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Regiospecific Synthesis of Benzoxepines through Pd-Catalyzed Carbene Migratory Insertion and C−C Bond Cleavage

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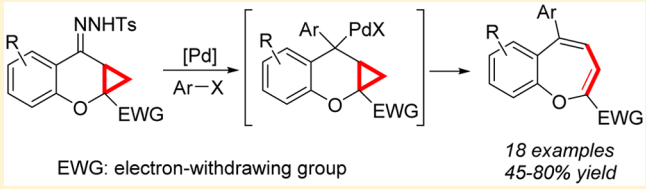
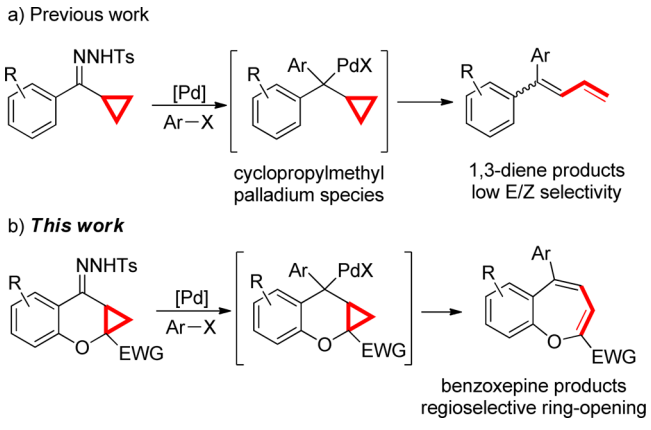
Supporting Information

ABSTRACT: A new method for the synthesis of benzoxepines via migratory insertion into a Pd carbene followed by C−C bond cleavage was developed. Various benzoxepines were constructed by the regioselective ring expansion concomitant with the introduction of an aryl group at their 5-position.



Carbon−carbon bond cleavage by means of transition metals has received considerable attention and provides new opportunities for the discovery of synthetically useful reactions that are otherwise difficult.[1,2] Among the strategies for this proposed transformation, β-carbon elimination of cyclopropyl carbinyl metal species is an appealing model on account of the high strain energy of cyclopropane.[2] Although the addition of M−M′ or R−M intermediates to the double bond of methylenecyclopropanes (MCPs) has been established as a common route for the generation of these transient cyclopropyl carbinyl metal species,[3] the process has been found to be highly dependent on the substitution pattern of the MCP, which forms isomeric products in some cases.[4] In 2012, we reported the Pd-catalyzed cross-coupling of cyclopropyl *N*-tosylhydrazones with aryl halides, leading to various linear 1,1-disubstituted 1,3-butadiene products (Scheme 1a).[5] The reaction provides a novel route toward cyclopropyl carbinyl palladium species via migratory insertion into a Pd carbene as the characteristic step.[6] Encouraged by this result, we speculated that the Pd-catalyzed carbene migratory insertion and β-carbon elimination processes might be further applied to strained bicyclic cyclopropane derivatives, which would undergo a regioselective ring-enlargement reaction to give medium-ring compounds (Scheme 1b).

Scheme 1. Formation of Cyclopropyl Carbinyl Palladium Species via Migratory Insertion into a Pd Carbene and Its Synthetic Application



The benzoxepine unit represents an important structural motif found in a variety of natural products[7] and biologically relevant compounds.[8] Consequently, a number of approaches involving C−O or/and C−C bond formation have been developed for the construction of this skeleton.[9,10] By extension, Langer and co-workers reported the synthesis of functionalized benzoxepines from benzopyrylium triflates and diazo esters through cyclopropanation and subsequent TFA-mediated ring expansion.[11] In this reaction, the bond cleavage is favored by the push−pull effect of the alkoxy and carbonyl groups in the 2,3-methanochromanone,[12] which belongs to a donor−acceptor (D−A)-substituted cyclopropane and would form a 1,3-zwitterionic intermediate.[13] However, the synthesis of benzoxepines through regioselective ring expansion of non-D−A-substituted cyclopropanes is still less explored, mainly because of the lack of efficient methods for their activation. Herein we report a Pd-catalyzed cross-coupling of aryl halides with oxabicyclo[4.1.0]heptyl *N*-tosylhydrazones that affords various benzoxepines via cyclopropyl carbinyl palladium intermediates.

To this end, *N*-tosylhydrazones **4** and **6** were prepared by three-step operations, as shown in Scheme 2.[14,15] Initially we attempted to synthesize 2,3-methanochromanones **3** by the cyclopropanation of chromone methyl ester with trimethylsulfoxonium iodide. However, only a 27% yield of **3** was obtained because of in situ saponification of the product.[15b] It was found to be more convenient to start with the cyclopropanation by using commercially available chromone-2-carboxylic acids **1**, and the reaction afforded cyclopropane carboxylic acid analogues **2** in up to 83% yield. Esterification[16] of acids **2** in EtOH and then treatment of the resulting products **3** with $TsNHNH_2$ gave the desired *N*-tosylhydrazones **4**. Condensa-

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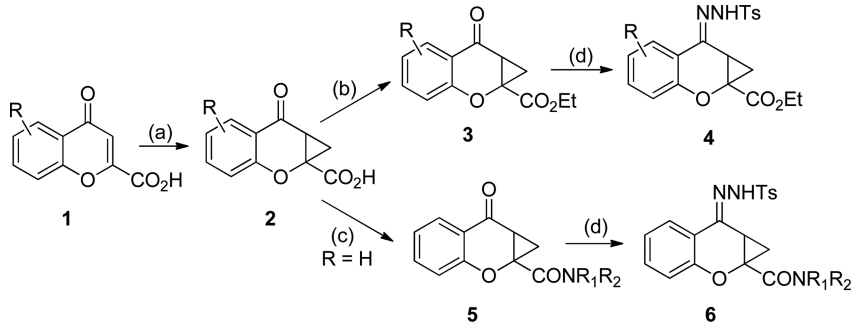
Scheme 2. Synthetic Routes to *N*-Tosylhydrazones 4 and 6[a]

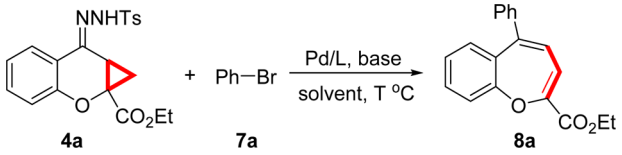


[a]Reaction conditions: (a) Me_3SOI, NaH, DMF, 0 °C to RT, 19 h; (b) PPh_3, CCl_4, NEt_3, EtOH, 0 to 100 °C; (c) R^1R^2NH, HATU, DMF, RT; (d) $TsNHNH_2$, MeOH, 65 °C.

tion of carboxylic acids **2** with amines using 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluranium hexafluorophosphate (HATU) coupling conditions afforded the corresponding amide analogues **5**,[15a] which were converted to *N*-tosylhydrazones **6** in good yields. Unfortunately, *N*-tosylhydrazones bearing an electron-donating group at the 2-position could not be prepared from their corresponding 2,3-methanochromanones. The D−A-substituted cyclopropanes in these 2,3-methanochromanones easily underwent ring opening to form 1,3-zwitterionic intermediates, which were trapped by MeOH as the nucleophile.[17]

The initial studies were carried out by using *N*-tosylhydrazone **4a** and bromobenzene (**7a**) as the substrates in the presence of $Pd_2(dba)_3$ (2.5 mol %), Xphos (5 mol %), and ^{t}BuOLi (2 equiv) in 1,4-dioxane at 80 °C. These are the optimized conditions for our previous reaction between cyclopropyl *N*-tosylhydrazones and aryl halides. To our disappointment, no ring-opening product was detected under such conditions (Table 1, entry 1). Increasing the catalyst loading or the temperature had no effect on the outcome of the reaction. Switching the base from ^{t}BuOLi to the stronger base ^{t}BuOK led to the desired benzoxepine **8a** in 15% yield (Table 1, entry 2). Further inspection of the conditions revealed that carbonates, including Na_2CO_3, K_2CO_3, and Cs_2CO_3, could remarkably improve the yield of **8a**, and among them, Cs_2CO_3 gave the best result (Table 1, entries 3−5). In our previous work, only $Pd_2(dba)_3$ catalyst with Xphos as the ligand could smoothly promote both the migratory insertion and *β*-carbon elimination processes. However, it was observed that the combination of $Pd_2(dba)_3$ with P(2-furyl)$_3$ or PCy_3, Pd$(PPh_3)_2Cl_2$, and Pd$(PPh_3)_4$ were all effective catalytic systems for present reaction (Table 1, entries 6−9). Other solvents, such as DMF, MeCN, and toluene, were screened and gave lower yields than 1,4-dioxane (Table 1, entries 10−12).

Table 1. Pd-Catalyzed Cross-Coupling of *N*-Tosylhydrazone 4a and bromobenzene (7a)[a]



entry	Pd/L	base	solvent	yield[b]
1	$Pd_2(dba)_3$/Xphos	^{t}BuOLi	1,4-dioxane	N.D.
2	$Pd_2(dba)_3$/Xphos	^{t}BuOK	1,4-dioxane	11%
3	$Pd_2(dba)_3$/Xphos	Cs_2CO_3	1,4-dioxane	82%
4	$Pd_2(dba)_3$/Xphos	K_2CO_3	1,4-dioxane	50%
5	$Pd_2(dba)_3$/Xphos	Na_2CO_3	1,4-dioxane	46%
6	$Pd_2(dba)_3$/P(2-furyl)$_3$	Cs_2CO_3	1,4-dioxane	41%
7	$Pd_2(dba)_3$/PCy_3	Cs_2CO_3	1,4-dioxane	75%
8	$Pd(PPh_3)_4$	Cs_2CO_3	1,4-dioxane	56%
9	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	1,4-dioxane	73%
10	$Pd_2(dba)_3$/Xphos	Cs_2CO_3	DMF	50%
11	$Pd_2(dba)_3$/Xphos	Cs_2CO_3	MeCN	41%
12	$Pd_2(dba)_3$/Xphos	Cs_2CO_3	toluene	67%

[a]Reaction conditions: **4a** (0.2 mmol), **7a** (0.4 mmol), palladium (5 mol %), ligand (10 mol %), base (2 equiv), solvent (2 mL), Ar, 100 °C. [b]NMR yields obtained using mesitylene as the internal standard.

With the optimized conditions in hand (Table 1, entry 3), an investigation of the scope and limitations of this ring-expansion reaction was performed. First, we examined the generality of the reaction by employing *N*-tosylhydrazone **4a** for the coupling with a variety of aryl halides. As shown in Table 2, both iodobenzene (**7a′**) and pseudohalide **7a″** worked well under the present reaction conditions to afford 5-phenylbenzoxepine **8a** in 73% and 58% yield, respectively (Table 2, entries 2 and 3). Bromobenzenes with a methyl group at the *para*, *meta*, or *ortho* position reacted with **4a** smoothly to give the corresponding benzoxepines **8b−d** in good yields (Table 2, entries 4−6). The reaction tolerated various functional groups such as methoxy, dioxymethylene, chloro, trifluoromethyl, and acetyl groups (Table 2, entries 7−11). Besides, 1-bromonaphthalene was also suitable for the reaction, yielding the desired product **8j** in 80% yield (Table 2, entry 12). We were pleased to find that 3-bromothiophene smoothly reacted with *N*-tosylhydrazone **4a** to give heterocyclic-substituted benzoxepine **8k** in 75% yield (Table 2, entry 13).

Next, 4-iodotoluene (**7b′**) was chosen as the coupling partner, and its reaction with various *N*-tosylhydrazones **4** or **6** was examined. As shown in Table 3, the reaction was found to be not significantly affected by the substituent on the aromatic ring of *N*-tosylhydrazones **4**, as benzoxepines **8l** and **8m** were isolated in yields of 67% and 71%, respectively (Table 3, entries 1 and 2). When the electron-withdrawing group at the 2-position of the *N*-tosylhydrazone was switched from the ester to an amide, the reaction led to the desired ring-expansion products **8n−p** in moderate to good yields (Table 3, entries 3−5). Notably, the oximes derived from 2,3-methanochromanones **5a−c** have been extensively explored as effective treatments for Parkinson's disease.[15] Therefore, the present reaction provides a method for the development of new medications based on these known therapeutic reagents.

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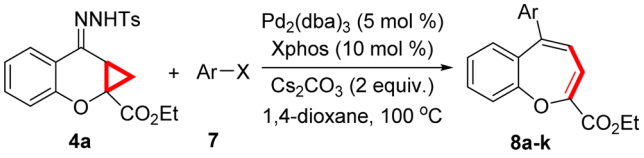
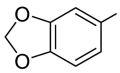
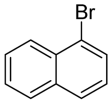
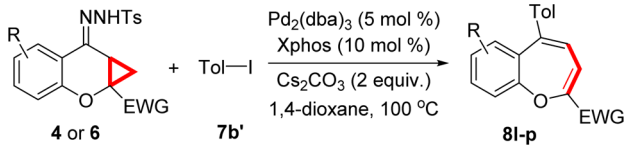
Table 2. Pd-Catalyzed Cross-Coupling of *N*-Tosylhydrazone 4a with Various Aryl Halides[a]

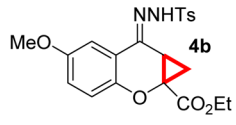
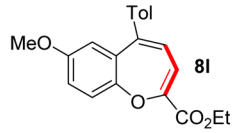
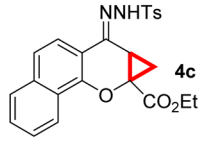
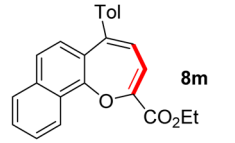
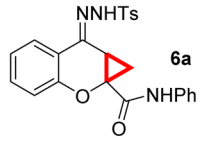
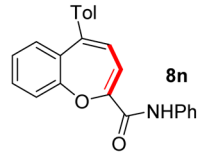
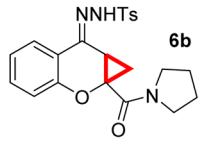
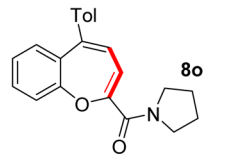
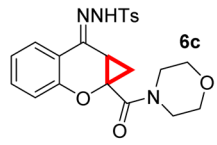
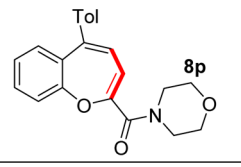


entry	halide **7**	product **8**	yield[b]
1	X = Br (**7a**)		66%
2	Ph−X X = I (**7a'**)	**8a**	73%
3	X = OTf (**7a''**)		58%
4	*p*-MeC_6H_4Br (**7b**)	**8b**	70%
5	*m*-MeC_6H_4Br (**7c**)	**8c**	71%
6	*o*-MeC_6H_4Br (**7d**)	**8d**	80%
7	*p*-$MeOC_6H_4Br$ (**7e**)	**8e**	71%
8	 (**7f**)	**8f**	66%
9	*p*-ClC_6H_4Br (**7g**)	**8g**	73%
10	*p*-$CF_3C_6H_4Br$ (**7h**)	**8h**	63%
11	*p*-AcC_6H_4Br (**7i**)	**8i**	47%
12	 (**7j**)	**8j**	80%
13	 (**7k**)	**8k**	75%

[a]Reaction conditions: *N*-tosylhydrazone **4a** (0.2 mmol), aryl halide (0.4 mmol), $Pd_2(dba)_3$ (5 mol %), Xphos (10 mol %), Cs_2CO_3 (2 equiv), 1,4-dioxane (2 mL), Ar, 100 °C. [b]Isolated yields.

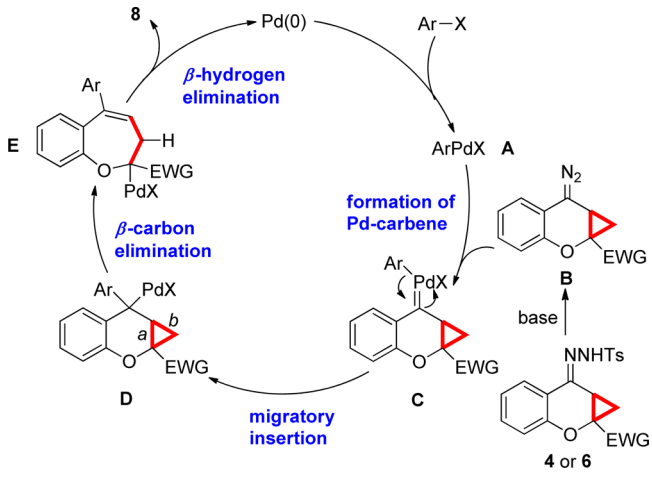
Table 3. Pd-Catalyzed Cross-Coupling of 4-Iodotoluene with Various *N*-Tosylhydrazones[a]



entry	*N*-tosylhydrazone	product	yield[b]
1	 **4b**	 **8l**	67%
2	 **4c**	 **8m**	71%
3	 **6a**	 **8n**	45%
4	 **6b**	 **8o**	70%
5	 **6c**	 **8p**	61%

[a]Reaction conditions: *N*-tosylhydrazone **4** or **6** (0.2 mmol), **7b′** (0.4 mmol), $Pd_2(dba)_3$ (5 mol %), Xphos (10 mol %), Cs_2CO_3 (2 equiv), 1,4-dioxane (2 mL), Ar, 100 °C. [b]Isolated yields.

Scheme 3. Proposed Reaction Mechanism



EXPERIMENTAL SECTION

General. Except for the syntheses of the starting materials, all of the reactions were performed under an argon atmosphere in a 10 mL microwave tube. 1,4-Dioxane was dried over CaH_2 before use. For chromatography, 200−300 mesh silica gel was employed. ^1H and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 on a 400 MHz NMR spectrometer. Chemical shifts (δ) are given in parts per million

A plausible mechanism for this Pd-catalyzed cross-coupling reaction of *N*-tosylhydrazones and aryl halides is proposed in Scheme 3. Oxidative addition of the aryl halide to Pd(0) gives Pd(II) complex **A**. Diazo compound **B** is generated in situ from the *N*-tosylhydrazone in the presence of Cs_2CO_3. Decomposition of diazo compound **B** by Pd(II) complex **A** affords Pd carbene intermediate **C**. Migratory insertion of the aryl group into the Pd carbene forms the bicyclic cyclopropyl carbinyl palladium species **D**. Regioselective cleavage of C−C bond ***a*** through β-carbon elimination leads to intermediate **E**, which undergoes β-H elimination to deliver benzoxepine **8** and regenerate the palladium catalyst to finish the catalytic cycle.

In conclusion, we have developed a novel method for the synthesis of benzoxepines through Pd-catalyzed cross-coupling of aryl halides with oxabicyclo[4.1.0]heptyl *N*-tosylhydrazones. The reaction further demonstrates the synthetic application of cyclopropyl carbinyl palladium species, which are formed via migratory insertion into the Pd carbene as the characteristic step. Various benzoxepines were constructed by the regioselective ring expansion concomitant with the introduction of an aryl group at their 5-position, which should be significant for drug discovery.

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referenced to the residual proton resonance of $CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.49 ppm) and the carbon resonance of $CDCl_3$ (77.16 ppm) or DMSO-d_6 (39.6 ppm), respectively. Coupling constants (J) are given in hertz. The abbreviations m, q, t, d, and s refer to multiplet, quartet, triplet, doublet, and singlet, respectively. Exact masses (HRMS) were recorded on a high-resolution magnetic mass spectrometer using electron impact ionization techniques. IR spectra are reported in wavenumbers (cm^{-1}). Melting points were measured with a heating speed of 3 °C/min. Unless otherwise noted, materials obtained from commercial suppliers were used without further purification.

Experimental Procedure for the Synthesis of *N*-Tosylhydrazones 4: Synthesis of 4a. To a solution of trimethylsulfoxonium iodide (1.69 g, 7.5 mmol) in DMF (10 mL) was added NaOH (0.4 g, 10 mmol) and chromone-2-carboxylic acid (**1a**) (0.95 g, 5 mmol). The reaction mixture was stirred at room temperature for 3 h. The reaction was then quenched with 1 N HCl, and the resulting mixture was extracted with EtOAc. The combined organic layers were concentrated to afford **2a** as an orange solid (0.84 g, 83%).

The resulting acid **2a** (408 mg, 2 mmol) was treated with a solution of PPh_3 (1.48 g, 4 mmol), Et_3N (300 mg, 3 mmol), and CCl_4 (10 mL) at 0 °C for 10 min, and then EtOH (184 mg, 4 mmol) dissolved in CCl_4 (5 mL) was added. The mixture was then stirred at 100 °C for an additional 3 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure, and the residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 10:1) to get the pure target ester **3a** (380 mg, 82%).

A solution of $TsNHNH_2$ (186 mg, 1 mmol) in methanol (1 mL) was stirred and heated to 65 °C until $TsNHNH_2$ was completely dissolved. Then ester **3a** (232 mg, 1 mmol) was added to the solution. After completion of the reaction as monitored by TLC, the crude product was obtained as a precipitate, which was washed with petroleum ether and then dried in vacuo to afford ethyl 7-(2-tosylhydrazono)-7,7a-dihydrocyclopropa[*b*]chromene-1a(1*H*)-carboxylate (**4a**) (368 mg, 92%) as a white solid. Mp 186−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 8.1 Hz, 2H), 7.31−7.26 (m, 1H), 7.01−6.92 (m, 2H), 4.26 (q, J = 7.1 Hz, 2H), 2.83−2.70 (m, J = 7.3 Hz, 1H), 2.42 (s, 3H), 2.04 (dd, J = 10.4, 6.0 Hz, 1H), 1.34 (t, J = 6.6 Hz, 1H), 1.29 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 152.3, 146.6, 144.5, 135.2, 132.4, 129.8, 128.3, 125.2, 122.4, 117.8, 115.6, 62.5, 61.2, 21.8, 21.4, 16.5, 14.2; EI-MS m/z (relative intensity) 400 (M^+, 3), 245 (25), 187 (54), 159 (43), 115 (100), 91 (78), 66 (45); HRMS (EI) calcd for $C_{20}H_{20}O_5N_2S_1$ $[M]^+$ 400.1087, found 400.1084.

*Ethyl 4-Methoxy-7-(2-tosylhydrazono)-7,7a-dihydrocyclopropa-[b]chromene-1a(1H)-carboxylate (**4b**).* Following the typical procedure above, **4b** (390 mg, 55% yield from **1b**) was obtained as a white solid. Mp 203−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.7 Hz, 2H), 7.77−7.64 (m, 2H), 7.34 (d, J = 7.8 Hz, 2H), 6.55 (d, J = 8.6 Hz, 1H), 6.47 (s, 1H), 4.29 (q, J = 7.0 Hz, 2H), 3.78 (s, 3H), 2.79−2.67 (m, 1H), 2.43 (s, 3H), 2.03 (dd, J = 10.1, 6.1 Hz, 1H), 1.35−1.29 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 163.4, 153.8, 148.0, 144.4, 135.3, 129.8, 128.4, 126.5, 111.0, 108.3, 101.1, 62.6, 61.5, 55.7, 21.8, 21.3, 16.8, 14.3; EI-MS m/z (relative intensity) 430 (M^+, 4), 275 (21), 246 (44), 218 (50), 174 (100), 159 (26), 91 (54); HRMS (EI) calcd for $C_{21}H_{22}O_6N_2S_1$ $[M]^+$ 430.1193, found 430.1189.

*Ethyl 7-(2-Tosylhydrazono)-7a,8-dihydrobenzo[h]cyclopropa[b]-chromene-8a(7H)-carboxylate (**4c**).* Following the typical procedure above, **4c** (420 mg, 57% yield from **1c**) was obtained as a white solid. Mp 209−210 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 7.6 Hz, 1H), 7.97 (d, J = 7.7 Hz, 2H), 7.84 (d, J = 8.7 Hz, 1H), 7.79 (s, 1H), 7.75 (d, J = 7.5 Hz, 1H), 7.59−7.47 (m, 2H), 7.40 (d, J = 8.8 Hz, 1H), 7.36 (d, J = 7.8 Hz, 2H), 4.33 (q, J = 7.0 Hz, 2H), 2.82−2.68 (m, 1H), 2.43 (s, 3H), 2.13 (dd, J = 10.1, 5.9 Hz, 1H), 1.41−1.34 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 148.8, 147.1, 144.5, 135.7, 135.3, 129.8, 128.4, 128.3, 127.7, 126.5, 124.7, 122.8, 122.0, 121.2, 109.7, 100.2, 62.6, 61.4, 21.8, 20.9, 16.8, 14.4; EI-MS m/z (relative intensity) 450 (M^+, 5), 266 (28), 238 (16), 209 (54), 165 (100), 150 (20), 139 (70), 91 (37); HRMS (EI) calcd for $C_{24}H_{22}O_5N_2S_1$ $[M]^+$ 450.1244, found 450.1243.

Experimental Procedure for the Synthesis of *N*-Tosylhydrazones 6: Synthesis of 6a. Acid **2a** (408 mg, 2 mmol) was dissolved in DMF (10 mL), and then 2-(1*H*-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) (836 mg, 2.2 mmol) and aniline (223.2 mg, 2.4 mmol) were added. The reaction mixture was stirred at room temperature overnight. The mixture was diluted with H_2O and extracted with EtOAc. The combined organic extracts were washed with H_2O and 1 N HCl and then dried over $MgSO_4$. The volatile compounds were removed in vacuo, and the residue was purified by flash column chromatography (SiO_2, petroleum ether/ethyl acetate = 5:1) to give amide **5a** (390 mg, 70%).

A solution of $TsNHNH_2$ (186 mg, 1 mmol) in methanol (1 mL) was stirred and heated to 65 °C until the $TsNHNH_2$ was completely dissolved. Then amide **5a** (279 mg, 1 mmol) was added to the solution. After completion of the reaction as monitored by TLC, the crude product was obtained as a precipitate, which was washed with petroleum ether and dried in vacuo to afford *N*-phenyl-7-(2-tosylhydrazono)-7,7a-dihydrocyclopropa[*b*]chromene-1a(1*H*)-carboxamide (**6a**) (406 mg, 91%) as a white solid. Mp 255−257 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 10.10 (s, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.73−7.60 (m, 3H), 7.41 (d, J = 7.9 Hz, 3H), 7.34 (t, J = 7.8 Hz, 2H), 7.19−7.09 (m, 2H), 7.04 (t, J = 7.5 Hz, 1H), 2.91 (dd, J = 10.5, 7.0 Hz, 1H), 2.36 (s, 3H), 1.98 (dd, J = 10.6, 6.0 Hz, 1H), 1.43 (t, J = 6.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 166.3, 151.6, 146.1, 143.5, 137.9, 136.1, 131.9, 129.6, 128.6, 127.7, 124.4, 122.4, 121.1, 118.2, 115.9, 63.1, 21.4, 21.1, 15.0; EI-MS m/z (relative intensity) 447 (M^+, 4), 262 (30), 220 (34), 171 (24), 131 (30), 115 (100), 91 (61), 65 (60); HRMS (EI) calcd for $C_{24}H_{21}O_4N_3S_1$ $[M]^+$ 447.1247, found 447.1246.

*4-Methyl-N′-(1a-(pyrrolidine-1-carbonyl)-1a,7a-dihydrocyclopropa[b]chromen-7(1H)-ylidene)benzenesulfonohydrazide (**6b**).* Following the typical procedure above, **6b** (400 mg, 51% yield from **2a**) was obtained as a white solid. Mp 204−206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.96 (s, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.64 (d, J = 7.9 Hz, 1H), 7.42 (d, J = 8.1 Hz, 2H), 7.39−7.31 (m, 1H), 7.05−6.91 (m, 2H), 3.67−3.56 (m, 1H), 3.50−3.41 (m, 1H), 3.36 (d, J = 6.9 Hz, 2H), 2.72 (dd, J = 10.7, 6.8 Hz, 1H), 2.37 (s, 3H), 1.90 (dd, J = 10.7, 6.2 Hz, 1H), 1.87−1.69 (m, 4H), 1.28 (t, J = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 164.6, 151.5, 146.0, 143.5, 136.1, 132.2, 129.6, 127.7, 124.58, 122.3, 117.5, 115.8, 64.3, 47.1, 26.0, 23.4, 21.1, 19.5, 13.8; EI-MS m/z (relative intensity) 426 ($[M + 1]^+$, 3), 270 (5), 240 (14), 198 (21), 144 (64), 115 (77), 98 (100), 70 (44); HRMS (EI) calcd for $C_{22}H_{24}O_4N_3S_1$ $[M + H]^+$ 426.1482, found 426.1479.

*(E)-4-Methyl-N′-(1a-(morpholine-4-carbonyl)-1a,7a-dihydrocyclopropa[b]chromen-7(1H)-ylidene)benzenesulfonohydrazide (**6c**).* Following the typical procedure above, **6c** (420 mg, 63% yield from **2a**) was obtained as a white solid. Mp 195−196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.98 (s, 1H), 7.82 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 8.1 Hz, 2H), 7.37−7.32 (m, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.94 (d, J = 8.3 Hz, 1H), 3.66−3.44 (m, 8H), 2.80 (dd, J = 10.7, 6.8 Hz, 1H), 2.37 (s, 3H), 1.83 (dd, J = 10.7, 6.7 Hz, 1H), 1.36 (t, J = 6.7 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 164.4, 151.2, 145.9, 143.6, 136.1, 132.3, 129.7, 127.7, 124.6, 122.6, 117.7, 116.0, 66.0, 63.8, 21.1, 18.2, 13.4; EI-MS m/z (relative intensity) 442 ($[M + 1]^+$, 2), 257 (21), 172 (36), 144 (59), 115 (100), 91 (64), 70 (63); HRMS (EI) calcd for $C_{22}H_{24}O_5N_3S_1$ $[M + H]^+$ 442.1431, found 442.1427.

Typical Procedure for Pd-Catalyzed Cross-Coupling of *N*-Tosylhydrazones with Aryl Halides: Cross-Coupling of 4a with 7a. $Pd_2(dba)_3$ (9 mg, 5 mol %), Xphos (9.5 mg, 10 mol %), Cs_2CO_3 (130 mg, 0.4 mmol), and *N*-tosylhydrazone **4a** (80 mg, 0.2 mmol) were suspended in dry 1,4-dioxane (2 mL) in a 10 mL microwave tube under argon. Bromobenzene (**7a**) (62.5 mg, 0.4 mmol) was then added via a syringe. The resulting solution was stirred at 100 °C for 12 h. After cooling to room temperature, the mixture was filtered through a short path of silica gel, eluting with ethyl acetate. The volatile compounds were removed in vacuo, and the crude residue was purified

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J. Org. Chem. 2016, 81, 2128−2134

by column chromatography (SiO_2, petroleum ether/EtOAc = 60:1) to give pure ethyl 5-phenylbenzo[*b*]oxepine-2-carboxylate (**8a**) as a light-yellow oil (38 mg, 66%). R_f = 0.4 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3033, 2983, 2220, 1734, 1638, 1625, 1496, 1446, 1314, 1177, 1156, 1023, 757, 691; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.6 Hz, 1H), 7.52−7.45 (m, 2H), 7.36−7.30 (m, 4H), 7.17 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 8.1 Hz, 1H), 5.66 (d, J = 2.2 Hz, 1H), 4.75 (d, J = 2.2 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 155.8, 150.9, 133.7, 131.7, 129.8, 128.5, 128.4, 124.9, 123.3, 120.6, 116.5, 102.3, 94.7, 84.7, 61.8, 14.3; EI-MS m/z (relative intensity) 292 (M^+, 16), 263 (40), 247 (30), 235 (50), 218 (89), 191 (100), 176 (47), 165 (63), 115 (24); HRMS (EI) calcd for $C_{19}H_{16}O_3$ $[M]^+$ 292.1094, found 292.1091.

*Ethyl 5-(p-Tolyl)benzo[b]oxepine-2-carboxylate (**8b**).* Light-yellow oil (43 mg, 70%); R_f = 0.5 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3057, 2982, 2219, 1734, 1625, 1599, 1484, 1446, 1315, 1218, 1156, 1022, 818, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 7.1 Hz, 1H), 7.18−7.11 (m, 3H), 7.08 (d, J = 8.0 Hz, 1H), 5.65 (d, J = 2.2 Hz, 1H), 4.73 (d, J = 2.2 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.35 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 155.6, 150.9, 138.6, 133.6, 131.6, 129.6, 129.1, 124.8, 120.6, 120.2, 116.7, 102.1, 94.9, 84.0, 61.7, 21.6, 14.3; EI-MS m/z (relative intensity) 306 (M^+, 9), 277 (14), 218 (41), 187 (55), 159 (43), 115 (100), 101 (48), 89 (40), 63 (23); HRMS (EI) calcd for $C_{20}H_{18}O_3$ $[M]^+$ 306.1250, found 306.1249.

*Ethyl 5-(m-Tolyl)benzo[b]oxepine-2-carboxylate (**8c**).* Light-yellow oil (43 mg, 71%); R_f = 0.5 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3056, 2981, 2211, 1735, 1625, 1599, 1492, 1447, 1314, 1224, 1177, 1155, 1023, 785, 756, 691; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.7 Hz, 1H), 7.36−7.24 (m, 3H), 7.24−7.11 (m, 3H), 7.08 (d, J = 8.1 Hz, 1H), 5.66 (d, J = 2.1 Hz, 1H), 4.74 (d, J = 2.1 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 155.7, 150.9, 138.0, 133.7, 132.3, 129.7, 129.4, 128.8, 128.3, 124.9, 123.1, 120.6, 116.6, 102.2, 94.9, 84.3, 61.7, 21.3, 14.3; EI-MS m/z (relative intensity) 306 (M^+, 16), 277 (32), 249 (50), 218 (100), 205 (44), 178 (39), 119 (65), 91 (28); HRMS (EI) calcd for $C_{20}H_{18}O_3$ $[M]^+$ 306.1250, found 306.1247.

*Ethyl 5-(o-Tolyl)benzo[b]oxepine-2-carboxylate (**8d**).* Light-yellow oil (49 mg, 80%); R_f = 0.5 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3061, 2981, 2217, 1734, 1627, 1599, 1494, 1448, 1315, 1226, 1177, 1156, 1023, 757; ^1H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.37−7.30 (m, 1H), 7.24−7.12 (m, 4H), 7.08 (d, J = 8.1 Hz, 1H), 5.64 (d, J = 2.1 Hz, 1H), 4.72 (d, J = 2.2 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 2.46 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 155.3, 150.9, 140.4, 133.7, 132.0, 129.8, 129.5, 128.6, 125.6, 124.9, 120.7, 117.0, 101.9, 93.5, 88.5, 61.8, 20.8, 14.3; EI-MS m/z (relative intensity) 306 (M^+, 10), 277 (17), 259 (15), 233 (96), 218 (100), 189 (47), 178 (40), 165 (16), 115 (13); HRMS (EI) calcd for $C_{20}H_{18}O_3$ $[M]^+$ 306.1250, found 306.1249.

*Ethyl 5-(4-Methoxyphenyl)benzo[b]oxepine-2-carboxylate (**8e**).* Light-yellow oil (46 mg, 71%); R_f = 0.3 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3071, 2981, 2838, 2218, 1734, 1625, 1607, 1512, 1315, 1250, 1177, 1157, 833, 757; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.34−7.27 (m, 1H), 7.18−7.11 (m, 1H), 7.07 (d, J = 8.1 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 5.65 (d, J = 2.2 Hz, 1H), 4.73 (d, J = 2.2 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 159.9, 155.5, 151.0, 133.5, 133.2, 129.4, 124.9, 120.7, 116.9, 115.4, 114.1, 102.1, 94.8, 83.4, 61.8, 55.4, 14.3; EI-MS m/z (relative intensity) 322 (M^+, 14), 293 (15), 277 (33), 249 (65), 205 (100), 178 (48), 152 (42), 119 (27), 74 (17); HRMS (EI) calcd for $C_{20}H_{18}O_4$ $[M]^+$ 322.1200, found 322.1194.

*Ethyl 5-(Benzo[d][1,3]dioxol-5-yl)benzo[b]oxepine-2-carboxylate (**8f**).* Light-yellow oil (44 mg, 66%); R_f = 0.3 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3073, 2981, 2904, 2212, 1733, 1638, 1601, 1497, 1479, 1446, 1235, 863, 837, 759; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.20−7.13 (m, 1H), 7.07 (d, J = 7.9 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 1.2 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 5.97 (s, 2H), 5.65 (d, J = 2.2 Hz, 1H), 4.72 (d, J = 2.2 Hz, 1H), 4.32 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 155.6, 150.9, 148.1, 147.5, 133.5, 129.6, 126.4, 124.9, 120.7, 116.6, 116.6, 111.7, 108.6, 102.2, 101.4, 94.7, 83.2, 61.8, 14.3; EI-MS m/z (relative intensity) 336 (M^+, 8), 279 (4), 263 (5), 233 (9), 205 (14), 149 (100), 104 (5), 74 (5); HRMS (EI) calcd for $C_{20}H_{16}O_5$ $[M]^+$ 336.0992, found 336.0991.

*Ethyl 5-(4-Chlorophenyl)benzo[b]oxepine-2-carboxylate (**8g**).* Light-yellow oil (47 mg, 73%); R_f = 0.5 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3059, 2983, 2222, 1734, 1639, 1572, 1495, 1446, 1264, 829, 760, 710; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 8.5 Hz, 2H), 7.37−7.27 (m, 3H), 7.16 (t, J = 7.1 Hz, 1H), 7.07 (d, J = 8.1 Hz, 1H), 5.67 (d, J = 2.3 Hz, 1H), 4.77 (d, J = 2.2 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 155.8, 150.8, 134.5, 133.6, 132.9, 130.0, 128.7, 124.8, 121.8, 120.4, 116.1, 102.7, 93.5, 85.7, 61.8, 14.3; EI-MS m/z (relative intensity) 328 (M^+, ^{37}Cl, 2), 326 (M^+, ^{35}Cl, 6), 297 (15), 269 (18), 234 (37), 218 (100), 189 (64), 176 (19), 163 (20); HRMS (EI) calcd for $C_{19}H_{15}O_3Cl$ [M^+, ^{35}Cl 100] 326.0704, found 326.0698, [M^+, ^{37}Cl 37.9] 328.0675, found 328.0677.

*Ethyl 5-(4-(Trifluoromethyl)phenyl)benzo[b]oxepine-2-carboxylate (**8h**).* Light-yellow oil (45 mg, 63%); R_f = 0.5 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3072, 2983, 2933, 2223, 1735, 1639, 1617, 1484, 1324, 1169, 1127, 1066, 843, 756; ^1H NMR (400 MHz, $CDCl_3$) δ 7.63−7.53 (m, 5H), 7.39−7.33 (m, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 5.69 (d, J = 2.2 Hz, 1H), 4.80 (d, J = 2.2 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 156.1, 150.7, 133.8, 132.6, 130.4, 130.3 (q, J = 293.3 Hz), 125.3 (q, J = 4.0 Hz), 124.8, 120.4, 115.6, 103.0, 93.1, 87.1, 61.8, 14.3; EI-MS m/z (relative intensity) 360 (M^+, 29), 331 (27), 303 (48), 286 (55), 218 (100), 189 (60), 176 (25), 149 (31); HRMS (EI) calcd for $C_{20}H_{15}O_3F_3$ $[M]^+$ 360.0968, found 360.0973.

*Ethyl 5-(4-Acetylphenyl)benzo[b]oxepine-2-carboxylate (**8i**).* Light-yellow oil (31 mg, 47%); R_f = 0.5 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3060, 2983, 2932, 2219, 1733, 1684, 1639, 1600, 1483, 1446, 1314, 1264, 839, 762; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.6 Hz, 2H), 7.61−7.52 (m, 3H), 7.36 (t, J = 7.8 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.08 (d, J = 8.2 Hz, 1H), 5.69 (d, J = 2.2 Hz, 1H), 4.80 (d, J = 2.2 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.61 (s, 3H), 1.31 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 162.6, 156.0, 150.8, 136.4, 133.8, 131.8, 130.4, 128.3, 128.2, 124.8, 120.4, 115.8, 103.0, 93.7, 88.1, 61.8, 26.8, 14.3; EI-MS m/z (relative intensity) 334 (M^+, 11), 305 (23), 291 (26), 235 (29), 218 (75), 189 (100), 176 (21), 163 (41), 73 (20); HRMS (EI) calcd for $C_{21}H_{18}O_4$ $[M]^+$ 334.1200, found 334.1198.

*Ethyl 5-(Naphthalen-1-yl)benzo[b]oxepine-2-carboxylate (**8j**).* Light-yellow oil (55 mg, 80%); R_f = 0.4 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3057, 2982, 2213, 1734, 1624, 1599, 1487, 1446, 1176, 1155, 1022, 773, 754; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (d, J = 8.2 Hz, 1H), 7.84 (t, J = 6.9 Hz, 2H), 7.73 (d, J = 7.1 Hz, 1H), 7.71−7.65 (m, 1H), 7.60−7.49 (m, 2H), 7.47−7.41 (m, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 8.2 Hz, 1H), 5.71 (d, J = 2.2 Hz, 1H), 4.82 (d, J = 2.2 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 155.6, 151.0, 133.7, 133.4, 133.3, 130.5, 130.0, 129.0, 128.3, 127.0, 126.5, 125.3, 125.0, 121.0, 120.6, 116.8, 102.3, 92.8, 89.6, 61.8, 14.2; EI-MS m/z (relative intensity) 342 (M^+, 8), 295 (13), 269 (30), 239 (48), 187 (39), 149 (58), 115 (100), 91 (54), 77 (34); HRMS (EI) calcd for $C_{23}H_{18}O_3$ $[M]^+$ 342.1250, found 342.1248.

*Ethyl 5-(Thiophen-3-yl)benzo[b]oxepine-2-carboxylate (**8k**).* Light-yellow oil (45 mg, 75%); R_f = 0.5 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3109, 2982, 2215, 1733, 1625, 1573, 1483, 1446, 1314, 1176, 1156, 1022, 868, 785, 753; ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 7.6 Hz, 1H), 7.49 (d, J = 1.9 Hz, 1H), 7.35−7.29 (m, 1H), 7.29−7.25 (m, 1H), 7.19−7.11 (m, 2H), 7.07 (d, J = 8.1 Hz, 1H), 5.67 (d, J = 1.9 Hz, 1H), 4.76 (d, J = 1.9 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 155.8, 150.9, 133.6, 129.97, 129.72, 129.0, 125.4, 124.8, 122.4, 120.5, 116.4, 102.7, 89.8, 84.2, 61.8, 14.3; EI-MS m/z (relative intensity) 298 (M^+, 10), 269 (25), 253 (20), 241 (55), 225 (43), 197

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J. Org. Chem. 2016, 81, 2128−2134

(100), 181 (21), 171 (28), 149 (59); HRMS (EI) calcd for $C_{17}H_{14}O_3S_1$ $[M]^+$ 298.0658, found 298.0663.

*Ethyl 7-Methoxy-5-(p-tolyl)benzo[b]oxepine-2-carboxylate (**8l**).* Light-yellow oil (45 mg, 67%); R_f = 0.3 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 2980, 2962, 2840, 2215, 1734, 1630, 1610, 1516, 1316, 1293, 1238, 1163, 1029, 817, 796; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 8.5 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 7.9 Hz, 2H), 6.71 (d, J = 8.6 Hz, 1H), 6.64 (d, J = 2.3 Hz, 1H), 5.67 (d, J = 2.1 Hz, 1H), 4.78 (d, J = 2.1 Hz, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 2.34 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 160.8, 156.8, 150.7, 138.3, 134.3, 131.4, 129.1, 120.5, 110.8, 108.8, 106.6, 102.5, 93.5, 84.0, 61.8, 55.7, 21.6, 14.3; EI-MS m/z (relative intensity) 336 (M^+, 12), 246 (18), 218 (20), 174 (38), 149 (100), 102 (12), 77 (11); HRMS (EI) calcd for $C_{21}H_{20}O_4$ $[M]^+$ 336.1356, found 336.1355.

*Ethyl 5-(p-Tolyl)naphtho[1,2-b]oxepine-2-carboxylate (**8m**).* Light-yellow oil (51 mg, 71%); R_f = 0.6 (petroleum ether/EtOAc = 20:1); IR (KBr, cm^{-1}) 3058, 2981, 2925, 2209, 1736, 1628, 1512, 1465, 1374, 1313, 1258, 1179, 1156, 1022, 817, 748; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06−7.95 (m, 1H), 7.88−7.80 (m, 1H), 7.69 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.54−7.49 (m, 2H), 7.41 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 5.54 (d, J = 2.4 Hz, 1H), 4.44−4.40 (m, 2H), 4.41−4.36 (m, 1H), 2.37 (s, 3H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.7, 151.7, 151.0, 138.8, 134.4, 131.6, 129.2, 128.9, 128.0, 127.3, 127.2, 127.1, 125.4, 122.3, 120.2, 113.5, 99.6, 96.1, 84.6, 61.9, 21.7, 14.4; EI-MS m/z (relative intensity) 356 (M^+, 8), 266 (38), 238 (20), 209 (67), 194 (49), 165 (100), 149 (50), 139 (78), 71 (40); HRMS (EI) calcd for $C_{24}H_{20}O_3$ $[M]^+$ 356.1407, found 356.1409.

*N-Phenyl-5-(p-tolyl)benzo[b]oxepine-2-carboxamide (**8n**).* Light-yellow oil (32 mg, 45%); R_f = 0.3 (petroleum ether/EtOAc = 10:1); IR (KBr, cm^{-1}) 3058, 2922, 2218, 1689, 1641, 1599, 1529, 1443, 1324, 1266, 1209, 1160, 818, 755; ^1H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.61 (d, J = 7.8 Hz, 3H), 7.39 (t, J = 7.8 Hz, 1H), 7.36−7.28 (m, 4H), 7.25 (d, J = 5.8 Hz, 1H), 7.21 (d, J = 8.4 Hz, 1H), 7.13 (t, J = 7.3 Hz, 1H), 7.03 (d, J = 7.7 Hz, 2H), 5.77 (s, 1H), 4.58 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 154.6, 153.2, 139.0, 137.4, 133.7, 131.6, 129.8, 129.3, 129.1, 125.7, 124.7, 121.6 120.2, 120.1, 119.5, 117.2, 98.1, 95.5, 83.5, 21.6; EI-MS m/z (relative intensity) 353 (M^+, 8), 261 (13), 233 (44), 189 (25), 268 (20), 149 (100), 115 (34), 77 (24); HRMS (EI) calcd for $C_{24}H_{19}O_2N$ $[M]^+$ 353.1410, found 353.1412.

*Pyrrolidin-1-yl(5-(p-tolyl)benzo[b]oxepin-2-yl)methanone (**8o**).* Light-yellow oil (46 mg, 70%); R_f = 0.3 (petroleum ether/EtOAc = 5:1); IR (KBr, cm^{-1}) 3057, 2971, 2877, 2218, 1725, 1647, 1625, 1512, 1484, 1441, 1243, 1224, 1099, 818, 767; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.7 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.32 (t, J = 8.5 Hz, 1H), 7.18−7.09 (m, 4H), 5.29 (d, J = 2.2 Hz, 1H), 4.60 (d, J = 2.1 Hz, 1H), 3.84 (t, J = 6.1 Hz, 2H), 3.53 (t, J = 6.5 Hz, 2H), 1.89−1.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.2, 155.2, 138.8, 133.7, 131.5, 129.8, 129.3, 124.5, 120.1, 119.8, 116.0, 99.0, 94.4, 84.5, 48.4, 46.9, 26.6, 23.9, 21.7; EI-MS m/z (relative intensity) 331 (M^+, 15), 262 (10), 233 (17), 218 (16), 149 (100), 98 (15), 55 (12); HRMS (EI) calcd for $C_{22}H_{21}O_2N$ $[M]^+$ 331.1567, found 331.1565.

*Morpholino(5-(p-tolyl)benzo[b]oxepin-2-yl)methanone (**8p**).* Light-yellow oil (42 mg, 61%); R_f = 0.4 (petroleum ether/EtOAc = 5:1); IR (KBr, cm^{-1}) 3057, 2924, 2856, 2219, 1727, 1651, 1512, 1484, 1442, 1265, 1116, 1033, 819, 764; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 7.6 Hz, 1H), 7.37 (d, J = 8.0 Hz, 2H), 7.32 (d, J = 8.1 Hz, 1H), 7.19−7.11 (m, 4H), 5.08 (d, J = 2.3 Hz, 1H), 4.66 (d, J = 2.3 Hz, 1H), 3.86−3.42 (m, 8H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 154.8, 154.2, 139.1, 133.7, 131.4, 130.0, 129.8, 129.4, 129.3, 124.7, 119.8, 116.0, 99.1, 94.2, 84.3, 67.2, 66.8, 47.4, 42.8, 21.7; EI-MS m/z (relative intensity) 347 (M^+, 37), 261 (39), 233 (69), 218 (100), 205 (48), 189 (93), 175 (32), 115 (38), 70 (53); HRMS (EI) calcd for $C_{22}H_{21}O_3N$ $[M]^+$ 347.1516, found 347.1513.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02413.

^1H and ^{13}C NMR spectra of all products (PDF)

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Notes

The authors declare no competing financial interest.

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