Highly Regioselective Palladium-Catalyzed Annulation Reactions of Heteroatom-Substituted Allenes for Synthesis of Condensed Heterocycles

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We have developed a highly regioselective synthesis of heterocycles *via* palladium-catalyzed annulation reaction of heteroatom-substituted allenes. Various aryl halides were reacted and one regioisomer was observed exclusively in all reactions. In addition, subsequent functionalizations of annulated products were carried out using alkyl metal reagents, and the introduction of alkyl moieties was accomplished.

Key words palladium; annulation; allene; heterocycle; alkyl metal reagent

Palladium-catalyzed annulation processes have proved to be extremely useful and powerful methods for the construction of diverse carbocycles and heterocycles.[1—4] Among them, reactions that involve carbopalladation of allenes, which generate π-allylpalladium intermediates, followed by internal nucleophilic attack by a heteroatom or carbanion, are particularly valuable (Fig. 1).[5—16] Larock *et al.* have extensively investigated the palladium-catalyzed annulation reactions of carbon-atom-substituted allenes using functionally substituted aryl iodides or vinyl halides.[13—16] Yields were generally high and most of the reactions are both stereo- and regioselective; however, the reactions sometimes afforded mixtures of regioisomers, especially in six-membered-ring formation.[13,14] Meanwhile, only one example of an annulation reaction of heteroatom-substituted allenes has been reported, and in that case the presence of the heteroatom on allenes and its electronic effect dominated the regioselectivity (Fig. 2).[17] With the aim of regioselectively synthesizing highly functionalized heterocycles, we employed heteroatom-substituted allenes for palladium-catalyzed annulation. We found that various aryl iodides and bromides reacted smoothly and that one regioisomer was produced exclusively both in five- and six-membered-ring formations. Furthermore, in the course of our extensive studies on the synthetic application of annulated products, we also found that alkyl metal reagents reacted unexpectedly in *S*N2′ fashion at the exomethylene carbon of the annulated products obtained by

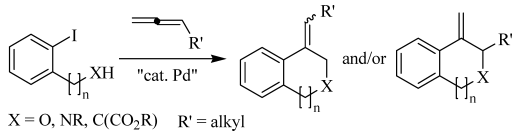

Fig. 1. Palladium-Catalyzed Annulation Reactions of Allenes

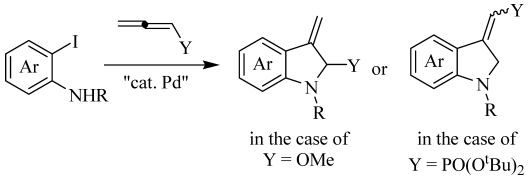

Fig. 2. Effect of Heteroatoms for Regioselectivity

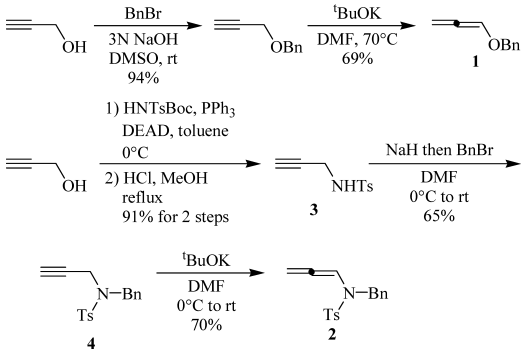

Fig. 3. Synthesis of Allenes (**1**, **2**)

the palladium-catalyzed annulation reaction. Several metal reagents were reactive and an alkyl moiety could be introduced by this process.

Synthesis of Heteroatom-Substituted Allenes Heteroatom-substituted allenes (**1**, **2**) used for the palladium-catalyzed annulation reaction were prepared according to the protocol as follows (Fig. 3).[18—20]

O-Substituted allene **1** was obtained *via* *O*-benzylation of propargyl alcohol followed by treatment with ^{t}BuOK in *N*,*N*-dimethylformamide (DMF) at 70 °C.

N-Substituted allene **2** was synthesized using commercially available *N*-Boc-*N*-tosylamide as a starting material. Mitsunobu reaction of *N*-Boc-*N*-tosylamide with propargyl alcohol, followed by removal of Boc using 3 N HCl in MeOH under reflux, afforded *N*-propargyl-*N*-tosylamide **3** in 91% yield. Benzylation of amide **3** and subsequent isomerization produced the desired allene **2**.

Palladium-Catalyzed Annulation Reactions of Allenes Using Various Aryl Iodides/Bromides (Table 1) With heteroatom-substituted allenes **1** and **2** in hand, we first examined the annulation reaction of them using various aryl iodides.

A variety of reaction conditions have been examined, and the use of an inorganic base, K_2CO_3, and a polar solvent, DMF, has proved to be effective for this process. All reactions were highly regioselective and only one regioisomer was observed.

In annulation of allene **1** using *N*-tosyl-2-iodoaniline as an aryl halide, the reaction proceeded smoothly at 80 °C in the

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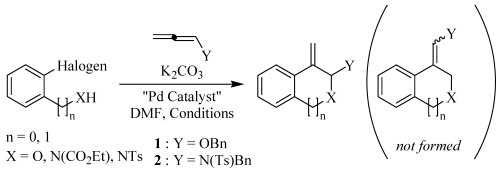
Table 1. Pd-Catalyzed Annulation Reaction of Allenes (**1**, **2**) Using Various Aryl Halides



Entry	Aryl halide	Allene	"Pd catalyst"[a]	Conditions	Product	Yield (%)
1		**1**	A	80 °C, 19 h	 **5**	99
2		**1**	A	80 °C, 1.5 h	 **6**	71
3		**1**	A	120 °C, 1 h	 **7**	75
4		**1**	A	120 °C, 2 h	 **8**	52
5		**1**	B	120 °C, 2 h		86
6		**2**	A	50 °C, 72 h	 **9**	81
7		**2**	A	80 °C, 16 h		65
8		**2**	B	100 °C, 1.5 h		99
9		**2**	A	50 °C, 40 h	**10**	42
10		**2**	B	80 °C, 2 h		62
11		**1**	A	80 °C, 19 h		0
12		**1**	B	120 °C, 2 h		75
13		**1**	A	120 °C, 4 h		54
14		**1**	B	120 °C, 2 h		52
15[b]		**1**	A	120 °C, 5 h		76

Reaction conditions: Aryl halide (1.0 eq), allene **1** or **2** (1.5—4.0 eq), K_2CO_3 (1.5—3.0 eq), $Pd(OAc)_2$ (10 mol%), P(2-Tol)$_3$ (15 mol%) and DMF (5 ml). *a*) "Pd Catalyst": A, $Pd(OAc)_2$; B, $Pd(OAc)_2$/P(2-Tol)$_3$. *b*) Bu_4NBr was added as an additive.

presence of 10 mol% of $Pd(OAc)_2$, and indoline **5** was obtained as the sole product in quantitative yield (entry 1). Similarly, reactions between allene **1** and *N*-ethoxycarbonyl-2-iodoaniline (entry 2) or *N*-tosyl-2-iodobenzylamine (entry 3) yielded the annulated products **6** and **7**, respectively, in good yield. In the case of 2-iodobenzyl alcohol, the addition of phosphine ligand, P(2-Tol)$_3$, improved the yield (entry 4 *vs.* 5) and afforded isochroman **8** in high yield (entry 5).

We also conducted an annulation reaction of *N*-substituted allene **2**. Namely, *N*-tosyl-2-iodoaniline reacted at a temperature as low as 50 °C, and indoline **9** was obtained in 81% yield (entry 6). In the reactions of 2-iodobenzyl alcohol and 2-iodophenol, the best results were obtained using a catalyst system such as $Pd(OAc)_2$/P(2-Tol)$_3$ (entries 8, 10).

Less reactive aryl bromides were also employed for annulation reactions of allene **1**. The reaction of 2-bromobenzyl alcohol did not proceed at all in the absence of phosphine ligand (entry 11). The addition of phosphine ligand, P(2-Tol)$_3$, increased the yield, and the annulated product **8** was obtained in relatively high yield at higher temperature (entry 12). In contrast, in the reaction of *N*-tosyl-2-bromobenzylamine, the addition of phosphine ligand did not increase the yield (entry 13 *vs.* 14). However, the use of tetrabutylammonium salt as an additive resulted in an enhancement in yield and tetrahydroisoquinoline **7** was obtained in 76% yield (entry 15).[22] Here again, the annulation reactions proceeded in a highly regioselective manner and one regioisomer was formed exclusively in all cases.

Regioselectivity of Annulation Reactions These annulation reactions most likely proceed as illustrated below, in a manner similar to that postulated by Larock.[13,15] Thus, the reaction begins with arylpalladium formation, followed by its addition to allene, producing a π-allylpalladium compound which readily undergoes intramolecular nucleophilic attack by an oxygen or nitrogen atom to give the annulated product. Although the nucleophilic attack can occur at the α- or γ-position relative to the heteroatom (Fig. 4), the product *via* α-attack was obtained exclusively in our annulation process, regardless of the bulkiness of the allene substituents. The cause of the selectivity can be considered to be either of the following: (1) the electronegativity of an oxygen or nitrogen atom on the allene makes the α-carbon more electron positive than the γ-position, therefore the nucleophilic attack occurs at the more substituted carbon or (2) the palladium complex has been reductively eliminated with the assistance of the heteroatom, and cyclization proceeds without participation of

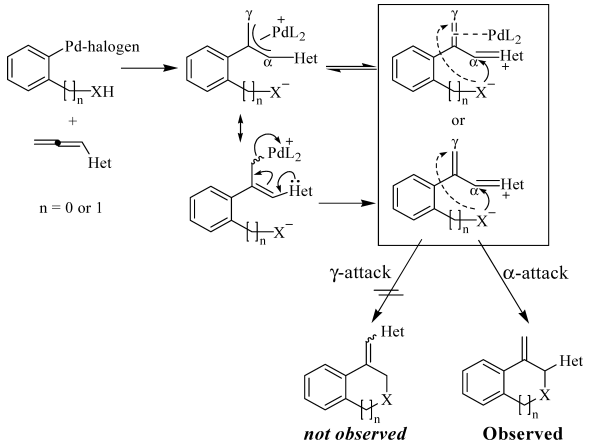
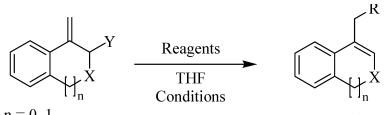


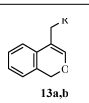
Fig. 4. Plausible Reaction Mechanism for High Regioselectivity

the palladium complex.[23] In such a case, the cyclization mode for α-attack is 5-*exo*-*trig* (for $n=0$) or 6-*exo*-*trig* (for $n=1$), and this may be an another reason for the selectivity. Although we do not have any evidence for the above mechanisms, it seems likely that the electronic effect, but not the steric effect, is the major controlling factor for the observed regioselectivity.[24]

Synthesis of 4-Alkyl-Substitued Condensed Heterocycles (Table 2) When annulated product **8** was treated with alkyllithium reagents such as BuLi and ^{t}BuLi, nucleophilic attack occurred at the exomethylene carbon and the substitution products were obtained in 60% and 87% yield, respectively (entries 1, 3). In the reaction of BuLi, the addition of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) enhanced the yield (91%, entry 2). Also, reactions of **7** and **5** with alkyllithium reagents proceeded in the same manner and substitution products were obtained in moderate to good yield (entries 4, 5, 8—11). Organocuprate, ^{t}BuCu(2-thienyl)CNLi$_2$, was also reactive in the reaction of tetrahydroisoquinoline **7**, and the substitution product was obtained in 83% yield (entry 6). Moreover, magnesium ate complex such as EtMe$_2$MgLi reacted smoothly with **7** and **5**, and substitution products were obtained in high yield (entries 7, 12). Interestingly, aryl metal reagents and alkynyl metal reagents were completely ineffective in this reaction; however, the reason for this as well as detailed reaction mechanism is obscure at present.

Table 2. Reaction of Alkyl Metal Reagents with Annulated Products



Entry	Substrate	Reagents	R	Product	Yield (%)
1		BuLi	Bu		60
2		BuLi+TMEDA	Bu		91
3	**8**	^{t}BuLi	^{t}Bu	**13a,b**	87
4		BuLi+HMPA	Bu		44
5		^{t}BuLi	^{t}Bu		60
6		^{t}BuCu(2-thienyl)CNLi$_2$	^{t}Bu		83
7	**7**	EtMe$_2$MgLi	Et	**14a-c**	79
8		BuLi	Bu		40
9		BuLi+HMPA	Bu		83
10		^{t}BuLi	^{t}Bu		68
11	**5**	^{t}BuLi+HMPA	^{t}Bu	**15a-c**	76
12		EtMe$_2$MgLi	Et		93

In conclusion, highly regioselective annulation was accomplished using heteroatom-substituted allenes. In addition, unprecedented *S*$_N$2′ reaction of alkyl metal reagents occurred at the exomethylene position of annulated products, and several alkyl moieties were introduced in good-to-high yields. Continuing studies to extend the scope of the substrates and to apply annulated products and products from the *S*$_N$2′ reaction for natural product synthesis are underway.

Experimental

General Procedures Melting points were measured with a Yazawa micro melting point apparatus and uncorrected. IR spectra were recorded on a SHIMADZU FTIR-8400. ^{1}H- and ^{13}C-NMR spectra were recorded on a JEOL JMN AL-400. Chemical shifts (δ) are given from tetramethylsilane (TMS) (0 ppm) as an internal standard for ^{1}H-NMR and ^{13}CDCl$_3$ (77.0 ppm) for ^{13}C-NMR. Mass spectra and high resolution mass spectra were measured on JEOL JMS-DX303 and MS-AX500 instruments, respectively.

Benzyl 1,2-Propadienyl Ether (1) Benzyl bromide (25.7 g, 0.15 mol) was added dropwise at 0 °C to a solution of propargyl alcohol (5.6 g, 0.10 mol) in DMSO (100 ml) and 3 N NaOH (50 ml) and the whole mixture was stirred at room temperature for 24 h. The reaction mixture was extracted with Et$_2$O (30 ml×3) and the combined ethereal layer was washed with brine (30 ml×3), and dried over MgSO$_4$. The ethereal layer was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane–AcOEt (19 : 1) as an eluent to give benzyl 2-propynyl ether (20.6 g, 94%) as a colorless oil. To a solution of benzyl 2-propynyl ether (6.1 g, 41.8 mmol) in DMF (30 ml), ^{t}BuOK (0.94 g, 8.4 mmol) was added at 0 °C and the whole mixture was stirred at 70 °C for 24 h. The reaction mixture was extracted with Et$_2$O (20 ml×3) and the combined ethereal layer was washed with brine (20 ml×3), and dried over MgSO$_4$. The ethereal layer was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane–AcOEt (19 : 1) as an eluent to give benzyl 1,2-propadienyl ether (**1**, 4.2 g, 69%) as a colorless oil. bp: 80 °C (22 mmHg, Kugelrohr). IR ν (NaCl) cm^{-1}: 1960, 3050. 400 MHz ^{1}H-NMR (CDCl$_3$) δ (ppm): 4.61 (2H, s), 5.47 (2H, d, J=6.0 Hz), 6.83 (1H, t, J=6.0 Hz), 7.29—7.35 (5H, m). 100 MHz ^{13}C-NMR (CDCl$_3$) δ (ppm): 70.6, 91.1, 121.5, 127.7, 127.8, 128.3, 137.2, 201.1. EI-MS *m*/*z* (relative intensity): 146 (M$^+$, 11.3), 91 (M$^+$−55, 100). HR-MS Calcd for $C_{10}H_{10}O$: 146.0732, Found: 146.0737.

***N*-(2-Propynyl)-4-methylphenylsulfonamide (3)** Under Ar atmosphere, DEAD (1.4 g, 25.0 mmol, 40% in toluene) was added dropwise at 0 °C to a solution of *N*-Boc-4-methylphenylsulfonamide (4.1 g, 15.0 mmol), propargyl alcohol (1.4 g, 25.0 mmol) and PPh$_3$ (6.6 g, 25.0 mmol) in tetrahydrofuran (THF) (50 ml) and the whole mixture was stirred for 2 h at the same temperature. After removal of THF under reduced pressure, the residue was extracted with AcOEt (30 ml×3) and dried over MgSO$_4$. The organic layer was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane–AcOEt (9 : 1) as an eluent to give *N*-Boc-*N*-(2-propynyl)-4-methylphenylsulfonamide as a yellow solid. A solution of *N*-Boc-*N*-(2-propynyl)-4-methylphenylsulfonamide and 3 N HCl (10 ml) in MeOH (30 ml) was heated under reflux for overnight. The reaction mixture was extracted with AcOEt (20 ml×3) and the combined organic layer was washed with brine (20 ml×3), and dried over MgSO$_4$. The organic layer was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane–AcOEt (9 : 1) as an eluent to give *N*-(2-propynyl)-4-methylphenylsulfonamide (**3**, 4.8 g, 91% for 2 steps) as a yellow solid. mp: 71—73 °C (recrystallized from hexane/acetone). IR ν (NaCl) cm^{-1}: 3261. 400 MHz ^{1}H-NMR (CDCl$_3$) δ (ppm): 2.11 (1H, t, J=2.4 Hz), 2.44 (3H, s), 3.83 (2H, dd, J=2.4, 6.2 Hz), 4.63 (1H, br), 7.31 (2H, d, J=8.4 Hz), 7.77 (2H, d, J=8.4 Hz). 100 MHz ^{13}C-NMR (CDCl$_3$) δ (ppm): 21.6, 32.9, 73.0, 77.9, 127.3, 129.6, 136.4, 143.8. EI-MS *m*/*z* (relative intensity): 209 (M$^+$, 3.0), 91 (M$^+$−118, 100). HR-MS Calcd for $C_{10}H_{11}NO_2S$: 209.0511, Found: 209.0490.

***N*-Benzyl-*N*-(2-propynyl)-4-methylphenylsulfonamide (4)** Under Ar atmosphere, a solution of *N*-(2-propynyl)-4-methylphenylsulfonamide (**3**, 0.31 g, 1.5 mmol) in DMF (5 ml) was added dropwise at 0 °C to a suspension

of NaH (0.090 g, 2.3 mmol, 60% in oil) in DMF (5 ml) and the mixture was stirred for 1 h at the same temperature. Benzyl bromide (0.36 g, 2.3 mmol) was added at 0 °C and the whole mixture was stirred at room temperature for overnight. The reaction mixture was extracted with Et_2O (15 ml×3) and the combined ethereal layer was washed with brine (15 ml×3), and dried over $MgSO_4$. The ethereal layer was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane–AcOEt (9 : 1) as an eluent to give *N*-benzyl-*N*-(2-propynyl)-4-methylphenylsulfonamide (**4**, 0.29 g, 65%) as a colorless oil. IR ν (NaCl) cm^{-1}: 1161, 1348. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.01 (1H, t, J=2.8 Hz), 2.45 (3H, s), 3.95 (2H, d, J=2.8 Hz), 4.36 (2H, s), 7.32—7.36 (7H, m), 7.80 (2H, d, J=8.4 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.6, 35.6, 49.8, 74.1, 76.2, 127.8, 128.0, 128.6, 128.7, 129.4, 134.8, 135.9, 143.5. EI-MS *m/z* (relative intensity): 299 (M^+, 0.9), 144 (M^+-155, 100). HR-MS Calcd for $C_{17}H_{17}NO_2S$: 299.0980, Found: 299.1017.

***N*-Benzyl-*N*-(1,2-propadienyl)-4-methylphenylsulfonamide (2)** To a solution of *N*-benzyl-*N*-(2-propynyl)-4-methylphenylsulfonamide (**4**, 0.11 g, 0.35 mmol) in DMF (10 ml), ^{t}BuOK (0.011 g, 0.10 mmol) was added at 0 °C and the whole mixture was stirred at room temperature for 24 h. The reaction mixture was extracted with Et_2O (20 ml×3) and the combined ethereal layer was washed with brine (20 ml×3), and dried over $MgSO_4$. The ethereal layer was removed under reduced pressure and the residue was purified by silica gel column chromatography using hexane–AcOEt (4 : 1) as an eluent to give *N*-benzyl-*N*-(1,2-propadienyl)-4-methylphenylsulfona-mide (**2**, 0.073 g, 70%) as a colorless oil. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.43 (3H, s), 4.29 (2H, s), 5.12 (2H, d, J=6.2 Hz), 6.82 (1H, t, J=6.2 Hz), 7.22—7.32 (7H, m), 7.70 (2H, d, J=8.4 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.6, 50.0, 88.0, 100.0, 127.1, 127.3, 127.7, 128.1, 129.6, 135.1, 136.1, 143.7, 201.9. EI-MS *m/z* (relative intensity): 299 (M^+, 3.4), 144 (M^+-155, 100). HR-MS Calcd for $C_{17}H_{17}NO_2S$: 299.0980, Found: 299.0961.

General Procedure for Annulation Reaction of Allenes (1, 2) Using Various Aryl Halides (Table 1) Under Ar atmosphere, a mixture of an aryl halide (1 eq), an allene (1.5—4.0 eq), K_2CO_3 (1.5—3.0 eq), $Pd(OAc)_2$ (10 mol%), $P(2\text{-Tol})_3$ (15 mol%) and DMF (5 ml) was allowed to react under the conditions as listed in Table 1. The reaction mixture was extracted with Et_2O (10 ml×3) and the combined ethereal layer was washed with brine (10 ml×3), and dried over $MgSO_4$. The ethereal layer was removed under reduced pressure and the residue was purified by silica gel column chromatography to give the annulated product.

Entry 1 According to the general procedure, from *N*-(4-methylfenylsulfonyl)-2-iodoaniline (0.19 g, 0.50 mmol), allene (**1**, 0.29 g, 2.0 mmol), K_2CO_3 (0.21 g, 1.5 mmol), $Pd(OAc)_2$ (0.011 g, 0.050 mmol) and DMF (5 ml) was obtained **5** (0.026 g, 99%) as a white solid.

2-Benzyloxy-3-methylene-1-(4-methylphenylsulfonyl)indoline (**5**): IR ν (neat) cm^{-1}: 1117, 1358, 1601. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.32 (3H, s), 4.63 (1H, d, J=11.3 Hz), 4.69 (1H, d, J=11.3 Hz), 5.33 (1H, s), 5.67 (1H, s), 6.02 (1H, s), 7.05 (1H, t, J=7.6 Hz), 7.13 (2H, d, J=8.2 Hz), 7.27—7.36 (7H, m), 7.61 (2H, d, J=8.2 Hz), 7.64 (1H, d, J=8.0 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.6, 67.4, 91.9, 109.4, 116.1, 121.0, 124.3, 127.1, 127.6, 128.4, 128.1, 128.2, 129.6, 130.1, 135.1, 137.1, 141.5, 142.5, 144.0. EI-MS *m/z* (relative intensity): 391 (M^+, 24.8), 91 (M^+-300, 100). HR-MS Calcd for $C_{23}H_{21}NO_3S$: 391.1242, Found: 391.1239.

Entry 2 According to the general procedure, from *N*-ethoxycarbonyl-2-iodoaniline (0.15 g, 0.5 mmol), allene (**1**, 0.11 g, 0.75 mmol), K_2CO_3 (0.10 g, 0.75 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol) and DMF (5 ml) was obtained **6** (0.11 g, 71%) as a colorless oil.

Ethyl 2-Benzyloxy-3-methyleneindoline-1-carboxylate (**6**): IR ν (KBr) cm^{-1}: 1060, 1270, 1380, 1410, 1470, 1600, 1720, 2925. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.36 (3H, t, J=7.2 Hz), 4.32 (2H, q, J=7.2 Hz), 4.54 (1H, d, J=11.4 Hz), 4.60 (1H, d, J=11.4 Hz), 5.37 (1H, s), 5.75 (1H, s), 6.15 (1H, s), 7.00 (1H, t, J=7.6 Hz), 7.21—7.34 (6H, m), 7.43 (1H, d, J=7.6 Hz), 7.78 (1H, d, J=8.0 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.6, 62.0, 67.4, 89.6, 108.2, 115.7, 120.3, 123.0, 127.0, 127.5, 127.8, 128.2, 130.1, 138.2, 142.3, 143.4, 153.0. EI-MS *m/z* (relative intensity): 309 (M^+, 29.4), 91 (M^+-218, 100). HR-MS Calcd for $C_{19}H_{19}NO_3$: 309.1365, Found: 309.1354.

Entry 3 According to the general procedure, from *N*-(4-methylfenylsulfonyl)-2-iodobenzylamine (0.39 g, 1.0 mmol), allene (**1**, 0.22 g, 1.5 mmol), K_2CO_3 (0.21 g, 1.5 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol) and DMF (5 ml) was obtained **7** (0.30 g, 75%) as a white solid.

3-Benzyloxy-4-methylene-2-(4-methylphenylsulfonyl)-1,2,3,4-tetrahydroisoquinoline (**7**): IR ν (neat) cm^{-1}: 1160, 1360, 1460, 1500, 2875, 2925, 3050. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.34 (3H, s), 4.46 (1H, d, J=16.0 Hz), 4.58 (1H, d, J=11.8 Hz), 4.61 (1H, d, J=16.0 Hz), 4.63 (1H, d, J=11.8 Hz), 5.20 (1H, s), 5,64 (1H, s), 5.83 (1H, s), 7.02 (1H, d, J=6.9 Hz), 7.12 (2H, d, J=8.3 Hz), 7.17—7.28 (6H, m), 7.50 (2H, d, J=7.9 Hz), 7.61 (2H, d, J=8.3 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.5, 43.4, 68.9, 85.4, 112.7, 124.6, 125.8, 127.0, 127.3, 127.5, 127.7, 128.1, 128.2, 129.3, 129.7, 130.8, 136.0, 137.2, 137.6, 143.3. EI-MS *m/z* (relative intensity): 405 (M^+, 3.8), 91 (M^+-311, 100). HR-MS Calcd for $C_{24}H_{23}NO_3S$: 405.1399, Found: 405.1387.

Entry 4 According to the general procedure, from 2-iodobenzyl alcohol (0.23 g, 1.0 mmol), allene (**1**, 0.22 g, 1.5 mmol), K_2CO_3 (0.21 g, 1.5 mmol), $Pd(OAc)_2$ (0.022 g, 0.1 mmol) and DMF (5 ml) was obtained **8** (0.13 g, 52%) as a colorless oil.

3-Benzyloxy-4-methyleneisochroman (**8**): IR ν (neat) cm^{-1}: 1050, 1110, 1450, 2900, 3025. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 4.61 (1H, d, J=14.8 Hz), 4.71 (1H, d, J=12.2 Hz), 4.86 (1H, d, J=12.2 Hz), 5.01 (1H, d, J=14.8 Hz), 5.17 (1H, s), 5.38 (1H, s), 5.71 (1H, s), 7.00—7.02 (1H, m), 7.18—7.38 (7H, m), 7.61—7.65 (1H, m). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 61.5, 69.0, 98.3, 110.8, 123.7, 124.1, 126.9, 127.6, 127.9, 128.3, 129.4, 133.3, 137.5, 138.0. EI-MS *m/z* (relative intensity): 252 (M^+, 2.1), 146 (M^+-106, 100). HR-MS Calcd for $C_{17}H_{16}O_2$: 252.1150, Found: 252.176.

Entry 5 According to the general procedure, from 2-iodobenzyl alcohol (0.12 g, 0.5 mmol), allene (**1**, 0.15 g, 1.0 mmol), K_2CO_3 (0.14 g, 1.0 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), $P(2\text{-Tol})_3$ (0.023 g, 0.075 mmol) and DMF (5 ml) was obtained **8** (0.11 g, 86%) as a colorless oil.

Entry 6 According to the general procedure, from *N*-(4-methylfenylsulfonyl)-2-iodoaniline (0.043 g, 0.12 mmol), allene (**2**, 0.051 g, 0.17 mmol), K_2CO_3 (0.024 g, 0.17 mmol), $Pd(OAc)_2$ (0.0026 g, 0.012 mmol) and DMF (5 ml) was obtained **9** (0.051 g, 81%) as a white solid.

2-[*N*-Benzyl-*N*-(4-methylphenylsulfonyl)amino]3-methylene-1-(4-methylphenylsulfonyl)indoline (**9**): IR ν (NaCl) cm^{-1}: 1173, 1364, 1599. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.33 (3H, s), 2.40 (3H, s), 4.15 (1H, d, J=15.2 Hz), 4.40 (1H, d, J=15.2 Hz), 5.38 (1H, s), 5.54 (1H, s), 6.57 (1H, s), 6.97—7.05 (6H, m), 7.15—7.22 (6H, m), 7.55 (2H, d, J=10.4 Hz), 7.57 (1H, d, J=8.0 Hz), 7.84 (2H, d, J=8.4 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.5 (two carbons), 48.4, 76.3, 108.6, 116.6, 120.6, 124.7, 127.2, 127.4, 127.7, 128.4, 128.7, 129.1, 129.2, 129.8, 130.0, 133.7, 135.3, 137.2, 141.2, 142.7, 143.4, 144.5. EI-MS *m/z* (relative intensity): 544 (M^+), 91 (M^+-453, 100). HR-MS Calcd for $C_{30}H_{28}N_2O_4S_2$: 544.1491, Found: 544.1492.

Entry 7 According to the general procedure, from 2-iodobenzyl alcohol (0.059 g, 0.25 mmol), allene (**2**, 0.15 g, 0.50 mmol), K_2CO_3 (0.069 g, 0.50 mmol), $Pd(OAc)_2$ (0.0056 g, 0.025 mmol) and DMF (5 ml) was obtained **10** (0.066 g, 65%) as a white solid.

3-[*N*-Benzyl-*N*-(4-methylphenylsulfonyl)amino]-3-methyleneisochroman (**10**): IR ν (NaCl) cm^{-1}: 1163, 1342. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.40 (3H, s), 4.25 (1H, d, J=15.6 Hz), 4.37 (1H, d, J=15.6 Hz), 4.58 (1H, d, J=14.6 Hz), 4.68 (1H, d, J=14.6 Hz), 5.26 (1H, s), 5.64 (1H, s), 6.28 (1H, s), 6.97 (1H, dd, J=3.6, 5.6 Hz), 7.12—7.24 (9H, m), 7.42 (1H, dd, J=3.6, 5.6 Hz), 7.62 (2H, d, J=8.4 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.6, 48.6, 66.2, 86.5, 112.5, 123.8, 124.3, 126.9, 127.4, 127.5, 127.7, 127.9, 128.8, 129.1, 131.4, 133.5, 136.6, 136.9, 137.3, 143.0. EI-MS *m/z* (relative intensity): 405 (M^+, 36.6), 145 (M^+-260, 100). HR-MS Calcd for $C_{24}H_{23}NO_3S$: 405.1399, Found: 405.1396.

Entry 8 According to the general procedure, from 2-iodobenzyl alcohol (0.015 g, 0.066 mmol), allene (**2**, 0.079 g, 0.26 mmol), K_2CO_3 (0.027 g, 0.20 mmol), $Pd(OAc)_2$ (0.0015 g, 0.0066 mmol), $P(2\text{-Tol})_3$ (0.0030 g, 0.0099 mmol) and DMF (5 ml) was obtained **10** (0.026 g, 99%) as a white solid.

Entry 9 According to the general procedure, from 2-iodophenol (0.052 g, 0.24 mmol), allene (**2**, 0.14 g, 0.47 mmol), K_2CO_3 (0.066 g, 0.47 mmol), $Pd(OAc)_2$ (0.0053 g, 0.024 mmol) and DMF (5 ml) was obtained **11** (0.039 g, 42%) as a white solid.

2-[*N*-Benzyl-*N*-(4-methylphenylsulfonyl)amino]3-methylene-2,3-dihydrobenzofuran (**11**): 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.44 (3H, s), 4.09 (1H, d, J=16.0 Hz), 4.27 (1H, d, J=16.0 Hz), 5.11 (1H, d, J=2.5 Hz), 5.45 (1H, d, J=2.5 Hz), 6.69 (1H, d, J=8.4 Hz), 6.87 (1H, t, J=7.6 Hz), 6.94 (1H, t, J=2.5 Hz), 7.08—7.17 (5H, m), 7.23—7.31 (4H, m), 7.72 (2H, d, J=8.4 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.5, 47.4, 92.3, 107.0, 110.2, 120.9, 121.2, 124.3, 127.1, 127.71, 127.74, 128.6, 129.5, 130.8, 136.5, 136.9, 141.0, 143.6, 160.9. EI-MS *m/z* (relative intensity): 391 (M^+, 17.8), 91 (M^+-300, 100). HR-MS Calcd for $C_{23}H_{21}NO_3S$: 391.1242, Found: 391.1250.

Entry 10 According to the general procedure, from 2-iodophenol (0.029 g, 0.13 mmol), allene (**2**, 0.078 g, 0.26 mmol), K_2CO_3 (0.036 g, 0.26 mmol), $Pd(OAc)_2$ (0.0029 g, 0.013 mmol), $P(2\text{-Tol})_3$ (0.0061 g,

0.020 mmol) and DMF (5 ml) was obtained **11** (0.032 g, 62%) as a white solid.

Entry 12 According to the general procedure, from 2-bromobenzyl alcohol (0.094 g, 0.50 mmol), allene (**1**, 0.29 g, 2.0 mmol), K_2CO_3 (0.14 g, 1.0 mmol), $Pd(OAc)_2$ (0.011 g, 0.050 mmol), P(2-Tol)$_3$ (0.023 g, 0.075 mmol) and DMF (5 ml) was obtained **8** (0.063 g, 75%) as a white solid.

Entry 13 According to the general procedure, from *N*-(4-methylpenylsulfonyl)-2-bromobenzylamine (0.17 g, 0.50 mmol), allene (**1**, 0.29 g, 2.0 mmol), K_2CO_3 (0.21 g, 1.5 mmol), $Pd(OAc)_2$ (0.011 g, 0.050 mmol) and DMF (5 ml) was obtained **7** (0.11 g, 54%) as a white solid.

Entry 14 According to the general procedure, from *N*-(4-methylpenylsulfonyl)-2-bromobenzylamine (0.17 g, 0.50 mmol), allene (**1**, 0.29 g, 2.0 mmol), K_2CO_3 (0.21 g, 1.5 mmol), $Pd(OAc)_2$ (0.011 g, 0.50 mmol), P(2-Tol)$_3$ (0.023 g, 0.075 mmol) and DMF (5 ml) was obtained **7** (0.11 g, 52%) as a white solid.

Entry 15 According to the general procedure, from *N*-(4-methylpenylsulfonyl)-2-bromobenzylamine (0.17 g, 0.50 mmol), allene (**1**, 0.29 g, 2.0 mmol), K_2CO_3 (0.21 g, 1.5 mmol), $Pd(OAc)_2$ (0.011 g, 0.050 mmol), Bu_4NBr (0.16 g, 0.50 mmol) and DMF (5 ml) was obtained **7** (0.15 g, 76%) as a white solid.

General Procedure for Reaction of Alkyl Metal Reagents with Annulated Products (Table 2) Under Ar atmosphere, an alkyl metal reagent was added dropwise at −78 °C to the THF solution of an annulated product, and the whole mixture was stirred at the same temperature. The reaction mixture was extracted with AcOEt (10 ml×3) and the combined organic layer was washed with brine (10 ml×3), and dried over $MgSO_4$. The organic layer was removed under reduced pressure and the residue was purified by silica gel column chromatography to give the substituted product.

Entry 1 According to the general procedure, from **8** (0.074 g, 0.30 mmol) and BuLi (0.46 ml, 0.59 mmol, 1.29 M in hexane solution) was obtained **13a** (0.036 g, 60%) as a colorless oil.

4-Pentyl-1*H*-isochromene (**13a**): IR ν (NaCl) cm^{-1}: 756, 1144, 1632, 2928. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, m), 1.33—1.37 (4H, m), 1.51—1.54 (2H, m), 2.32, (2H, t, J=8.0 Hz), 5.00 (2H, s), 6.46 (1H, s), 7.02 (1H, d, J=7.6 Hz), 7.12 (1H, d, J=7.6 Hz), 7.16 (1H, t, J=7.6 Hz), 7.26 (1H, t, J=7.6 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.2, 22.6, 27.7, 28.5, 31.7, 68.3, 116.1, 120.2, 123.9, 126.4, 127.9, 129.0, 131.5, 142.2. EI-MS *m/z* (relative intensity): 202 (M^+, 100). HR-MS Calcd for $C_{14}H_{18}O$: 202.1358, Found: 202.1359.

Entry 2 According to the general procedure, from **8** (0.076 g, 0.30 mmol), BuLi (0.93 ml, 1.20 mmol, 1.29 M in hexane solution) and TMEDA (0.17 g, 1.44 mmol) was obtained **13a** (0.055 g, 91%) as a colorless oil.

Entry 3 According to the general procedure, from **8** (0.076 g, 0.30 mmol) and ^{t}BuLi (0.55 ml, 0.60 mmol, 1.10 M in pentane solution) was obtained **13b** (0.053 g, 87%) as a colorless oil.

4-(2,2-Dimethylpropyl)-1*H*-isochromene (**13b**): IR ν (NaCl) cm^{-1}: 758, 1123, 1624, 2953. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.93 (9H, s), 2.27 (2H, s), 4.94 (2H, s), 6.40 (1H, s), 7.01 (1H, d, J=7.6 Hz), 7.14 (1H, t, J=7.0 Hz), 7.19—7.23 (2H, m). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 30.0, 31.7, 40.2, 68.8, 114.0, 121.0, 124.0, 126.1, 127.6, 128.4, 132.7, 144.7. EI-MS *m/z* (relative intensity): 202 (M^+, 75.2), 145 (M^+−57, 100). HR-MS Calcd for $C_{14}H_{18}O$: 202.1358, Found: 202.1344.

Entry 4 According to the general procedure, from **7** (0.089 g, 0.22 mmol), BuLi (0.26 ml, 0.33 mmol, 1.26 M in hexane solution) and HMPA (0.070 g, 0.39 mmol) was obtained **14a** (0.034 g, 44%) as a colorless oil.

2-(4-Methylphenylsulfonyl)-4-pentyl-1,2-dihydroisoquinoline (**14a**): IR ν (film) cm^{-1}: 1169, 1350, 1639. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, J=7.4 Hz), 1.31—1.50 (6H, m), 2.36 (3H, s), 2.37 (2H, t, J=7.4 Hz), 4.51 (2H, s), 6.58 (1H, s), 6.98 (1H, d, J=7.4 Hz), 7.09 (1H, t, J=7.4 Hz), 7.11 (1H, t, J=7.4 Hz), 7.16 (1H, d, J=7.4 Hz), 7.21 (2H, d, J=8.2 Hz), 7.64 (2H, d, J=8.2 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.2, 21.6, 22.5, 28.3, 29.8, 31.6, 47.7, 121.6, 122.4, 122.8, 125.5, 127.0, 127.1, 127.7, 128.6, 130.0, 131.3, 134.6, 143.6. EI-MS *m/z* (relative intensity): 355 (M^+, 16.5), 142 (M^+−213, 100). HR-MS Calcd for $C_{21}H_{25}NO_2S$: 355.1601, Found: 355.1607.

Entry 5 According to the general procedure, from **7** (0.071 g, 0.18 mmol) and ^{t}BuLi (0.15 ml, 0.21 mmol, 1.40 M in pentane solution) was obtained **14b** (0.037 g, 60%) as a colorless oil.

4-(2,2-Dimethylpropyl)-2-(4-methylphenylsulfonyl)-1,2-dihydroisoquinoline (**14b**): IR ν (film) cm^{-1}: 1169, 1348, 1628. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.84 (9H, s), 2.35 (3H, s), 2.35 (2H, s), 4.47 (2H, s), 6.56 (1H, s), 6.98 (1H, d, J=7.4 Hz), 7.08 (1H, t, J=7.4 Hz), 7.14—7.16 (2H, m), 7.20 (2H, d, J=8.2 Hz), 7.63 (2H, d, J=8.2 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.5, 29.98, 31.8, 48.2, 120.6, 122.4, 125.5, 125.6, 128.6, 126.9, 127.9, 127.3, 128.1, 129.4, 132.6, 134.6, 143.7. EI-MS *m/z* (relative intensity): 355 (M^+, 30.6), 142 (M^+−213, 100). HR-MS Calcd for $C_{21}H_{25}NO_2S$: 355.1601, Found: 355.1582.

Entry 6 According to the general procedure, from **7** (0.070 g, 0.17 mmol) and ^{t}BuCu(2-thienyl)CNLi$_2$, prepared from lithium 2-thienylcycanocuprate (1.2 ml, 0.30 mmol, 0.25 M in THF solution) and ^{t}BuLi (0.25 ml, 0.34 mmol, 1.46 M in pentane solution), was obtained **14b** (0.050 g, 83%) as a colorless oil.

Entry 7 According to the general procedure, from **7** (0.070 g, 0.17 mmol) and $EtMe_2MgLi$, prepared from methyl lithium (1.3 ml, 1.50 mmol, 1.14 M in Et_2O solution) and EtMgBr (0.74 ml, 0.74 mmol, 1.0 M in THF solution), was obtained **14c** (0.064 g, 79%) as a colorless oil.

4-Propyl-2-(4-methylphenylsulfonyl)-1,2-dihydroisoquinoline (**14c**): IR ν (film) cm^{-1}: 1169, 1350, 1636. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.93 (3H, t, J=7.3 Hz), 1.53 (2H, sext, J=7.3 Hz), 2.36 (3H, s), 2.36 (2H, t, J=7.3 Hz), 4.51 (2H, s), 6.59 (1H, s), 6.98 (1H, d, J=7.3 Hz), 7.08 (1H, d, J=7.3 Hz), 7.11 (1H, t, J=7.3 Hz), 7.17 (1H, t, J=7.3 Hz), 7.21 (2H, d, J=7.9 Hz), 7.64 (2H, d, J=7.9 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 13.9, 21.7, 29.7, 31.9, 47.7, 121.6, 122.2, 122.9, 125.5, 127.0, 127.1, 127.6, 128.6, 129.5, 131.3, 134.7, 143.6. EI-MS *m/z* (relative intensity): 327 (M^+, 38.8), 172 (M^+−155, 100). HR-MS Calcd for $C_{19}H_{21}NO_2S$: 327.1293, Found: 327.1290.

Entry 8 According to the general procedure, from **5** (0.030 g, 0.077 mmol) and BuLi (0.26 ml, 0.38 mmol, 1.45 M in hexane solution) was obtained **15a** (0.011 g, 40%) as a colorless oil.

1-(4-Methylphenylsulfonyl)-3-pentylindole (**15a**): IR ν (film) cm^{-1}: 1173, 1367. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (3H, t, J=7.1 Hz), 1.32—1.34 (4H, m), 1.67 (2H, quint, J=7.1 Hz), 2.32 (3H, s), 2.63 (2H, t, J=7.1 Hz), 7.19—7.31 (5H, m), 7.46 (1H, d, J=7.6 Hz), 7.72 (2H, d, J=8.5 Hz), 7.97 (1H, d, J=8.3 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.1, 21.6, 22.5, 24.9, 28.6, 32.6, 113.7, 119.4, 122.5, 122.8, 123.6, 124.4, 126.6, 129.6, 131.1, 135.26, 135.29, 144.5. EI-MS *m/z* (relative intensity): 341 (M^+, 56.6), 130 (M^+−211, 100). HR-MS Calcd for $C_{20}H_{23}NO_2S$: 341.1450, Found: 341.1440.

Entry 9 According to the general procedure, from **5** (0.030 g, 0.077 mmol), BuLi (0.12 ml, 0.15 mmol, 1.26 M in hexane solution) and HMPA (0.033 g, 0.18 mmol) was obtained **15a** (0.022 g, 83%) as a colorless oil.

Entry 10 According to the general procedure, from **5** (0.030 g, 0.077 mmol) and ^{t}BuLi (0.26 ml, 0.38 mmol, 1.46 M in pentane solution) was obtained **15b** (0.018 g, 68%) as a colorless oil.

3-(2,2-Dimethylpropyl)-1-(4-methylphenylsulfonyl)indole (**15b**): IR ν (film) cm^{-1}: 1173, 1362. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.91 (9H, s), 2.32 (3H, s), 2.54 (2H, s), 7.17—7.19 (5H, m), 7.46 (1H, d, J=7.8 Hz), 7.72 (2H, d, J=7.8 Hz), 7.97 (1H, d, J=8.1Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 21.6, 29.7, 32.0, 38.6, 100.5, 113.6, 120.1, 120.8, 122.8, 124.1, 124.4, 126.6, 129.6, 132.3, 135.2, 144.6. EI-MS *m/z* (relative intensity): 341 (M^+, 34.6), 284 (M^+−57, 100). HR-MS Calcd for $C_{20}H_{23}NO_2S$: 341.1450, Found: 341.1440.

Entry 11 According to the general procedure, from **5** (0.030 g, 0.077 mmol), BuLi (0.26 ml, 0.38 mmol, 1.46 M in pentane solution) and HMPA (0.066 g, 0.37 mmol) was obtained **15b** (0.011 g, 40%) as a colorless oil.

Entry 12 According to the general procedure, from **5** (0.042 g, 0.11 mmol) and $EtMe_2MgLi$, prepared from methyl lithium (0.53 ml, 0.60 mmol, 1.14 M in Et_2O solution) and EtMgBr (0.33 ml, 0.32 mmol, 1.0 M in THF solution), was obtained **15c** (0.032 g, 93%) as a colorless oil.

1-(4-Methylphenylsulfonyl)-3-propylindole (**15c**): IR ν (film) cm^{-1}: 1173, 1369. 400 MHz ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.96 (3H, t, J=7.3 Hz), 1.70 (2H, sext, J=7.3 Hz), 2.32 (3H, s), 2.62 (2H, t, J=7.3 Hz), 7.18—7.30 (5H, m), 7.46 (1H, d, J=7.6 Hz), 7.73 (2H, d, J=8.3 Hz), 7.96 (1H, d, J=8.3 Hz). 100 MHz ^{13}C-NMR ($CDCl_3$) δ (ppm): 14.0, 21.6, 22.1, 27.0, 113.6, 119.3, 119.5, 122.6, 122.8, 122.9, 123.3, 124.4, 126.4, 126.6, 135.2, 144.5. EI-MS *m/z* (relative intensity): 313 (M^+, 100), 284 (M^+−29, 96). HR-MS Calcd for $C_{18}H_{19}NO_2S$: 313.1137, Found: 313.1153.

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21) All the structures of annulated products were confirmed by ^{1}H-NMR, ^{13}C-NMR, ^{1}H-COSY, HMQC and NOESY.
22) Larock carried out his annulation reactions in the presence of tetrabutylammonium chloride[13—16]; however, the role of such an ammonium salt is obscure at present.
23) The asymmetric induction for this reaction with BINAP as a chiral ligand according to Larocks' report[16] did not show any chiral induction. This observation may support the latter mechanism.
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