalladation reaction proves to be a powerful and attractive reaction in organic synthesis because carbon−carbon and carbon−halide bonds are formed atom-economically and simultaneously.[17] However, the halopalladation of acetylenes is still traditionally limited to the terminal alkynes or activated alkynes,[17−31] and the regio- as well as stereoselective halopalladation of unsymmetrical internal alkynes has not been achieved until our recent works on the halopalladation of haloalkynes[32−34] and aromatic ynol ethers[35] (Scheme 1). Pursuing our interest in this area, we envisioned that the haloallylation[36] of ynamides[37−40] would constitute a straightforward pathway for the regio- and stereoselective synthesis of multisubstituted enamides. To this end, we hope to report such a new protocol possessing the distinctive advantages in terms of the atom-economy and practicability over the precedent procedures.[5−16]

Conditions for the Pd-catalyzed haloallylation of ynamides were explored using aromatic ynamide **1a** as the substrate. As a result, treatment of **1a** with 5 mol % of $PdCl_2$ in THF at room temperature for 4 h formed enamide **3aa** in 30% yield (entry 1, Table 1).

Scheme 1. Pd-Catalyzed Haloallylation of Alkynes



The screening of the solvents using $PdCl_2$ as the catalyst proved that dichloroethane (DCE) was the most suitable solvent for this reaction, producing enamide **3aa** in 88% yield (entries 1−8, Table 1). Furthermore, the reaction could be scaled up to 10 mmol to give **3aa** in 86% yield with 2.5 mol % of $PdCl_2$ as the catalyst (entry 8, Table 1). The stereochemistry of the enamide products was determined by X-ray diffraction analysis of enamide **3ca**. Among the catalysts we tested, $PdCl_2$ worked the best, although other palladium sources such as $Pd(OAc)_2$, $Pd(PhCN)_2Cl_2$, and $Pd(MeCN)_2Cl_2$ also worked well (entries 9−11, Table 1). Finally, we chose 5 mol % of $PdCl_2$ as the catalyst, dichloroethane as the solvent, and room temperature as the optimal reaction conditions for the chloroallylation of ynamides.

With the optimized reaction conditions in hand, we then probed the scope and limitations of this reaction using various ynamides, and the results are summarized in Table 2. Pleasingly, various functional groups including F, Cl, Br, and OMe groups were well tolerated in this transformation (entries 1−9, Table 2). For example, ynamide **1b** resulted in the desired enamide **3ba** in 84% yield under the standard conditions (entry 1, Table 2). When *ortho*-substituted ynamide **1j** was employed as a substrate, the reaction formed enamide **3ja** as two rotamers at a ratio of 5:1

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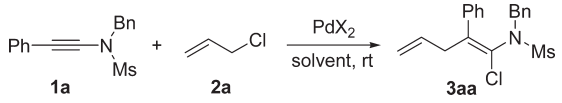
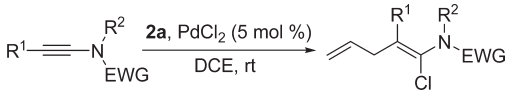
Table 1. Screening of the Reaction Conditions[a]

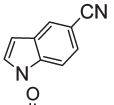


entry	PdX_2	solvent	yield[b] (%)
1	$PdCl_2$	THF	30
2	$PdCl_2$	DMSO	NR
3	$PdCl_2$	dioxane	76
4	$PdCl_2$	toluene	79
5	$PdCl_2$	HOAc	23
6	$PdCl_2$	EtOAc	83
7	$PdCl_2$	CH_2Cl_2	80
8	$PdCl_2$	DCE	88 (86)[c]
9	$Pd(OAc)_2$	DCE	83
10	$Pd(PhCN)_2Cl_2$	DCE	84
11	$Pd(MeCN)_2Cl_2$	DCE	80

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.50 mmol), and Pd catalyst (0.013 mmol) in 1 mL of solvent at rt for 4 h. [b] Isolated yield. [c] 10 mmol scale.

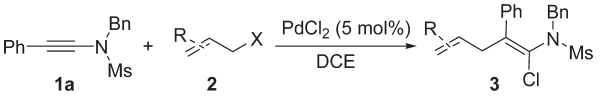
Table 2. Chloroallylation of Ynamides with 2a[a]

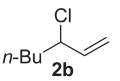
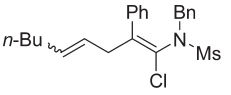
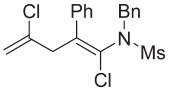
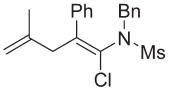
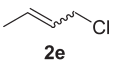
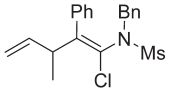
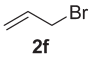
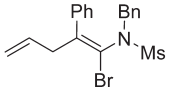


entry	1	R^1	NR^2EWG	yield (%)[b]
1	**1b**	4-F-C_6H_4	NMsBn	84 (**3ba**)
2	**1c**	4-Cl-C_6H_4	NMsBn	76 (**3ca**)
3	**1d**	4-Br-C_6H_4	NMsBn	75 (**3da**)
4	**1e**	3-Br-C_6H_4	NMsBn	73 (**3ea**)
5	**1f**	4-Me-C_6H_4	NMsBn	84 (**3fa**)
6	**1g**	4-*t*-Bu-C_6H_4	NMsBn	73 (**3ga**)
7	**1h**	4-MeO-C_6H_4	NMsBn	77 (**3ha**)
8	**1i**	3,4-MeO_2-C_6H_3	NMsBn	71 (**3ia**)
9	**1j**	2-Cl-C_6H_4	NMsBn	70 (**3ja**)[c]
10	**1k**	2-naphthyl	NMsBn	80 (**3ka**)
11	**1l**	*n*-C_9H_{19}	NMsBn	72 (**3la**)
12	**1m**	Ph	NMsBu	71 (**3ma**)[d]
13	**1n**	Ph	NMsPh	85 (**3na**)
14	**1o**	Ph	NTsBn	76 (**3oa**)
15	**1p**	Ph	$NTsCH_2CH{=}CH_2$	81 (**3pa**)
16	**1q**	Ph		68 (**3qa**)
17	**1r**	Ph		84 (**3ra**)
18	**1s**	Ph		NR (**3sa**)[e]

[a] Reaction conditions: **1** (0.25 mmol), **2a** (0.50 mmol), and $PdCl_2$ (0.013 mmol) in 1 mL of DCE at rt for 3−6 h. [b] Isolated yield. [c] 5:1 mixture of two rotamers. [d] *E*/*Z* = 13/1. [e] The reaction was carried out at 50 °C.

Table 3. Pd-Catalyzed Haloallylation of 1a with 2[a]



entry	2	3	yield (%)[b]
1[c]			66 (**3ab**)[d]
2			60 (**3ac**)
3			72 (**3ad**)
4			messy
5			messy

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.37−0.50 mmol), and $PdCl_2$ (0.013 mmol) in 1 mL of DCE at rt for 8 h. [b] Isolated yield. [c] The reaction was performed at 50 °C. [d] *4E*/*4Z* = 2/1.

in 70% yield (entry 9, Table 2). This was confirmed by variable temperature NMR experiments and GC−MS analysis. Beside the aromatic ynamides, the reaction of aliphatic ynamide **1l** also proceeded to provide enamide **3la** in 72% yield (entry 11, Table 2). In addition, the effects of substituents on the nitrogen atom of ynamides were also briefly investigated. For instance, ynamides with an *N*-butyl group **1m** and an *N*-phenyl group **1n** produced the corresponding enamides **3ma** and **3na** in respective yields of 71% and 85% (entries 12 and 13, Table 2). Interestingly, phenylethynyl oxazolidinone (**1q**) and indole-derived ynamide (**1r**) afforded the desired products **3qa** and **3ra** in good yields, while phenylethynyl pyrrolidinone (**1s**) was reluctant to couple with **2a**, even at elevated temperature (entries 16−18, Table 2).

Next, the haloallylation reaction was studied using substituted allyl halides and ynamide **1a** (Table 3). For example, allylic chloride **2b** afforded the desired enamide **3ab** in 66% yield with 2:1 mixture of *E*/*Z* isomers (entry 1, Table 3). Additionally, the reaction of 2-chloro-substituted allyl chloride (**2c**) and 2-methyl-substituted allyl chloride (**2d**) occurred smoothly to give the corresponding products **3ac** and **3ad** in 60% and 72% yields, respectively (entries 2 and 3, Table 2). However, crotyl chloride (**2e**) and allyl bromide (**2f**) failed to give the desired enamides due to the formation of some unidentified byproducts (entries 4 and 5, Table 2).

We then sought to examine the synthetic utility of this chloroallylation strategy for the synthesis of tetrasubstituted enamides. For example, we tried the Suzuki coupling of enamide **3aa** and the tetrasubstituted enamides **4** were obtained in good yields by treating **3aa** with 1.5 equiv of $PhB(OH)_2$, 2.0 equiv of K_3PO_4, 5 mol % of $Pd(OAc)_2$, and 10 mol % of Xphos[41] in THF (Scheme 2).

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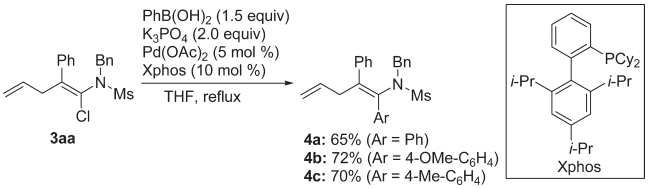
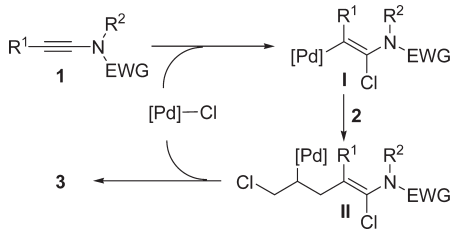
Scheme 2. Suzuki Coupling of 3aa



Scheme 3. Proposed Mechanism



To shed light on the possible mechanism of this reaction, ynamide **1a** was treated with 0.5 equiv of allylpalladium(II) chloride dimer in dichloroethane at room temperature. However, no desired enamide product **3aa** was detected, and ynamide **1a** was recovered in 86% yield after stirring for 10 h. As such, the allylpalladium intermediate seems to be unlikely for this reaction and a chloropalladation mechanism is thus proposed in Scheme 3. It is well documented that the polarization of the triple bond of ynamides enables the regioselective addition of nucleophiles at the α-position to the nitrogen atom.[37,38] Thus, the *cis*-halopalladation of ynamides selectively forms the vinyl palladium intermediate **I**, followed by the carbopalladation with allyl halide **2** to yield the alkyl palladium intermediate **II**. Finally, β-Cl elimination[42,43] produces enamide **3**, together with the regeneration of the palladium catalyst (Scheme 3).

In conclusion, we have succeeded in implementing an efficient method for the regio- and stereoselective synthesis of highly substituted enamides by the Pd-catalyzed chloroallylation of ynamides with allyl chlorides. It is worth to mention that the reaction is typically performed only in the presence of 5 mol % of $PdCl_2$ at room temperature, and the omission of special ligands, bases, and inert atmosphere makes it mild, practical and atom-economic procedure for the preparation of multisubstituted enamides. Further synthetic applications of this method will be described in due course.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, the reactions were conducted under air atmosphere. Column chromatography was performed using silica gel (300−400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz NMR spectrometers. MS and microanalysis were performed in the state authorized analytical center of Zhejiang Normal University. $PdCl_2$, $Pd(OAc)_2$, $Pd(MeCN)_2Cl_2$, and $Pd(PhCN)_2Cl_2$ were obtained commercially and used without further purification.

General Procedure for the Preparation of Ynamides. Ynamides were prepared according to the method reported by Hsung.[39] The spectroscopic data of ynamides **1a,c,f,h,m,o**−**s** were consistent with the literature,[39,40] and the characteristic data of unreported ynamides are listed as follows.

Ynamide ***1b***: yield 78% as a white solid; mp 78−80 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.95 (s, 3 H), 4.70 (s, 2 H), 6.92−7.03 (m, 2 H), 7.31−7.52 (m, 7 H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −110.8; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.0, 55.9, 70.5, 81.6, 115.6 (d, J = 21.9 Hz), 118.5 (d, J = 3.7 Hz), 128.8, 128.9, 129.0, 133.5 (d, J = 8.3 Hz), 134.5, 162.4 (d, J = 247.9 Hz); MS (EI, m/z) 303 (M^+, 10), 224 (25), 197 (17); HRMS (EI) calcd for $C_{16}H_{14}FNO_2S$ (M^+) 303.0729, found 303.0720.

Ynamide ***1d***: yield 82% as a yellow solid; mp 76−78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.94 (s, 3 H), 4.70 (s, 2 H), 7.15−7.24 (m, 2 H), 7.39−7.49 (m, 7 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.1, 55.9, 70.8, 83.1, 121.5, 122.1, 128.9, 128.9, 129.0, 131.6, 132.7, 134.4; MS (EI, m/z) 365 (4), 363 (M^+, 4), 286 (10), 360 (10); HRMS (EI) calcd for $C_{16}H_{14}BrNO_2S$ (M^+) 362.9929, found 362.9935.

Ynamide ***1e***: yield 81% as a yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.96 (s, 3 H), 4.72 (s, 2 H), 7.15 (t, J = 8.0 Hz, 1 H), 7.25−7.33 (m, 1 H), 7.38−7.55 (m, 7 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.2, 55.9, 70.4, 83.3, 122.1, 124.6, 128.9, 128.9, 129.0, 129.7, 129.8, 131.0, 133.8, 134.4; MS (EI, m/z) 365 (3), 363 (M^+, 3), 286 (7), 360 (8); HRMS (EI) calcd for $C_{16}H_{14}BrNO_2S$ (M^+) 362.9929, found 362.9930.

Ynamide ***1g***: yield 65% as a white solid; mp 88−90 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 9 H), 2.93 (s, 3 H), 4.71 (s, 2 H), 7.32 (s, 4 H), 7.39−7.52 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.2, 34.8, 38.9, 55.9, 71.6, 81.3, 119.4, 125.3, 128.7, 128.8, 129.0, 131.4, 134.6, 151.5; MS (EI, m/z) 341 (M^+, 20), 262 (30), 206 (46), 179 (20); HRMS (EI) calcd for $C_{20}H_{23}NO_2S$ (M^+) 341.1449, found 341.1453.

Ynamide ***1i***: yield 83% as a white solid; mp 104−106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.95 (s, 3 H), 3.86 (s, 3 H), 3.88 (s, 3 H), 4.71 (s, 2 H), 6.78 (d, J = 8.4 Hz, 1 H), 6.86 (d, J = 2.0 Hz, 1 H), 6.96−7.21 (m, 1 H), 7.39−7.51 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 38.9, 55.9, 55.9, 55.9, 71.4, 80.5, 111.0, 114.5, 114.7, 125.2, 128.7, 128.8, 129.0, 134.7, 148.6, 149.5; HRMS (ESI) calcd for $C_{18}H_{19}NO_4S$ (M^+) 345.1035, found 345.1030.

Ynamide ***1j***: yield 81% as a yellow solid; mp 70−72 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.97 (s, 3 H), 4.74 (s, 2 H), 7.19−7.55 (m, 9 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.1, 56.0, 69.1, 87.2, 122.6, 126.5, 128.9, 128.9, 128.9, 129.1, 129.2, 132.6, 134.4, 135.3; MS (EI, m/z) 321 (2), 319 (M^+, 7), 242 (7), 262 (21); HRMS (EI) calcd for $C_{16}H_{14}ClNO_2S$ (M^+) 319.0434, found 319.0435.

Ynamide ***1k***: yield 72% as a white solid; mp 118−120 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.98 (s, 3 H), 4.76 (s, 2 H), 7.41−7.55 (m, 8 H), 7.72−7.81 (m, 3 H), 7.88 (s, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.1, 56.0, 72.1, 82.3, 119.8, 126.6, 126.6, 127.6, 127.7, 128.0, 128.3, 128.8, 128.9, 129.1, 131.0, 132.6, 133.0, 134.6; MS (EI, m/z) 335 (M^+, 20), 281 (18), 256 (43), 229 (30); HRMS (EI) calcd for $C_{20}H_{17}NO_2S$ (M^+) 335.0980, found 335.0976.

Ynamide ***1l***: yield 70% as a yellow solid; mp 38−40 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 6.4 Hz, 3 H), 1.26 (s, 12 H), 1.39−1.52 (m, 2 H), 2.17−2.30 (m, 2 H), 2.83 (s, 3 H), 4.54 (s, 2 H), 7.30−7.51 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 18.4, 22.7, 28.7, 28.8, 29.1, 29.3, 29.5, 31.9, 38.1, 55.6, 71.3, 73.1, 128.5, 128.6, 128.9, 134.9; HRMS (ESI) calcd for $C_{19}H_{29}NO_2S$ (M^+) 335.1919, found 335.1927.

Ynamide ***1n***: yield 87% as a yellow solid; mp 66−68 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.17 (s, 3 H), 7.31−7.61 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 36.9, 71.0, 82.0, 122.3, 125.6, 128.2, 128.4, 128.4, 129.5, 131.6, 138.7; MS (EI, m/z) 271 (M^+, 50), 264 (35), 219 (52), 192 (50); HRMS (EI) calcd for $C_{15}H_{13}NO_2S$ (M^+) 271.0667, found 271.0664.

General Procedure for Pd-Catalyzed Chloroallylation of Ynamides with Allyl Chloride. To a mixture of **1a** (71 mg, 0.25 mmol) and $PdCl_2$ (2.2 mg, 0.013 mmol) in 1 mL of DCE was added **2a** (42 μL, 0.50 mmol). After being stirred for 4 h at rt, the reaction mixture was concentrated and purified by column chromatography on silica gel to give 80 mg (yield 88%) of **3aa** as a white solid: mp 56−58 °C;

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R_f = 0.37 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.81 (s, 3 H), 3.23 (d, J = 6.0 Hz, 2 H), 4.26 (d, J = 13.6 Hz, 1 H), 4.43 (d, J = 13.6 Hz, 1 H), 4.95−5.04 (m, 2 H), 5.55−5.72 (m, 1 H), 6.75 (d, J = 7.2 Hz, 2 H), 7.08−7.32 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.9, 40.7, 52.9, 117.1, 126.1, 127.3, 127.6, 127.9, 128.3, 128.5, 130.0, 132.2, 133.6, 138.1, 143.0; MS (EI, m/z) 363 (1), 361 (M^+, 3), 326 (5), 284 (6); HRMS (EI) calcd for $C_{19}H_{20}ClNO_2S$ (M^+) 361.0903, found 361.0906.

Compound ***3ba***: yield 84% as a white solid; mp 78−80 °C; R_f = 0.35 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.93 (s, 3 H), 3.13−3.25 (m, 2 H), 4.21 (d, J = 13.2 Hz, 1 H), 4.47 (d, J = 13.2 Hz, 1 H), 4.98−5.06 (m, 2 H), 5.55−5.67 (m, 1 H), 6.63−6.72 (m, 2 H), 6.77 (t, J = 8.8 Hz, 2 H), 7.08 (d, J = 7.2 Hz, 2 H), 7.20−7.30 (m, 3 H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ −114.5; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.5, 40.8, 52.7, 114.5 (d, J = 21.3 Hz), 117.3, 126.0, 128.4, 128.5, 129.7 (d, J = 8.0 Hz), 130.0, 132.1, 133.5, 133.8 (d, J = 3.4 Hz), 142.6, 161.9 (d, J = 245.1 Hz); MS (EI, m/z) 381 (0.6), 379 (M^+, 2), 344 (4), 302 (8), 300 (26); HRMS (EI) calcd for $C_{19}H_{19}ClFNO_2S$ (M^+) 379.0809, found 379.0808.

Compound ***3ca***: yield 76% as a white solid; mp 70−72 °C; R_f = 0.27 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.94 (s, 3 H), 3.13−3.26 (m, 2 H), 4.20 (d, J = 13.2 Hz, 1 H), 4.47 (d, J = 13.2 Hz, 1 H), 4.95−5.04 (m, 2 H), 5.53−5.67 (m, 1 H), 6.62 (d, J = 8.4 Hz, 2 H), 7.01−7.15 (m, 4 H), 7.20−7.32 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.4, 40.5, 52.7, 117.3, 126.1, 127.7, 128.3, 128.4, 129.3, 129.9, 131.9, 133.1, 133.3, 136.3, 142.5; MS (EI, m/z): 397 (2), 395 (M^+, 3), 362 (3), 360 (10); HRMS (EI) calcd for $C_{19}H_{19}Cl_2NO_2S$ (M^+) 395.0514, found 395.0516.

Crystal data for **3ca** ($C_{19}H_{19}Cl_2NO_2S$, 395.05): orthorhombic, space group $P2(1)/c$, a = 7.0335(5) Å, b = 35.053(2) Å, c = 8.2257(6) Å, U = 1946.4(2) Å^3, Z = 4, specimen 0.312 × 0.106 × 0.035 mm^3, T = 296(2) K, SIEMENS P4 diffractometer, absorption coefficient 0.453 mm^{-1}, reflections collected 14402, independent reflections 3411 [R(int) = 0.0603], refinement by full-matrix least-squares on F^2, data/restraints/parameters 3411/2/235, goodness-of-fit on F^2 = 1.036, final R indices [$I > 2\sigma(I)$] R1 = 0.0497, wR2 = 0.1122, R indices (all data) R1 = 0.1072, wR2 = 0.1288, largest diff peak and hole 0.161 and −0.224 e Å^{-3}. Crystal data of **3ca** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 834590.

Compound ***3da***: yield 75% as a white solid; mp 106−108 °C; R_f = 0.35 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.95 (s, 3 H), 3.13−3.24 (m, 2 H), 4.21 (d, J = 13.2 Hz, 1 H), 4.48 (d, J = 13.2 Hz, 1 H), 4.98−5.06 (m, 2 H), 5.57−5.64 (m, 1 H), 6.57 (d, J = 8.4 Hz, 2 H), 7.08 (d, J = 7.2 Hz, 2 H), 7.19−7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.4, 40.5, 52.7, 117.4, 121.4, 126.1, 128.4, 128.5, 129.7, 130.0, 130.7, 132.0, 133.4, 136.8, 142.6; MS (EI, m/z): 441 (1), 439 (M^+, 1), 406 (4), 404 (4); HRMS (EI) calcd for $C_{19}H_{19}BrClNO_2S$ (M^+) 439.0008, found 439.0009.

Compound ***3ea***: yield 73% as a white solid; mp 70−72 °C; R_f = 0.34 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.92 (s, 3 H), 3.10−3.23 (m, 2 H), 4.20 (d, J = 13.2 Hz, 1 H), 4.48 (d, J = 13.2 Hz, 1 H), 4.95−5.05 (m, 2 H), 5.52−5.66 (m, 1 H), 6.55 (s, 1 H), 6.92 (d, J = 7.6 Hz, 1 H), 7.01−7.12 (m, 3 H), 7.22−7.34 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.4, 40.5, 52.6, 117.5, 121.5, 126.5, 127.1, 128.5, 128.6, 129.1, 129.9, 130.4, 130.4, 131.8, 133.1, 139.9, 142.2; MS (EI, m/z): 441 (2), 439 (M^+, 2), 406 (7), 404 (7); HRMS (EI) calcd for $C_{19}H_{19}BrClNO_2S$ (M^+) 439.0008, found 439.0013.

Compound ***3fa***: yield 84% as a white solid; mp 102−104 °C; R_f = 0.40 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.29 (s, 3 H), 2.82 (s, 3 H), 3.22 (d, J = 6.0 Hz, 2 H), 4.27 (d, J = 13.6 Hz, 1 H), 4.42 (d, J = 13.6 Hz, 1 H), 4.98−5.05 (m, 2 H), 5.59−5.67 (m, 1 H), 6.68 (d, J = 8.0 Hz, 2 H), 6.94 (d, J = 7.6 Hz, 2 H), 7.11 (d, J = 7.2 Hz, 2 H), 7.21−7.32 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.2, 40.0, 40.7, 53.0, 117.0, 125.9, 127.8, 128.3, 128.4, 128.5, 130.0, 132.4, 133.7, 135.1, 137.0, 142.9; MS (EI, m/z) 377 (1), 375 (M^+, 3), 298 (7), 296 (20); HRMS (EI) calcd for $C_{20}H_{22}ClNO_2S$ (M^+) 375.1060, found 375.1064.

Compound ***3ga***: yield 73% as a yellow oil; R_f = 0.48 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.30 (s, 9 H), 2.83 (s, 3 H), 3.22 (dd, J = 6.0, 1.3 Hz, 2 H), 4.24 (d, J = 13.6 Hz, 1 H), 4.44 (d, J = 13.6 Hz, 1 H), 4.95−5.11 (m, 2 H), 5.62−5.74 (m, 1 H), 6.73−6.79 (m, 2 H), 7.03−7.09 (m, 2 H), 7.13−7.27 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 31.3, 34.5, 39.9, 40.7, 53.1, 116.9, 124.5, 126.0, 127.5, 128.2, 128.4, 129.8, 132.5, 133.7, 135.1, 142.8, 150.2; MS (EI, m/z) 419 (1), 417 (M^+, 3), 341 (6), 338 (20); HRMS (EI) calcd for $C_{23}H_{28}ClNO_2S$ (M^+) 417.1529, found 417.1526.

Compound ***3ha***: yield 77% as a yellow oil; R_f = 0.28 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.87 (s, 3 H), 3.16−3.25 (m, 2 H), 3.77 (s, 3 H), 4.24 (d, J = 13.6 Hz, 1 H), 4.43 (d, J = 13.6 Hz, 1 H), 4.97−5.06 (m, 2 H), 5.57−5.70 (m, 1 H), 6.65 (d, J = 8.0 Hz, 2 H), 6.73 (d, J = 8.4 Hz, 2 H), 7.09 (d, J = 7.2 Hz, 2 H), 7.20−7.30 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.9, 40.8, 53.0, 55.2, 113.0, 116.9, 125.7, 128.3, 128.4, 129.2, 129.9, 130.3, 132.5, 133.7, 142.6, 158.8; MS (EI, m/z) 393 (1), 391 (M^+, 3), 314 (9), 312 (28); HRMS (EI) calcd for $C_{20}H_{22}ClNO_3S$ (M^+) 391.1009, found 391.1010.

Compound ***3ia***: yield 71% as a yellow oil; R_f = 0.17 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.97 (s, 3 H), 3.12−3.28 (m, 2 H), 3.78 (s, 3 H), 3.85 (s, 3 H), 4.17 (d, J = 13.6 Hz, 1 H), 4.38 (d, J = 13.6 Hz, 1 H), 4.96−5.08 (m, 2 H), 5.60−5.70 (m, 1 H), 6.38 (dd, J = 8.4, 2.0 Hz, 1 H), 6.60 (d, J = 8.4 Hz, 1 H), 6.72 (d, J = 2.0 Hz, 1 H), 7.02 (d, J = 7.2 Hz, 2 H), 7.13−7.22 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.8, 40.7, 53.2, 55.8, 55.8, 110.2, 111.7, 116.9, 120.2, 125.8, 128.1, 128.2, 129.7, 130.5, 132.8, 133.5, 142.4, 148.0, 148.2; MS (EI, m/z): 423 (1), 421 (M^+, 3), 344 (11), 342 (35); HRMS (EI) calcd for $C_{21}H_{24}ClNO_4S$ (M^+) 421.1115, found 421.1117.

Compound ***3ja***: yield 70% as a yellow oil; 5:1 mixture of two rotamers; R_f = 0.44 (hexanes/EtOAc = 6/1); ^{1}H NMR (C_2D_6SO, 400 MHz, 90 °C) δ 2.84 (s, 3 H), 3.21−3.42 (m, 2 H), 4.39 (s, 2 H), 4.92−5.10 (m, 2 H), 5.50−5.71 (m, 1 H), 7.07−7.31 (m, 9 H); ^{13}C NMR (C_2D_6SO, 100 MHz, 90 °C) δ 39.0, 53.6, 117.7, 126.5, 128.4, 128.7, 129.5, 129.7, 129.7, 129.8, 129.8, 131.5, 132.3, 132.5, 134.7, 136.5, 140.4; MS (EI, m/z) 397 (2), 395 (M^+, 3), 362 (3), 360 (10); HRMS (EI) calcd for $C_{19}H_{19}Cl_2NO_2S$ (M^+) 395.0514, found 395.0508.

Compound ***3ka***: yield 80% as a yellow oil; R_f = 0.40 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.83 (s, 3 H), 3.28−3.34 (m, 2 H), 4.29 (d, J = 13.6 Hz, 1 H), 4.45 (d, J = 13.6 Hz, 1 H), 4.98−5.12 (m, 2 H), 5.62−5.78 (m, 1 H), 7.01−7.09 (m, 4 H), 7.17 (t, J = 7.6 Hz, 2 H), 7.31−7.40 (m, 1 H), 7.44−7.50 (m, 2 H), 7.60−7.69 (m, 2 H), 7.78−7.90 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.8, 40.8, 52.8, 117.2, 125.9, 126.1, 126.2, 126.3, 126.8, 127.2, 127.5, 128.4, 128.4, 128.5, 130.0, 132.2, 132.4, 132.6, 133.6, 135.6, 143.2; MS (EI, m/z): 413 (2), 411 (M^+, 6), 334 (26), 332 (79); HRMS (EI) calcd for $C_{23}H_{22}ClNO_2S$ (M^+) 411.1060, found 411.1058.

Compound ***3la***: yield 72% as a yellow oil; R_f = 0.48 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 6.8 Hz, 3 H), 0.95−1.30 (m, 14 H), 1.86 (t, J = 8.8 Hz, 2 H), 2.86 (d, J = 6.0 Hz, 2 H), 3.03 (s, 3 H), 4.20 (d, J = 13.2 Hz, 1 H), 4.77 (d, J = 13.2 Hz, 1 H), 4.88−4.97 (m, 2 H), 5.51−5.62 (m, 1 H), 7.29−7.37 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 22.7, 27.0, 29.3, 29.3, 29.5, 29.8, 31.9, 33.0, 36.3, 38.9, 51.9, 116.5, 122.2, 128.4, 128.5, 130.0, 132.9, 134.4, 145.6; HRMS (ESI) calcd for $C_{22}H_{34}ClNO_2S$ (M^+) 411.1999, found 411.2002.

Compound ***3ma***: yield 71% as a yellow oil; E/Z > 13/1; R_f = 0.46 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78 (t, J = 7.2 Hz, 3 H), 0.95−1.15 (m, 2 H), 1.25−1.42 (m, 2 H) 2.85 (s, 3 H), 3.27−3.48 (m, 4 H), 5.05−5.21 (m, 2 H), 5.71−5.86 (m, 1 H), 7.27−7.44 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.6, 19.9, 29.6, 39.1, 40.8, 49.1, 117.2, 126.6, 127.7, 128.0, 128.2, 132.4, 138.5, 142.6; MS (EI, m/z) 329 (0.7), 327 (M^+, 2), 292 (7), 250 (2), 248 (6).

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Anal. Calcd for $C_{16}H_{22}ClNO_2S$: C, 58.61; H, 6.76; Cl, 10.81; N, 4.27. Found: C, 58.78; H, 6.95; Cl, 10.64; N, 4.16.

Compound ***3na***: yield 85% as a colorless oil; R_f = 0.44 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.97 (s, 3 H), 3.27−3.37 (m, 2 H), 5.04−5.13 (m, 2 H), 5.68−5.82 (m, 1 H), 7.03−7.11 (m, 2 H), 7.19−7.33 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.4, 40.2, 117.3, 126.3, 127.1, 127.8, 127.9, 128.0, 128.1, 129.1, 132.1, 138.2, 139.5, 142.5; MS (EI, *m*/*z*) 349 (2), 347 (M^+, 6), 270 (18), 268 (56); HRMS (EI) calcd for $C_{18}H_{18}ClNO_2S$ (M^+) 347.0747, found 347.0748.

Compound ***3oa***: yield 76% as a yellow oil; R_f = 0.57 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.44 (s, 3 H), 3.16−3.32 (m, 2 H), 4.08 (d, *J* = 13.2 Hz, 1 H), 4.31 d, *J* = 13.2 Hz, 1 H), 4.95−5.08 (m, 2 H), 5.56−5.71 (m, 1 H), 6.62 (d, *J* = 7.2 Hz, 2 H), 6.94 (d, *J* = 7.2 Hz, 2 H), 7.11 (t, *J* = 7.2 Hz, 2 H), 7.18−7.31 (m, 6 H), 7.54 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 41.0, 52.0, 117.0, 125.6, 127.1, 127.5, 128.1, 128.2, 128.3, 128.9, 129.4, 130.2, 132.4, 133.5, 135.2, 138.4, 143.9, 144.3; MS (EI, *m*/*z*) 439 (1), 437 (M^+, 3), 284 (5), 282 (14); HRMS (EI) calcd for $C_{25}H_{24}ClNO_2S$ (M^+) 437.1216, found 437.1214.

Compound ***3pa***: yield 81% as a white solid; mp 78−80 °C; R_f = 0.57 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.37 (s, 3 H), 3.26−3.37 (m, 2 H), 3.49−3.61 (m, 1 H), 3.68−3.78 (m, 1 H), 5.02−5.16 (m, 4 H), 5.38−5.52 (m, 1 H), 5.55−5.82 (m, 1 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 7.27−7.35 (m, 5 H), 7.52 (d, *J* = 8.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 40.8, 51.8, 117.1, 120.2, 126.4, 127.5, 127.9, 128.4, 128.7, 129.4, 131.5, 132.6, 135.2, 138.8, 143.1, 144.1; HRMS (ESI) calcd for $C_{21}H_{22}ClNO_2S$ (M^+) 387.1060, found 387.1059.

Compound ***3qa***: yield 68% as a colorless oil; R_f = 0.41 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.33 (d, *J* = 6.4 Hz, 2 H), 3.53 (t, *J* = 8.0 Hz, 2 H), 4.14 (t, *J* = 8.0 Hz, 2 H), 5.03−5.14 (m, 2 H), 5.68−5.77 (m, 1 H), 7.20−7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.7, 45.1, 62.3, 117.3, 123.8, 127.3, 128.0, 128.4, 132.4, 138.1, 140.9, 155.8; HRMS (ESI) calcd for $C_{14}H_{14}ClNO_2$ (M^+) 263.0713, found 263.0706.

Compound ***3ra***: yield 84% as yellow oil; R_f = 0.56 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.51−3.68 (m, 2 H), 5.15−5.30 (m, 2 H), 5.85−5.98 (m, 1 H), 6.55−6.63 (m, 1 H), 6.92−7.24 (m, 6 H), 7.28−7.31 (m, 1 H), 7.46 (d, *J* = 7.2 Hz, 1 H), 7.58−7.69 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.8, 103.3, 103.6, 115.7, 117.6, 118.2, 122.4, 123.3, 126.1, 127.0, 128.0, 128.4, 129.8, 131.0, 132.7, 135.6, 137.3, 138.8; MS (EI, *m*/*z*) 320 (24), 318 (M^+, 75), 303 (40), 283 (75); HRMS (EI) calcd for $C_{20}H_{15}ClN_2$ (M^+) 318.0924, found 318.0917.

Compound ***3ab***: yield 66% as a colorless oil; 4*E*/4*Z* = 2/1; R_f = 0.47 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz), major isomer δ 0.82−1.02 (m, 3 H), 1.22−1.42 (m, 4 H), 1.22−1.42 (m, 2 H), 2.79 (s, 3 H), 3.14−3.23 (m, 2 H), 4.25 (d, *J* = 13.6 Hz, 1 H), 4.41 (d, *J* = 13.6 Hz, 1 H), 5.11−5.28 (m, 1 H), 5.32−5.43 (m, 1 H), 6.68−6.81 (m, 2 H), 7.05−7.41 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz), major isomer δ 13.9, 22.0, 31.4, 32.1, 39.7, 39.9, 52.9, 123.4, 127.1, 127.5, 128.0, 128.3, 128.4, 130.1, 130.2, 133.6, 133.7, 138.2, 144.0; MS (EI, *m*/*z*) 419 (2), 417 (M^+, 5), 340 (15), 338 (43). Anal. Calcd for $C_{23}H_{28}ClNO_2S$: C, 66.09; H, 6.75; Cl, 8.48; N, 3.35. Found: C, 66.33; H, 6.52; Cl, 8.21; N, 3.59.

Compound ***3ac***: yield 60% as a yellow oil; R_f = 0.34 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.76 (s, 3 H), 3.44−3.56 (m, 2 H), 4.26 (d, *J* = 13.6 Hz, 1 H), 4.43 (d, *J* = 13.6 Hz, 1 H), 5.07−5.13 (m, 2 H), 6.69−6.78 (m, 2 H), 7.07−7.28 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 39.9, 45.8, 53.0, 114.2, 127.6, 127.8, 128.1, 128.5, 128.6, 128.7, 130.0, 133.5, 136.7, 137.1, 140.5; HRMS (ESI) calcd for $C_{19}H_{19}Cl_2NO_2S$ (M^+) 395.0514, found 395.0518.

Compound ***3ad***: yield 72% as a yellow oil; R_f = 0.46 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.67 (s, 3 H), 2.82 (s, 3 H), 3.14 (d, *J* = 14.6 Hz, 1 H), 3.29 (d, *J* = 14.6 Hz, 1 H), 4.29 (d, *J* = 13.6 Hz, 1 H), 4.46 (d, *J* = 13.6 Hz, 1 H), 4.59 (s, 1 H), 4.69 (s, 1 H), 6.77−6.82 (m, 2 H), 7.10−7.31 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 22.6, 39.9, 44.6, 53.0, 112.7, 126.7, 127.2, 127.6, 128.0, 128.3, 128.5, 130.0, 133.7, 138.0, 140.4, 143.1; MS (EI, *m*/*z*): 377 (3), 375 (M^+, 10), 298 (14), 296 (46); HRMS (EI) calcd for $C_{20}H_{22}ClNO_2S$ (M^+) 375.1060, found 375.1066.

General Procedure for the Suzuki Coupling of 3aa. To a mixture of $PhB(OH)_2$ (37 mg, 0.30 mmol), $Pd(OAc)_2$ (2.3 mg, 0.01 mmol), K_3PO_4 (43 mg, 0.40 mmol), and Xphos (9.5 mg, 0.02 mmol) in 2 mL of THF was added **3aa** (72 mg, 0.20 mmol) under nitrogen. After being stirred at 70 °C for 6 h, the reaction was quenched with water, extracted with EtOAc, dried, and concentrated. Column chromatography on silica gel gave 53 mg (yield: 65%) of **4a** as a colorless oil: R_f = 0.36 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.90 (s, 3 H), 2.92−3.06 (m, 1 H), 3.08−3.21 (m, 1 H), 3.98 (d, *J* = 14.0 Hz, 1 H), 4.23 (d, *J* = 14.0 Hz, 1 H), 4.82−4.98 (m, 2 H), 5.51−5.65 (m, 1 H), 6.83−7.01 (m, 2 H), 7.10−7.25 (m, 5 H), 7.29−7.45 (m, 8 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.1, 41.6, 52.6, 116.4, 127.1, 128.0, 128.3, 128.3, 128.4, 128.6, 128.9, 129.8, 130.2, 134.9, 135.2, 135.9, 136.4, 139.9, 140.6; HRMS (ESI) calcd for $C_{25}H_{25}NO_2S$ (M^+) 403.1606, found 403.1608.

Compound ***4b***: yield 72% yield as a yellow oil; R_f = 0.46 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.92 (s, 3 H), 2.94−3.08 (m, 1 H), 3.09−3.21 (m, 1 H), 3.81 (s, 3 H), 4.00 (d, *J* = 14.2 Hz, 1 H), 4.21 (d, *J* = 14.2 Hz, 1 H), 4.82−4.98 (m, 2 H), 5.52−5.76 (m, 1 H), 6.83−6.98 (m, 4 H), 7.19−7.25 (m, 5 H), 7.27−7.39 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 40.1, 41.6, 52.5, 55.3, 113.8, 116.3, 127.0, 128.0, 128.3, 128.6, 128.7, 128.9, 130.2, 131.2, 134.6, 135.4, 136.1, 139.0, 140.1, 159.5; HRMS (ESI) calcd for $C_{26}H_{27}NO_3S$ (M^+) 433.1712, found 433.1709.

Compound ***4c***: yield 70% yield as a colorless oil; R_f = 0.37 (hexanes/EtOAc = 6/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.98 (s, 3 H), 2.40 (s, 3 H), 3.02−3.20 (m, 2 H), 4.03 (d, *J* = 14.2 Hz, 1 H), 4.18 (d, *J* = 14.2 Hz, 1 H), 4.84−5.01 (m, 2 H), 5.54−5.72 (m, 1 H), 6.85−7.02 (m, 2 H), 7.03−7.18 (m, 7 H), 7.19−7.35 (m, 2 H), 7.36−7.53 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.3, 40.1, 41.6, 52.6, 116.4, 127.1, 128.0, 128.3, 128.6, 128.9, 129.1, 129.8, 130.2, 133.5, 134.9, 135.3, 136.0, 138.2, 139.4, 140.7; HRMS (ESI) calcd for $C_{26}H_{27}NO_2S$ (M^+) 417.1762, found 417.1760.

■ ASSOCIATED CONTENT

Supporting Information. Spectroscopic data of ynamides **1b,d,e,g,i**−**l,n** and all of the products as well as the crystallographic data of **3ca** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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