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Rhodium-Catalyzed Carbonylative [3+2+1] Cycloaddition of Alkyne-Tethered Alkylidenecyclopropanes to Phenols in the Presence of Carbon Monoxide

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2014 년 6 월

위 원 장 _____ (인)

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Abstract

We have developed a novel Rh-catalyzed carbonylative [3+2+1] cycloaddition of alkyne-tethered alkylidenecyclopropanes, for the facile synthesis of bicyclic phenols in high yields. The reaction tolerated carbon and heteroatoms in the tether.

Keywords: Rhodium-catalyst, carbonylative, [3+2+1] cycloaddition, alkylidenecyclopropanes, Phenol, Carbon monoxide

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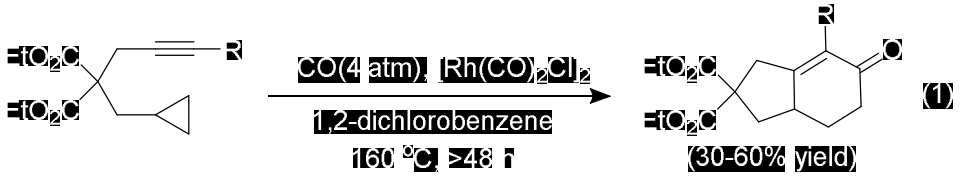
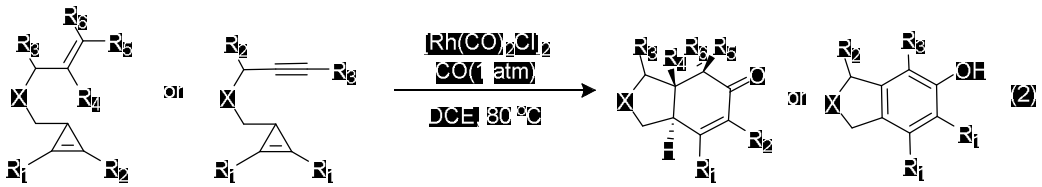
Introduction

Many useful reactions have been developed for the synthesis of cyclic compounds. Transition-metal-catalyzed cycloadditions have been extensively used in the synthesis of cyclic compounds.[1] Recently, cycloisomerization has increasing attention because it can be used to prepare a variety of cyclic compounds from readily available substrates.[2] Our group have been engaged in the study of cycloisomerization and cycloaddition reactions of various unsaturated hydrocarbons.[3] During our studies on the cycloisomerization of alkylidenecyclopropanes, Shi et al. reported a gold-catalyzed cycloisomerization reaction.[4] Moreover, alkylidenecyclopropanes have been used in the nickel-catalyzed [3+2+2] cycloaddition with activated alkenes.[5] However, the rhodium-catalyzed intramolecular carbocyclization of alkylidenecyclopropanes is known to form a complex mixture of products.[6] During our catalyst screening process, we discovered a formal [3+2+1] cycloaddition of alkylidenecyclopropanes to afford phenol derivatives in the presence of rhodium catalyst and carbon monoxide. In contrast to our expectation, the carbonylative [3+2+1] cycloaddition reaction has been rarely reported.[7] In addition, the formation of a six-membered ring by [3+2+1] carbonylative carbocyclization has not been well developed, because of the difficulty in introducing the required three-carbon component. An evident source of three-carbon units would be cyclopropane. Koga

and Narasaka reported the Rh-catalyzed [3+2+1] cycloaddition of yne-cyclopropanes having no neighboring double bond to the cyclopropane.[7a] However, unfortunately, the preliminary result was acquired under harsh conditions, apparently due to the difficulty of ring-opening of an isolated cyclopropane moiety under the reaction conditions of Rh(I) catalysis (eq 1).

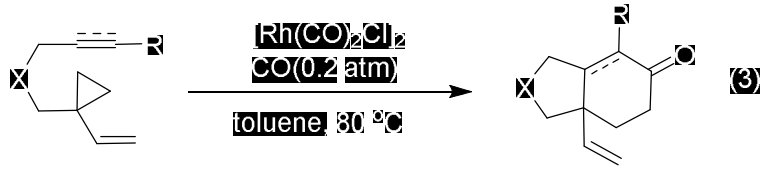


The presence of a neighboring double bond is necessary for metal coordination, which facilitates the ring opening of cyclopropane under much milder conditions.[8] A few years ago, Wang and coworkers[7b] reported a carbocyclization of yne-cyclopropenes to afford phenol derivatives, which has a double bond in the three-membered ring for metal coordination and has much higher strain energy than cyclopropane (eq 2).



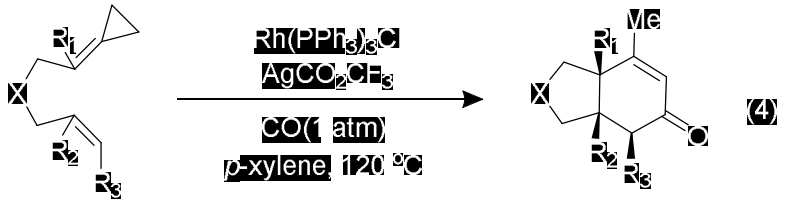
At the same time, Yu and coworkers reported Rh(I)-catalyzed

[3+2+1] reaction of 1-yne/ene-vinylcyclopropanes, to reach bicyclic cyclohexenone and cyclohexanone derivatives.[7c] Similar to cyclopropens, the vinyl group was found to act as an activating group that might show high reactivity in the carbocyclization reaction (eq 3).



(3)

Furthermore, Evans and coworkers in 2012 reported Rh(I)-catalyzed [3+2+1] carbocyclization of alkenylidenecyclopropanes to provide cis-fused bicyclohexenones in a highly efficient and stereoselective manner (eq 4).[7e]



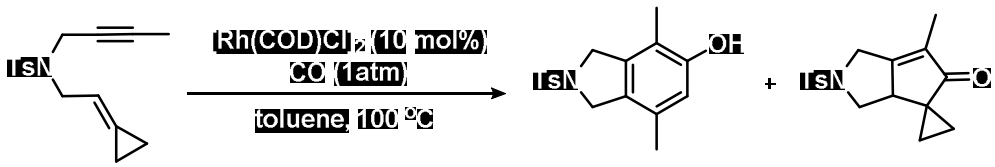
(4)

We have been studied the Rh(I)-catalyzed [3+2+1] carbonylative

carbocyclization of alkylidenecyclopropanes, for the synthesis of bicyclic phenols. The catalytic process developed in this study can be employed in the synthesis of phenol derivatives, which are present in biologically active compounds,[9] natural products,[10] and chiral catalysts,[11] and they can also be used in phenol resin.

Results and Discussion

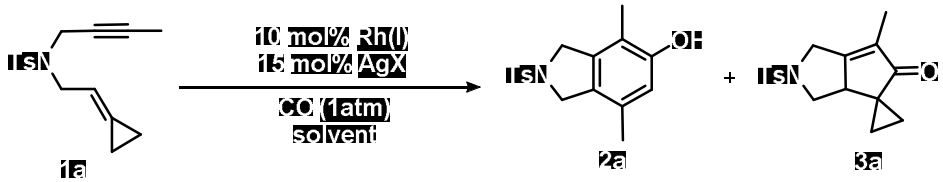
The requisite alkylidenecyclopropane substrates were easily prepared by using known procedures.[12] Compound **1a** (*N*-(but-2-yn-1-yl)-*N*-(2-cyclopropylideneethyl)-4-methylbenzenesolf-onamide) was chosen as a model substrate. A solution of **1a** and $[Rh(COD)Cl]_2$ (10 mol%) in toluene was heated at 100 °C under an atmosphere of CO (1 atm) for 11h. Compounds **2a** and **3a** were isolated in 21% and 15%, respectively (eq 1).



Compound **2a** was the product of a formal [3+2+1] cycloadditio n, a phenol derivative. Compound 2a was synthesized by a rhodium-catalyzed [2+2+2] cycloaddition of 1,6-diynes with vinylene carbonate.[13] Compound **3a** was the Pauson-Khand reaction product. Similar Pauson-Khand reaction products have been reported by de Meijere.[14] Encouraged by the formation of compound **2a**, we endeavored to optimize the reaction conditions to obtain **2a** as a major product. The reaction conditions used in our processes are shown in Table 1. The yield of desired product **2a** was highly sensitive to the rhodium catalyst, the reaction solvent, and the reaction temperature used. When the same reaction was carried out using 1,4-dioxane as the solvent at 100 °C for 6 h, a mixture cont

aining of **2a** and **3a** in 61% and 11% yield, respectively, was isol ated (entry 2). When [Rh(dppp)$_2$Cl] was used as the catalyst in 1,4-dioxane, the yields of **2a** and **3a** were decreased to 44% and 2%, respectively (entry 3). To our delight, the use of Rh(PPh$_3$)$_3$ Cl as a catalyst in 1,4-dioxane at 100 °C for 13 h afforded **2a** a s the sole product in 64% yield (entry 4). Encouraged by this re sult, we studied the use of a cationic rhodium complex generated by the reaction of Rh(PPh$_3$)$_3$Cl with AgX as a catalyst in 1,4-dio xane at 100 °C (entries 5-13). Interestingly, when $AgSbF_6$ or $AgClO_4$ was used as the source of a counteranion, no reaction was observed (entries 5 and 8). In the presence of $AgBF_4$, $AgPF_6$, AgOTs, and $AgSO_3CF_3$ as the source of a counteranion in 1,4-dioxane at 100 °C, 39-59% yield of **2a** was isolated (entries 6, 7, 9, and 10). When the reaction was carried out using $AgCO_2CF_3$ in 1,4-dioxane at 100 °C for 6 h, the yield of **2a** increased to 69% (entry 11). Increasing the quantity of Rh(PPh$_3$)$_3$Cl (10 mol%) and $AgCO_2CF_3$ (15 mol%) increased the yield of **2a** (77%) (entry 12). Furthermore, the reaction time was decreased to 2 h by using xylenes as the reaction solvent at 120 °C. The highest yield of **2a** (91%) was obtained in the presence of 10 mol% Rh(PPh$_3$)$_3$Cl and 15 mol% $AgCO_2CF_3$ (entry 13). The Structure of **2a** was confirmed by using X-ray diffraction crystallography (Figure 1).

Table 1. Optimization for Rh(I)-Catalyzed Carbonylative Cycloaddition[a]



entry	Catalyst/AgX	solvent	Temp (°C)	Time (h)	2a[c] (%)	3a[c] (%)
1	$[Rh(COD)Cl]_2$	toluene	100	11	21	15
2	$[Rh(COD)Cl]_2$	dioxane	"	6	61	11
3	$Rh(dppp)_2Cl$	"	"	6	44	2
4	$Rh(PPh_3)_3Cl$	"	"	13	64	
5	"/$AgSbF_6$[b]	"	"	6	NR	
6	"/$AgBF_4$[b]	"	"	6	55	
7	"/$AgPF_6$[b]	"	"	6	56	
8	"/$AgClO_4$[b]	"	"	6	NR	
9	"/AgOTs[b]	"	"	12	59	
10	"/$AgSO_3CF_3$[b]	"	"	7	39	
11	"/$AgCO_2CF_3$[b]	"	"	6	69	
12	"/ "	"	"	6	77	
13	"/ "	xylenes	120	2	91	

[a] Conditions: Substrate concentration 0.055 M. [b] $Rh(PPh_3)_3Cl$ (5 mol%) and AgX (7.5 mol%) were used. [c] Isolated yields.

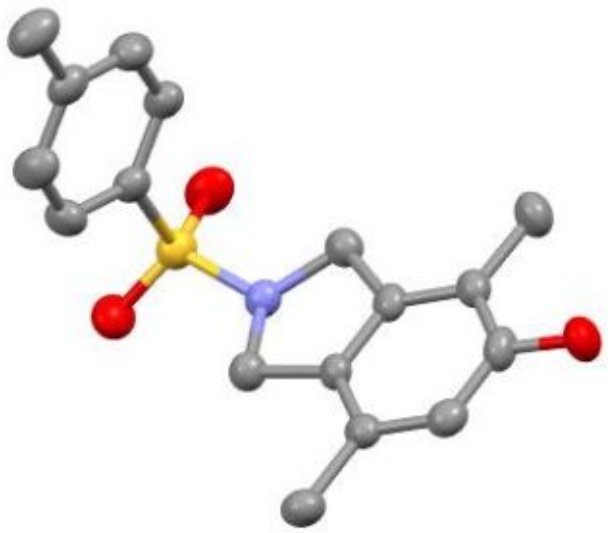
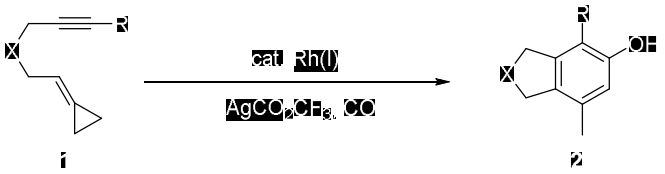


Figure 1. X-ray structure of **2a.**

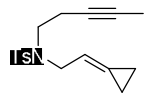
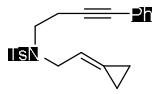
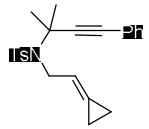
To further expand the scope of the reaction, a variety of alkylidenecyclopropanes were investigated under the optimized reaction conditions (Table 2). A diverse range of substrates were tolerated under the optimized reaction conditions, resulting in the high yields (74-91%) of compound **2**.

However, the nitrogen-tethered 1,6-enynes with a terminal alkyne or a vinyl group on the terminal alkyne afforded relatively lower yields (19% and 23% yields, respectively) (entries 2 and 7).[15] For nitrogen-tethered substrates, the introduction of an electron-donating group(-OMe) or electron-withdrawing groups (-Cl or -CF_3) on the aryl ring did not improve the reaction (entries 4-6) .

Table 2. Rh(I)−Catalyzed [3+2+1] Cycloaddition Reactions[a]

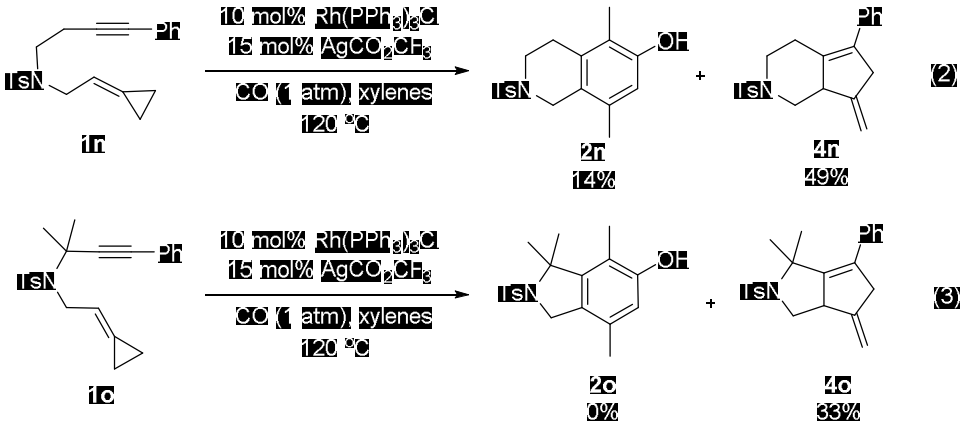


1 2

entry	1	X	R	yield (%)[b] 2
1	**1a**	N−Ts	Me	**2a**, 91
2	**1b**	N−Ts	H	**2b**, 19
3	**1c**	N−Ts	Ph	**2c**, 83
4	**1d**	N−Ts	C_6H_4−Cl−4	**2d**, 75
5	**1e**	N−Ts	C_6H_4−OMe−4	**2e**, 79
6	**1f**	N−Ts	C_6H_4−CF_3−4	**2f**, 74
7	**1g**	N−Ts	CH=CH_2	**2g**, 23
8	**1h**	N−Ts	cyclopropyl	**2h**, 85
9	**1i**	O	Me	**2i**, 88
10	**1j**	O	Ph	**2j**, 84
11	**1k**	C(CO_2Et)$_2$	Me	**2k**, 74
12	**1l**	C(CO_2Et)$_2$	Ph	**2l**, 84
13	**1m**			**2m**, 52
14	**1n**			**2n**, 14
15	**1o**			NR

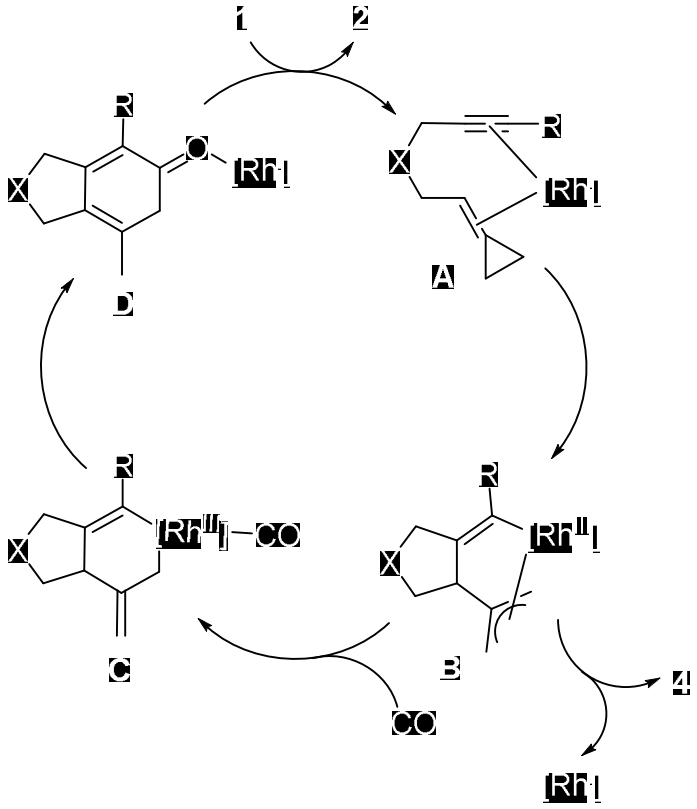
[a] Reaction conditions: 10 mol% Rh(PPh_3)$_3$Cl, 15 mol% $AgCO_2CF_3$, 1 atm CO in xylenes (0.055 M) at 120 °C for ~3 h. [b] Isolated yields.

Interestingly, for an enyne with a cyclopropyl group on the terminal alkyne, the reaction proceeded smoothly to afford a cyclopropylbenzene derivative in 85% yield (entry 8). Cyclopropylbenzene can be used in the synthesis of potent and selective α_{2C}-agonists[16] or norepinephrine reuptake inhibitors.[17] Both carbon- and oxygen-linked 1,6-enynes could be used in the reaction with similar results (entries 9-12). When 1,7-enynes were used in the reaction, the yield of a reaction was highly dependent upon the substituent on the alkyne. When a 1,7-enyne bearing a methyl group on the alkyne was used as the substrate, the corresponding product, tetrahydroisoquinolinol, was isolated in 52% yield (entry 13). This is the first reported the transformation of nitrogen-tethered 1,7-enynes to isoquinolinols.[18] Tetrahydroisoquinolines are present in various potent cytotoxic agents that display a range of antitumor activities, antimicrobial, and other interesting biological activity depending on their structures.[19] However, for a 1,7-enyne bearing a phenyl substituent on the alkyne, was known to be inert in the gold-catalyzed cycloisomerization,[4] the reaction was sluggish under our optimized reaction conditions. The phenol derivative was isolated in a low yield (14%), whereas the 1-methylene-hexahydro-1*H*-indene (**4n**) was isolated as the major product in 49% yield (entry 14 and eq 2).



The presence of a *gem*-dimethyl group at the propargylic position does not result in any carbonylation and the 4-methylene-hexahydropentalene derivative was isolated in 33% yield (eq 3). The formation of compound **4** from alkylidenecyclopropanes has been reported in the palladium-catalyzed cycloaddition reaction.[20] When the same reaction was conducted without CO, the reaction became slow and the yield of 4-methylene-hexahydropentalene did not improve. The presence of CO is beneficial for the reaction, even though the reaction to form **4** is not related to the carbonylation reaction.[15,21]

On the basis of the related previous studies,[22,23] a plausible reaction mechanism is outlined in Scheme 1. Alkylidenecyclopropane (**1**) in the presence of a rhodium catalyst [Rh] undergoes a reaction to form a rhodium(I) intermediate (**A**), followed by a ring opening of



Scheme 1. Proposed Reaction Mechanism

the cyclopropane moiety and the oxidative addition to the rhodium center to form B. In the formation of intermediate B, the rhodium center was inserted into the distal bond of the cyclopropane ring. A reductive cyclization followed by demetallation leads to compound 4. Coordination of CO to B leads to the formation of intermediate C. Insertion of CO, reductive elimination, and a 1,3–hydride shift leads to intermediate D. Subsequent isomerization of D affords the final product 2.

Conclusion

In summary, we developed a novel rhodium-catalyzed carbonylative [3+2+1] cycloaddition of alkylidenecyclopropanes under mild reaction conditions, for the synthesis of phenols. A variety of tethers (nitrogen-, oxygen-, and *gem*-diester) could be employed to construct hetero- and carbobicyclic skeletons. The tether length allows the formation of 5,6- and 6,6-bicyclic systems. The products possess a phenol ring bearing a vinyl or a cyclopropyl substituent, which will provide access for further functionalization and operation.[24]

Experimental Section

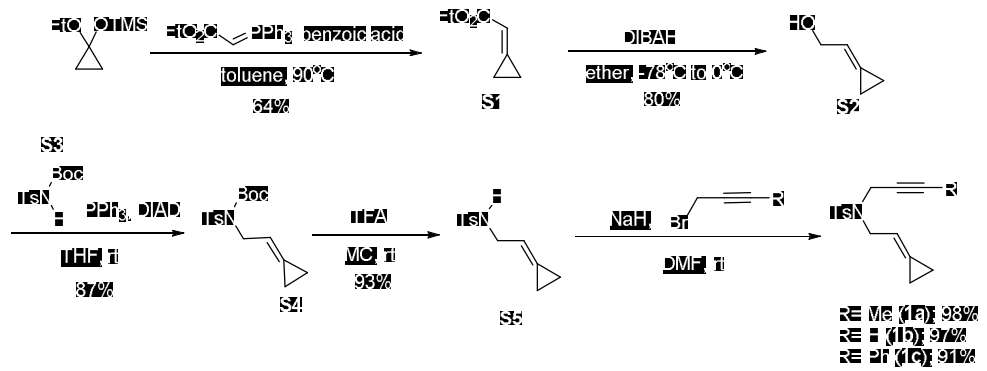
Chemicals and Reagents All solvents were dried and distilled according to standard methods before use. Solvents utilized in this work were obtained from Samchun Pure Chemicals (hexanes, ethyl acetate, diethyl ether, dichloromethane, tetrahydrofuran, and acetone). Reactions were carried out in a flame-dried glassware equipped with a stirring bar and capped with a rubber septum under N_2, unless otherwise indicated. Elevated temperatures were maintained in thermostat-controlled oil baths. High purity CO (99.95%) was used.

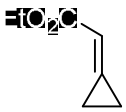
Reagents were purchased from Sigma-Aldrich, Alfa Aesar, or TCI and were used as received. $Rh(PPh_3)_3Cl$ and $AgCO_2CF_3$ were purchased from Aldrich and Strem Chemical Co. Reactions were monitored by thin-layer chromatography on 0.25 mm E. Merck silica gel plates (60F-254). The TLC plates were visualized by UV-light (254 nm) and treatment with acidic *p*-anisaldehyde and $KMnO_4$ stain followed by gentle heating. Workup procedures were done in air. Flash column chromatography was carried out on Merck 60 silica gel (230 – 400 mesh).

Physical Methods ^1H and ^{13}C NMR spectra were recorded with Bruker (300 MHz) and Varian spectrometer (400 MHz) spectrometer. ^1H NMR spectra were referenced to residual TMS (0 ppm) and reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets,

ddd = doublet of doublet of doublets, dt = doublets of triplets, td = triplet of doublets, qd = quartet of doublets, br s = broad singlet, m = multiplet). Chemical shifts of the ^{13}C NMR spectra were measured relative to $CDCl_3$ (77.16 ppm) or acetone-d_6 (29.84 ppm). IR spectra were measured on a Thermo Scientific Nicolet 6700 spectrometer. High-Resolution Mass Spectra were obtained at the Korea Basic Science Institute (Daegu, South Korea) on a Jeol JMS 700 high resolution mass spectrometer. X-Ray Diffraction (XRD) data were obtained at the Research Institute of Advanced Material (Seoul National University, South Korea) on a Brucker New D8 Advance.

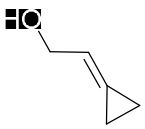
II. General procedure for the Synthesis of Substrates and their Characterization Data





(S1) A suspension of 4.02 mL (20.0 mmol) of (1-ethoxycyclopropoxy)trimethylsilane, 9.06 g (26.0 mmol) of ethyl (triphenylphosphoranylidene)acetate and 0.318 g (2.60 mmol) of benzoic acid in 55 mL of toluene is stirred at a bath temperature of 90 °C for 20 h. Purification by silica gel flash chromatography directly (15:1 petroleum ether/diethyl ether) provided **S1** (1.61 g, 64%).

Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.22 – 6.20 (m, 1 H), 4.19 (q, J = 7.1 Hz, 2 H), 1.47 – 1.40 (m, 2 H), 1.28 (t, J = 7.1 Hz, 3 H), 1.24 – 1.18 (m, 2 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 166.3, 145.1, 111.1, 60.2, 14.4, 4.7, 2.1 ppm.

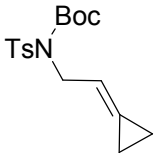


(S2) To a solution of **S1** (1.62 g, 12.8 mmol) in Et_2O (26 mL) was added a 1.0 M solution of DIBAH (28.2 mL, 28.2 mmol) in hexane at −78 °C and the reaction mixture was warmed to 0 °C for 3 h, then, quenched by MeOH and sat. Rochelle salt at 0 °C. After the solution was stirred for 1h, the precipitate was filtrated through a Celite pad and the organic layer was washed with brine, dried over anhydrous $MgSO_4$. Rotary evaporation led to the isolation of **S2** (0.864 g, 80%).

Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.02 (ddd, J = 6.1, 4.1, 2.0 Hz, 1 H), 4.31 – 4.26 (m, 2 H), 1.47 (t, J = 5.7 Hz, 1 H), 1.16 – 1.05 (m, 4 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 124.8, 117.4, 63.4, 1.8, 1.7 ppm.

(S3) A solution of Boc_2O (2.64 mL, 11.5 mmol) in dichloromethane (3 mL) was added dropwise at room temperature to a solution of triethylamine (1.53 mL, 11.0 mmol), DMAP (0.122 g, 1.0 mmol) and *p*−toluenesulfonamide (1.71 g, 10.0 mmol) in dichloromethane (13 mL). The colorless reaction mixture was stirred at room temperature for 5 h. After completion the solvent was removed under vacuum, the residue was diluted with ethyl acetate (60 mL) and 1N HCl (40 mL). An organic layer was washed with water, brine and then dried over $MgSO_4$ and concentrated on a rotary evaporator to give a white solid. Crystallization from hot hexane (10 mL) gave **S3** (2.44 g, 90%).

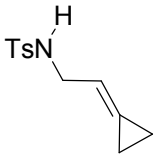
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.0 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 2.45 (s, 3 H), 1.39 (s, 9 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.2, 144.8, 136.0, 129.6, 128.3, 84.2, 28.0, 21.8 ppm.



(S4) A solution of triphenylphosphine (171 mg, 0.651 mmol), **S2** (49.8 mg, 0.592 mmol) and **S3** (177 mg, 0.651 mmol) in dry THF (2 mL) was stirred for 10 minutes. Diisopropyl azodicarboxylate (0.128 mL, 0.651 mmol) was then added at 0 °C. The reaction mixture was stirred at 25 °C for 8 h. The solvent was removed by a rotary evaporator and the residue was purified by silica gel flash chromatography (15:1 hexane/acetone) to afford the desired substrate **S4** (174 mg, 87%).

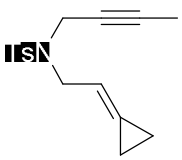
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 2 H),

7.28 (d, J = 8.0 Hz, 2 H), 5.94 (tp, J = 5.9, 2.0 Hz, 1 H), 4.61 – 4.57 (m, 2 H), 2.43 (s, 3 H), 1.35 (s, 9 H), 1.13 – 1.08 (m, 4 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.0, 144.0, 137.6, 129.2, 128.0, 126.4, 113.6, 84.1, 47.9, 28.0, 21.7, 2.3, 2.1 ppm. **HRMS (EI)** calc. for $[C_{17}H_{23}NO_4S, M]^+$ 337.1348, found 337.1349.



(S5) To a solution of **S4** (364 mg, 1.08 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.402 mL, 5.40 mmol) and the mixture was stirred at room temperature for 3 h. The reaction was quenched by saturated aqueous $NaHCO_3$ solution and was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (4:1 hexane/acetone) to afford the desired substrate **S5** (238 mg, 93%).

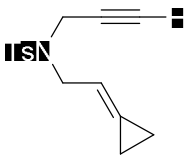
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 5.68 (tdd, J = 6.0, 4.0, 2.1 Hz, 1 H), 4.51 (t, J = 5.6 Hz, 1 H), 3.77 – 3.68 (m, 2 H), 2.43 (s, 3 H), 1.05 – 0.97 (m, 4 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5, 137.2, 129.7, 127.3, 126.3, 113.1, 44.8, 21.6, 2.1, 2.0 ppm.



(1a) To a solution of **S5** (285 mg, 1.2mmol) in DMF (12 mL) was added NaH (34.6 mg, 1.44 mmol) at 0 °C and the mixture was stirred for 1 h at the same temperature. Then, 1-bromo-2-butyne (0.126 mL, 1.44 mmol)

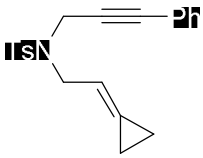
was added at 0 °C and the mixture was stirred for 16 h at room temperature. The reaction was quenched by water and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (dichloromethane) to afford the desired substrate **1a** (340 mg, 98%).

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 5.75 – 5.65 (m, 1 H), 4.00 (d, *J* = 1.7 Hz, 2 H), 3.94 (d, *J* = 6.9 Hz, 2 H), 2.43 (s, 3 H), 1.54 (s, 3 H), 1.14 – 1.01 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 136.4, 129.3, 128.4, 128.0, 112.3, 81.2, 72.0, 47.9, 36.4, 21.6, 3.3, 2.7, 2.0 ppm.



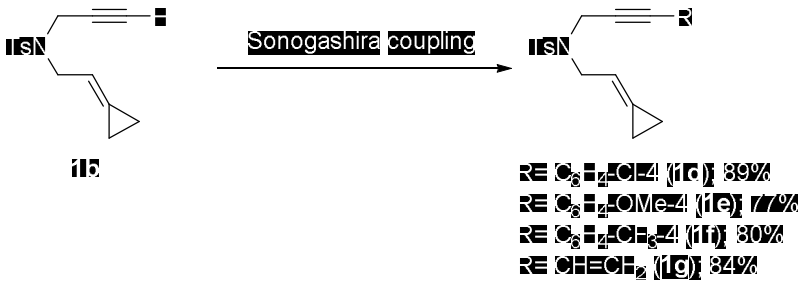
(1b) Prepared according to the procedure for **1a**, using propargyl bromide solution instead of 1-bromo-2-butyne. Yield of **1b**: 97%.

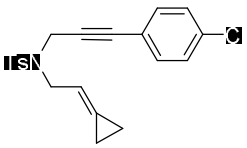
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 5.79 – 5.63 (m, 1 H), 4.08 (d, *J* = 2.4 Hz, 2 H), 3.98 (d, *J* = 6.9 Hz, 2 H), 2.43 (s, 3 H), 1.98 (t, *J* = 2.5 Hz, 1 H), 1.13 – 1.04 (m, 4 H) ppm. ^{13}C NMR (101 MHz, acetone) δ 144.3, 137.6, 130.3, 129.3, 128.5, 112.6, 77.8, 75.0, 48.5, 36.4, 21.4, 2.7, 2.2 ppm.



(1c) Prepared according to the procedure for **1a**, using (3-bromo-1-propynyl)benzene solution. Yield of **1c**: 91%.

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2 H), 7.31 – 7.21 (m, 5 H), 7.06 (dd, *J* = 8.0, 1.4 Hz, 2 H), 5.84 – 5.70 (m, 1 H), 4.28 (s, 2 H), 4.04 (d, *J* = 6.9 Hz, 2 H), 2.33 (s, 3 H), 1.20 – 1.01 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 136.1, 131.5, 129.6, 128.9, 128.4, 128.2, 127.9, 122.4, 112.1, 85.4, 82.0, 48.1, 36.7, 21.5, 2.8, 2.0 ppm.

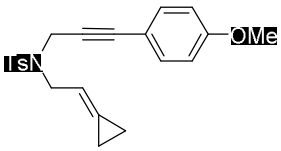




(1d) A mixture of **1b** (116 mg, 0.42 mmol), 1-chloro-4-iodobenzene (120 mg, 0.504 mmol), Et_3N (0.586 mL, 4.2 mmol), $PdCl_2(PPh_3)_2$ (8.8 mg, 0.0126 mmol), and CuI (2.4 mg, 0.0126 mmol) were dissolved in 3 mL of DMF in a schlenk flask wrapped with aluminum foil. The mixture was stirred for 12 h at room temperature. The completion of reaction was checked by TLC. Then, the reaction mixture was

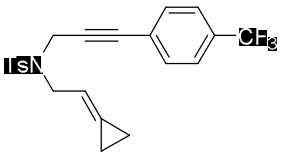
poured into water and was extracted with NH_4Cl and AcOEt. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude products were purified by flash column chromatography using silica gel (15:1 hexane/ethyl acetate) to afford the desired substrate **1d** (144 mg, 89%).

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2 H), 7.28 – 7.19 (m, 4 H), 6.98 (d, *J* = 8.6 Hz, 2 H), 5.84 – 5.70 (m, 1 H), 4.27 (s, 2 H), 4.03 (d, *J* = 6.9 Hz, 2 H), 2.34 (s, 3 H), 1.17 – 1.01 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.5, 136.1, 134.4, 132.7, 129.6, 129.0, 128.6, 127.9, 120.9, 112.0, 84.3, 83.2, 48.2, 36.6, 21.5, 2.8, 2.0 ppm.



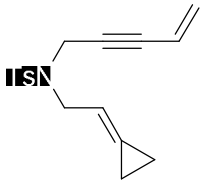
(1e) Prepared according to the procedure for **1a**, using 4−iodoanisole. Yield of **1e**: 77%.

Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2 H), 7.25 (d, *J* = 7.0 Hz, 2 H), 7.00 (d, *J* = 8.9 Hz, 2 H), 6.76 (d, *J* = 8.9 Hz, 2 H), 5.81 – 5.72 (m, 1 H), 4.27 (s, 2 H), 4.03 (d, *J* = 6.9 Hz, 2 H), 3.80 (s, 3 H), 2.35 (s, 3 H), 1.16 – 1.04 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 143.4, 136.2, 133.0, 129.5, 128.8, 127.9, 114.6, 113.8, 112.1, 85.3, 80.6, 55.4, 48.1, 36.8, 21.6, 2.8, 2.0 ppm.



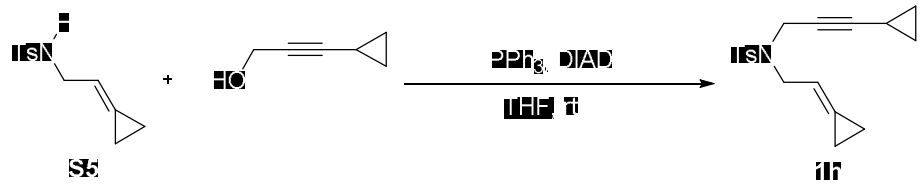
(1f) A mixture of **1b** (110 mg, 0.40 mmol), 4−iodobenzotrifluoride (0.071 ml, 0.48 mmol), Et_3N (0.558 mL, 4.0 mmol), $PdCl_2(PPh_3)_2$ (8.4 mg, 0.012 mmol), and CuI (2.3 mg, 0.012 mmol) were dissolved in 3 mL of DMF in a schlenk flask wrapped with aluminum foil. The mixture was stirred for 12 h at 50 °C. The completion of reaction was checked by TLC. Then, the reaction mixture was poured into water and was extracted with NH_4Cl and AcOEt. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude products were purified by flash column chromatography using silica gel (15:1 hexane/ethyl acetate) to afford the desired substrate **1f** (134 mg, 80%).

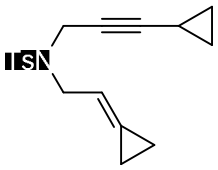
White solid; **mp**: 75−77 °C; **IR** (Neat) 2986, 2956, 2926, 1936, 1806, 1613 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.3 Hz, 2 H), 7.50 (d, J = 8.1 Hz, 2 H), 7.25 (d, J = 8.2 Hz, 2 H), 7.16 (d, J = 8.0 Hz, 2 H), 5.85 – 5.70 (m, 1 H), 4.30 (s, 2 H), 4.04 (d, J = 6.9 Hz, 2 H), 2.33 (s, 3 H), 1.18 – 1.03 (m, 4 H) ppm. **^{13}C NMR** (101 MHz, acetone) δ 144.5, 137.2, 132.8, 130.4, 130.1, 129.6, 128.6, 127.3, 126.1 (q, J = 3.9 Hz), 123.6, 112.6, 86.0, 84.4, 48.9, 37.1, 21.3, 2.9, 2.26 ppm. **HRMS (EI)** calc. for $[C_{22}H_{20}F_3NO_2S, M]^+$ 419.1167, found 419.1165.



(1g) A mixture of $PdCl_2(PPh_3)_2$ (17.5 mg, 0.025 mmol), n−butylamine (0.494 mL, 5.0 mmol), CuI (9.5 mg, 0.050 mmol), **1b** (138 mg, 0.50 mmol), and 1.0 M solution of vinyl bromide (1.0 mL, 1.0 mmol) in THF were dissolved in 3 mL of THF in a schlenk flask wrapped with aluminum foil. The mixture was stirred for 12 h at 45 °C. The completion of reaction was checked by TLC. Then, the reaction mixture was poured into water and was extracted with NH_4Cl and AcOEt. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude products were purified by flash column chromatography using silica gel (15:1 hexane/ethyl acetate) to afford the desired substrate **1g** (127 mg, 84%).

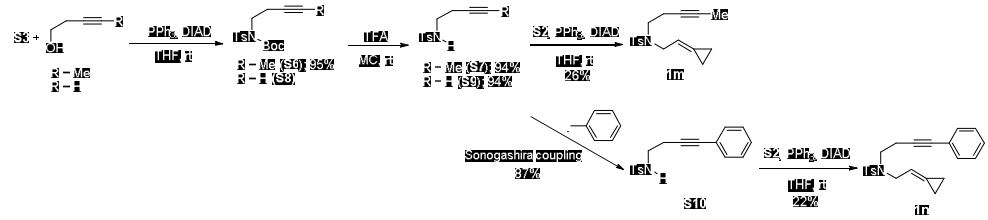
White solid; **mp**: 48−49 °C; **IR** (Neat) 2982, 1876, 1728, 1598 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 2 H), 7.29 (d, *J* = 8.0 Hz, 2 H), 5.76 – 5.67 (m, 1 H), 5.50 (ddt, *J* = 17.2, 11.2, 1.9 Hz, 1 H), 5.33 (ddd, *J* = 19.6, 14.2, 2.4 Hz, 2 H), 4.18 (d, *J* = 1.8 Hz, 2 H), 3.96 (d, *J* = 6.9 Hz, 2 H), 2.42 (s, 3 H), 1.16 – 1.01 (m, 4 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.4, 136.1, 129.5, 128.9, 127.9, 127.2, 116.4, 112.0, 84.0, 82.9, 48.1, 36.6, 21.6, 2.7, 2.0 ppm. **HRMS (EI)** calc. for $[C_{17}H_{19}NO_2S, M]^+$ 301.1136, found 301.1138.

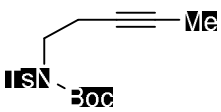




(1h) A solution of triphenylphosphine (144 mg, 0.55 mmol), 3-cyclopropylprop-2-yn-1-ol (72.1 mg, 0.75 mmol) and **S5** (119 mg, 0.50 mmol) in dry THF (2 mL) was stirred for 10 minutes. Diisopropyl azodicarboxylate (0.108 mL, 0.55 mmol) was then added at 0 °C. The reaction mixture was stirred at 25 °C for 12 h. The solvent was removed on a rotary evaporator and the residue was purified by silica gel flash chromatography (15:1 hexane/ethyl acetate) to afford the desired substrate **1h** (82.0 mg, 52%).

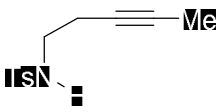
White solid; **mp**: 64–66 °C; **IR** (Neat) 3009, 2245, 1918, 1738, 1597 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 5.77 – 5.65 (m, 1 H), 4.01 (d, J = 1.9 Hz, 2 H), 3.94 (d, J = 6.9 Hz, 2 H), 2.44 (s, 3 H), 1.14 – 1.02 (m, 4 H), 1.00 – 0.90 (m, 1 H), 0.64 – 0.58 (m, 2 H), 0.34 – 0.28 (m, 2 H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.2, 136.4, 129.4, 128.4, 127.9, 112.2, 89.0, 68.0, 47.8, 36.3, 21.6, 7.9, 2.7, 2.0, 0.1, −0.7 ppm. **HRMS (FAB)** calc. for $[C_{18}H_{21}NO_2S, M+H]^+$ 316.1371, found 316.1370.





(S6) A solution of triphenylphosphine (2.89 g, 11.0 mmol), 3-pentyn-1-ol (0.924 mL, 10.0 mmol) and **S3** (2.98 g, 11.0 mmol) in dry THF (36 mL) was stirred for 10 minutes. Diisopropyl azodicarboxylate (2.17 mL, 11.0 mmol) was then added at 0 °C. The reaction mixture was stirred at 25 °C for 12 h. The solvent was removed on a rotary evaporator and the residue was purified by silica gel flash chromatography (15:1 hexane/ethyl acetate) to afford the desired substrate **S6** (3.21 g, 95%).

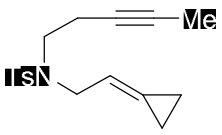
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 3.95 (dd, J = 8.0, 7.0 Hz, 2 H), 2.63 – 2.53 (m, 2 H), 2.44 (s, 3 H), 1.76 (t, J = 2.5 Hz, 3 H), 1.34 (s, 9 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 144.2, 137.4, 129.3, 127.9, 84.4, 77.9, 75.3, 45.8, 27.9, 21.7, 20.3, 3.6 ppm.



(S7) To a solution of **S6** (3.11 g, 9.21 mmol) in CH_2Cl_2 (16 mL) was added TFA (3.43 mL, 46.1 mmol) and the mixture was stirred at room temperature for 3 h. The reaction was quenched by sat. aq. $NaHCO_3$. And the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were

washed with brine, dried over $MgSO_4$. **S7** (2.05 g, 94%) was isolated from the reaction solution by rotary evaporation.

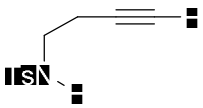
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2 H), 7.32 (d, *J* = 8.2 Hz, 2 H), 4.91 (t, *J* = 6.1 Hz, 1 H), 3.05 (q, *J* = 6.4 Hz, 2 H), 2.43 (s, 3 H), 2.27 (pd, *J* = 5.0, 2.4 Hz, 2 H), 1.74 (t, *J* = 2.5 Hz, 3 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.6, 137.0, 129.8, 127.1, 78.5, 75.0, 42.1, 21.6, 20.0, 3.5 ppm.



(1m) A solution of triphenylphosphine (254 mg, 0.967 mmol), **S2** (73.9 mg, 0.879 mmol) and **S7** (229 mg, 0.967 mmol) in dry THF (4 mL) was stirred for 10 minutes. Diisopropyl azodicarboxylate (0.190 mL, 0.967 mmol) was then added at 0 °C. The reaction mixture was stirred at 25 °C for 12 h. The solvent was removed on a rotary evaporator and the residue was purified by silica gel flash chromatography (15:1 Petroleum ether/diethyl ether) to afford the desired substrate **1m** (69.3 mg, 26%).

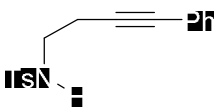
White solid; **mp**: 43–45 °C; **IR** (Neat) 2920, 2865, 1595 cm^{-1}; **^{1}H NMR** (400 MHz, acetone) δ 7.75 (d, *J* = 8.3 Hz, 2 H), 7.43 (d, *J* = 8.3 Hz, 2 H), 5.66 – 5.57 (m, 1 H), 4.00 (d, *J* = 6.8 Hz, 2 H), 3.25 – 3.17 (m, 2 H), 2.44 (s, 3 H), 2.40 – 2.30 (m, 2 H), 1.70 (t, *J* = 2.6 Hz, 3 H), 1.12 – 1.03 (m, *J* = 1.0 Hz, 4 H) ppm. **^{13}C NMR** (101 MHz, acetone) δ 144.1, 138.5, 130.5, 128.2, 127.9, 113.7, 77.7, 76.5, 50.1, 47.2, 21.3, 19.9, 3.2, 2.7, 2.1 ppm. **HRMS (EI)** calc. for [$C_{17}H_{21}NO_2S$,

M]$^+$ 303.1293, found 303.1293.



(S9) A solution of triphenylphosphine (1.44 g, 5.5 mmol), 3-butyn-1-ol (0.378 mL, 5 mmol) and **S3** (1.49 g, 5.5 mmol) in dry THF (18 mL) was stirred for 10 minutes. Diisopropyl azodicarboxylate (1.08 mL, 5.5 mmol) was then added at 0 °C. The reaction mixture was stirred at 25 °C for 12 h. The solvent was removed on a rotary evaporator and the residue was purified by silica gel flash chromatography (15:1 hexane/ethyl acetate) provided **S8.** To a solution of **S8** in CH_2Cl_2 (9 mL) was added TFA (1.86 mL, 25 mmol) and the mixture was stirred at room temperature for 2 h. The reaction was quenched by sat. aq. $NaHCO_3$. And the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$. **S9** (2.05 g, 94%) was isolated from the reaction solution by rotary evaporation.

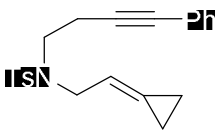
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 4.93 (t, *J* = 6.2 Hz, 1 H), 3.11 (q, *J* = 6.5 Hz, 2 H), 2.43 (s, 3 H), 2.38 – 2.32 (m, 2 H), 2.02 – 1.98 (m, 1 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7, 136.9, 129.9, 127.1, 80.4, 71.0, 41.7, 21.6, 19.8 ppm.



(S10) A mixture of $PdCl_2(PPh_3)_2$ (70.2 mg, 0.10 mmol), n-butylamine (1.98 mL, 20 mmol), CuI (38.1 mg, 0.20 mmol), **S9** (447 mg, 2.0 mmol), and Iodobenzene

(0.268 mL, 2.4 mmol) in THF were dissolved in 12 mL of THF in a schlenk flask wrapped with aluminum foil. The mixture was stirred for 12 h at 45 °C. The completion of reaction was checked by TLC. Then, the reaction mixture was poured into water and was extracted with NH_4Cl and AcOEt. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude products were purified by flash column chromatography using silica gel (3:1 hexane/ethyl acetate) to afford the desired substrate **S10** (573 mg, 87%).

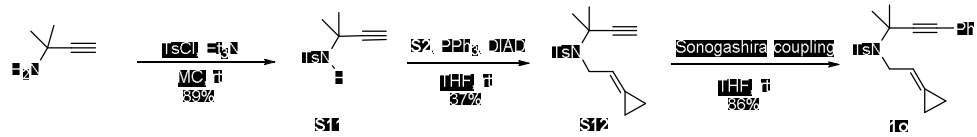
Yellow solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 2 H), 7.37 – 7.32 (m, 2 H), 7.32 – 7.27 (m, 5 H), 4.89 – 4.80 (m, 1 H), 3.19 (q, J = 6.5 Hz, 2 H), 2.57 (t, J = 6.5 Hz, 2 H), 2.42 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.7, 137.1, 131.7, 129.9, 128.4, 128.3, 127.2, 123.0, 85.6, 83.0, 42.0, 21.6, 20.8 ppm.

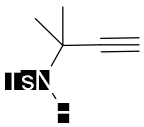


(1n) A solution of triphenylphosphine (346 mg, 1.33 mmol), **S2** (101 mg, 1.21 mmol) and **S10** (435 mg, 1.33 mmol) in dry THF (5 mL) was stirred for 10 minutes. Diisopropyl azodicarboxylate (0.260 mL, 1.33 mmol) was then added at 0 °C. The reaction mixture was stirred at 25 °C for 12 h. The solvent was removed on a rotary evaporator and the residue was purified by silica gel flash chromatography (15:1 hexane/ethyl acetate) provided **1n** (97.3 mg, 22%).

White solid; **IR** (Neat) 3052, 2987, 2939, 1737, 1596 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, J = 8.2 Hz, 2 H), 7.39 – 7.33 (m,

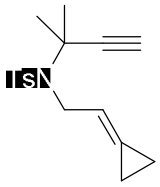
2 H), 7.32 – 7.25 (m, 5 H), 5.70 – 5.63 (m, 1 H), 4.03 (d, J = 6.9 Hz, 2 H), 3.41 – 3.33 (m, 2 H), 2.70 – 2.63 (m, 2 H), 2.42 (s, 3 H), 1.13 – 1.00 (m, J = 12.4, 5.3 Hz, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3, 137.2, 131.6, 129.8, 128.3, 127.9, 127.8, 127.2, 123.4, 112.9, 86.7, 82.2, 49.8, 46.1, 21.6, 20.2, 2.7, 1.9 ppm.





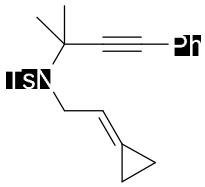
(S11) A solution of 2−methyl−3−butyn−2−amine (1.05 mL, 10.0 mmol), TsCl (0.95 g, 5.0 mmol) and Et_3N (1.39 mL, 10.0 mmol) in dry CH_2Cl_2 (15 mL) was stirred for 12 h. The reaction mixture was extracted with NH_4Cl and AcOEt, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude products were purified by flash column chromatography using silica gel (3:1 hexane/ethyl acetate) to afford the desired substrate **S11** (1.06 g, 89%).

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.0 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 5.23 (s, 1 H), 2.42 (s, 3 H), 2.08 (s, 1 H), 1.54 (s, 6 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 138.9, 129.3, 127.7, 85.5, 71.3, 50.0, 30.8, 21.6 ppm.



(S12) To a solution of triphenylphosphine (372 mg, 1.42 mmol) in THF (5 mL) was added Diisopropyl azodicarboxylate (0.279 mL, 1.42 mmol) at 0 °C, followed by the addition of the **S2** (109 mg, 1.29 mmol) and **S11** (337 mg, 1.42 mmol). The reaction mixture was stirred at 25 °C for 12 h. The solvent was removed on a rotary evaporator and the residue was purified by silica gel flash chromatography (15:1 hexane/ethyl acetate) provided **S12** (145 mg, 37%).

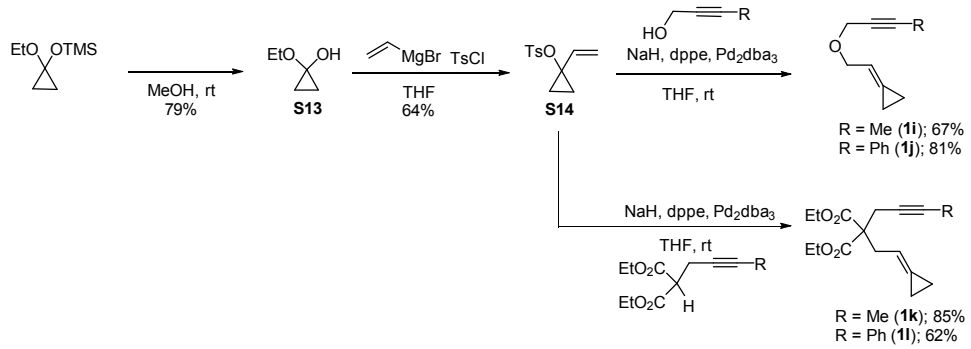
White solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 6.02 (tp, *J* = 6.2, 2.0 Hz, 1 H), 4.32 – 4.25 (m, 2 H), 2.41 (s, 3 H), 2.31 (s, 1 H), 1.68 (s, 6 H), 1.12 – 1.05 (m, *J* = 1.5 Hz, 4 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 142.9, 140.0, 129.4, 127.3, 124.8, 116.9, 86.7, 71.7, 56.2, 49.6, 30.8, 21.6, 2.3, 2.1 ppm. **HRMS (EI)** calc. for $[C_{17}H_{21}NO_2S, M]^+$ 303.1293, found 303.1296.

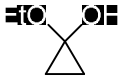


(1o) A mixture of $PdCl_2(PPh_3)_2$ (16.7 mg, 0.024 mmol), n−butylamine (0.469 mL, 4.75 mmol), CuI (9.0 mg, 0.0475 mmol), **S12** (144 mg, 0.475 mmol), and Iodobenzene (0.064 mL, 0.57 mmol) in THF were dissolved in 3 mL of THF in a schlenk flask wrapped with aluminum foil. The mixture was stirred for 12 h at room temperature. The completion of reaction was checked by TLC. Then, the reaction mixture was poured into water and was extracted with NH_4Cl and

AcOEt. The organic layer was dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude products were purified by flash column chromatography using silica gel (15:1 hexane/ethyl acetate) to afford the desired substrate **1o** (155 mg, 86%).

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.3 Hz, 2 H), 7.32 – 7.23 (m, 3 H), 7.23 – 7.18 (m, 4 H), 6.06 (tp, J = 6.1, 2.0 Hz, 1 H), 4.37 – 4.31 (m, 2 H), 2.35 (s, 3 H), 1.75 (s, 6 H), 1.11 – 1.04 (m, J = 2.8, 1.3 Hz, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.8, 139.8, 131.6, 129.4, 128.3, 128.2, 127.4, 124.6, 122.7, 117.2, 91.9, 83.5, 56.8, 49.8, 31.0, 21.5, 2.3, 2.1 ppm. HRMS (FAB) calc. for $[C_{18}H_{21}NO_2S, M+H]^+$ 316.1371, found 316.1371. HRMS (FAB) calc. for $[C_{23}H_{25}NO_2S, M]^+$ 379.1606, found 379.1609.





(S13) (1−Ethoxycyclopropoxy)trimethylsilane (2.01 mL, 10.0 mmol) was added all at once to MeOH (7 mL), and the solution was stirred at room temperature for 21 h. **S13** (807

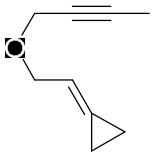
mg, 79%) was isolated from the reaction solution by rotary evaporation.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (q, *J* = 7.1 Hz, 2 H), 3.45 (d, *J* = 1.4 Hz, 1 H), 1.21 (td, *J* = 7.1, 2.1 Hz, 3 H), 0.96 – 0.91 (m, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 85.8, 62.1, 15.5, 14.5 ppm.

(S14) To a solution of **S13** (511 mg, 5.0 mmol) in THF (15 mL) was added 1.0 M solution of vinylmagnesium bromide (10.0 mL, 10.0 mmol) in THF at 0 °C and the mixture was stirred for 2 h at room temperature and then at reflux for 2 h. The mixture was cooled to 0 °C, followed by the addition of the TsCl (1.91 g, 10.0 mmol). The solution was stirred at 0 °C for 14 h. The reaction was quenched by H_2O. And the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude products were purified by flash column chromatography using silica gel (15:3, petroleum ether/diethyl ether) to afford the desired substrate **S14** (763 mg, 64%).

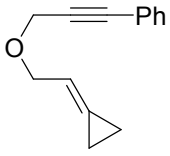
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 5.89 (dd, *J* = 17.2, 10.8 Hz, 1 H), 5.10 (d, *J* = 17.1 Hz, 1 H), 5.01 (d, *J* = 10.8 Hz, 1 H), 2.44 (s, 3 H), 1.35 (q, *J* = 6.2 Hz, 2 H), 0.96 – 0.89 (m, 2 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 136.6, 135.2, 129.8, 128.0, 113.6, 65.5, 21.8, 14.1

ppm.



(1i) A solution of 2-butyn-1-ol (0.202 mL, 2.7 mmol) in THF (3 mL) was added NaH at 0 °C. After the solution was stirred at rt for 20 min, the solution was transferred via cannula over a mixture of **S14** (238 mg, 1.00 mmol), Pd_2dba_3 (18.3 mg, 0.020 mmol) and 1,2-bis(diphenylphosphino)ethane (dppe, 2mol%) in THF (2 mL), previously stirred for 15 min at room temperature. The reaction mixture was allowed to stir for 10 min at rt, poured into water and extracted with ether. The combined organic layers were dried, filtered and concentrated and the crude product was purified by flash chromatography (19:1 hexane/diethyl ether) to give **1i** (124 mg, 91%).

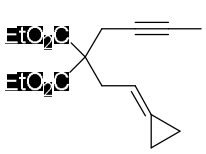
Colorless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.98 – 5.89 (m, 1 H), 4.20 – 4.15 (m, 2 H), 4.12 – 4.08 (m, 2 H), 1.86 (td, J = 2.3, 0.5 Hz, 3 H), 1.16 – 1.05 (m, 4 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 127.5, 114.2, 82.2, 75.2, 69.6, 57.4, 3.6, 2.3, 1.7 ppm. **HRMS (EI)** calc. for $[C_{17}H_{21}NO_2S, M-H]^+$ 135.0810, found 135.0809.



(1j) Prepared according to the procedure for **1i**, using 3-phenyl-2-propyn-1-ol instead of 2-butyn-1-ol. Yield of **1j**: 81%.

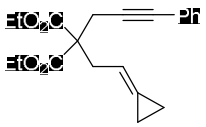
Yellow oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.48 – 7.42 (m, 2 H), 7.34

– 7.28 (m, 3 H), 6.02 – 5.92 (m, 1 H), 4.37 (s, 2 H), 4.31 – 4.25 (m, 2 H), 1.16 – 1.10 (m, *J* = 1.1 Hz, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 131.8, 128.5, 128.4, 128.2, 122.9, 114.2, 86.1, 85.4, 69.9, 57.7, 2.5, 1.9 ppm.



(1k) Prepared according to the procedure for **1i**, using diethyl 2-(but-2-yn-1-yl)malonate. Yield of **1k**: 85%.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.63 – 5.56 (m, 1 H), 4.24 – 4.14 (m, 4 H), 2.93 (d, *J* = 7.5 Hz, 2 H), 2.72 (q, *J* = 2.5 Hz, 2 H), 1.75 (t, *J* = 2.6 Hz, 3 H), 1.24 (t, *J* = 7.1 Hz, 6 H), 1.12 – 0.96 (m, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 126.9, 111.7, 78.5, 73.8, 61.4, 57.3, 34.6, 23.0, 14.1, 3.6, 3.0, 1.9 ppm.



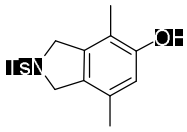
(1l) Prepared according to the procedure for **1i**, using diethyl 2-(3-phenylprop-2-yn-1-yl)malonate. Yield of **1l**: 62%.

Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.34 (m, 2 H), 7.30 – 7.26 (m, 3 H), 5.70 – 5.59 (m, 1 H), 4.30 – 4.15 (m, 4 H), 3.05 – 2.98 (m, *J* = 8.9 Hz, 4 H), 1.26 (t, *J* = 7.1 Hz, 6 H), 1.13 – 1.01 (m, 4 H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 131.7, 128.3, 128.0, 127.3, 123.5, 111.6, 84.9, 83.3, 61.6, 57.5, 34.9, 23.6,

14.2, 3.1, 2.1 ppm.

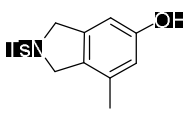
General procedure for Rh-catalyzed carbonylative [3+2+1] cycloaddition of alkyne-tethered Alkylidenecyclopropanes and Characterization Data

$Rh(PPh_3)_3Cl$ (15.3 mg, 0.0165 mmol) and $AgCO_2CF_3$ (5.5 mg, 0.0248mmol) were weighed into a Schlenk tube under an atmosphere of nitrogen and the tube was wrapped in aluminium foil. Then CO was bubbled through the solution from a balloon via a needle for 10 min. Anhydrous xylenes (1 mL) was added to the tube fitted with a carbon monoxide balloon (1 atm) and the resulting solution was stirred at 120 °C for *ca.*45minutes. The alkylidenecyclopropanes (0.165 mmol) in xylenes (2 mL) was added with a syringe and the mixture was allowed to stir at 120 °C. When the reaction was complete, xylenes was concentrated *in vacuo*. Purification by silica gel flash chromatography (3:1 hexane/ethyl acetate) furnished the bicyclic phenol.

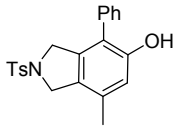


(2a) White solid; **mp**: 209~210 °C (decomp.); **IR** (Neat) 3456, 2853, 1596, 1519 cm^{-1}; **^{1}H NMR** (400 MHz, acetone) δ 8.11 (s, 1 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.41 (d, J = 8.0 Hz, 2 H), 6.56 (s, 1 H), 4.52 (s, 2 H), 4.46 (s, 2 H), 2.38 (s, 3 H), 2.08 (s, 3 H), 2.02 (s, 3 H) ppm. **^{13}C NMR** (101

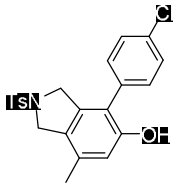
MHz, DMSO) δ 154.9, 143.6, 135.7, 133.0, 130.0, 129.8, 127.5, 124.5, 115.5, 115.2, 53.3, 52.8, 21.0, 18.1, 11.7 ppm. **HRMS (EI)** calc. for $[C_{17}H_{19}NO_3S, M]^+$ 317.1086, found 317.1082.



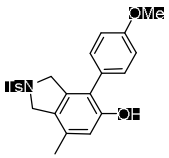
(2b) White solid; **mp**: 191–195 °C (decomp.); **IR** (Neat) 3464, 3429, 3381, 2964, 2926, 2843, 1742, 1598 cm^{-1}; **^{1}H NMR** (400 MHz, acetone) δ 8.23 (s, 1 H), 7.78 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 2 H), 6.54 – 6.48 (m, 2 H), 4.49 (s, 2 H), 4.43 (s, 2 H), 2.38 (s, 3 H), 2.11 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, acetone) δ 158.4, 144.4, 138.0, 134.9, 134.5, 130.6, 128.5, 126.7, 116.5, 107.4, 54.7, 53.2, 21.3, 18.6 ppm. **HRMS (EI)** calc. for $[C_{16}H_{17}NO_3S, M]^+$ 303.0929, found 303.0926.



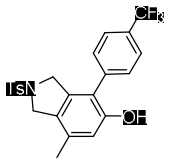
(2c) White solid; **mp**: 186–189 °C (decomp.); **IR** (Neat) 3431, 2918, 2850, 1921, 1576, 1541 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2 H), 7.51 – 7.44 (m, 2 H), 7.43 – 7.37 (m, 1 H), 7.30 (dd, *J* = 8.5, 0.6 Hz, 2 H), 7.26 – 7.21 (m, 2 H), 6.70 (s, 1 H), 5.08 (s, 1 H), 4.53 (s, 2 H), 4.39 (s, 2 H), 2.40 (s, 3 H), 2.17 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.6, 143.7, 135.6, 133.8, 133.8, 133.3, 129.9, 129.7, 129.4, 128.6, 127.6, 127.1, 120.8, 116.1, 53.7, 53.1, 21.6, 18.7 ppm. **HRMS (EI)** calc. for $[C_{22}H_{21}NO_3S, M]^+$ 379.1242, found 379.1240.



(2d) White solid; **mp**: 213–214 °C (decomp.); **IR** (Neat) 3445, 3068, 2919, 2851, 1919, 1807, 1577, 1543 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 7.31 (d, *J* = 8.0 Hz, 2 H), 7.19 (d, *J* = 8.4 Hz, 2 H), 6.69 (s, 1 H), 4.78 (s, 1 H), 4.53 (s, 2 H), 4.36 (s, 2 H), 2.41 (s, 3 H), 2.19 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.5, 143.8, 135.7, 134.7, 133.8, 133.8, 132.3, 130.8, 129.9, 129.9, 127.6, 127.5, 119.7, 116.3, 53.6, 53.1, 21.6, 18.7 ppm. **HRMS (EI)** calc. for $[C_{22}H_{20}ClNO_3S, M]^+$ 413.0852, found 413.0850.

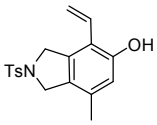


(2e) Pale yellow solid; **mp**: 148–155 °C (decomp.); **IR** (Neat) 3465, 3014, 2970, 1739 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.20 – 7.13 (m, 2 H), 7.04 – 6.98 (m, 2 H), 6.70 (s, 1 H), 4.94 (s, 1 H), 4.53 (s, 2 H), 4.38 (s, 2 H), 3.86 (s, 3 H), 2.41 (s, 3 H), 2.18 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 152.8, 143.7, 135.8, 133.9, 133.1, 130.6, 129.9, 127.6, 127.1, 125.5, 120.5, 115.9, 115.2, 55.5, 53.8, 53.1, 21.6, 18.7 ppm. **HRMS (EI)** calc. for $[C_{23}H_{23}NO_4S, M]^+$ 409.1348, found 409.1349.

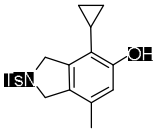


(2f) White solid; **mp**: 207–209 °C (decomp.); **IR** (Neat) 3444, 2947, 2360, 1711, 1619, 1599 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 – 7.69 (m, 4 H), 7.39 (d,

J = 7.9 Hz, 2 H), 7.32 (d, *J* = 7.9 Hz, 2 H), 6.70 (s, 1 H), 4.83 (s, 1 H), 4.53 (s, 2 H), 4.37 (s, 2 H), 2.41 (s, 3 H), 2.19 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 152.3, 143.7, 137.9, 135.4, 134.0, 133.6, 130.6, 130.3, 129.8 (d, *J* = 1.3 Hz), 127.6, 127.5, 126.3 (q, *J* = 3.7 Hz), 125.2, 119.5, 116.4, 53.4, 52.8, 21.5, 18.6 ppm. **HRMS (EI)** calc. for $[C_{23}H_{20}F_3NO_3S, M]^+$ 447.1116, found 447.1119.

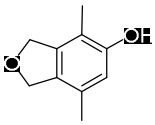


(2g) Pale yellow solid; **mp**: 186−190 °C (decomp.); **IR** (Neat) 3468, 2969, 1738 cm^{-1}; **^{1}H NMR** (400 MHz, acetone) δ 8.60 (s, 1 H), 7.83 (d, *J* = 8.2 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 6.78 (dd, *J* = 18.1, 11.9 Hz, 1 H), 6.64 (s, 1 H), 5.64 (dd, *J* = 18.1, 1.5 Hz, 1 H), 5.33 (dd, *J* = 11.9, 1.6 Hz, 1 H), 4.66 (s, 2 H), 4.46 (s, 2 H), 2.39 (s, 3 H), 2.12 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, acetone) δ 156.0, 144.5, 135.9, 134.8, 133.4, 131.2, 130.6, 128.5, 127.3, 118.0, 117.2, 117.0, 55.0, 53.0, 21.3, 18.5 ppm. **HRMS (EI)** calc. for $[C_{18}H_{19}NO_3S, M]^+$ 329.1086, found 329.1088.

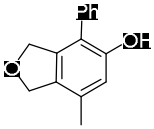


(2h) Pale yellow solid; **mp**: 159−161 °C (decomp.); **IR** (Neat) 3433, 3008, 2823, 1738, 1595 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2 H), 7.33 (d, *J* = 8.0 Hz, 2 H), 6.59 (s, 1 H), 5.60 (s, 1 H), 4.65 (s, 2 H), 4.45 (s, 2 H), 2.41 (s, 3 H), 2.11 (s, 3 H), 1.59 – 1.50 (m, 1 H), 1.03 – 0.96 (m, 2 H), 0.55 – 0.50 (m, 2 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 155.4, 143.7, 137.4, 133.9, 132.5, 129.9, 127.6, 126.9, 118.1, 115.7,

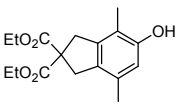
53.3, 52.7, 21.6, 18.6, 6.8, 5.4 ppm. **HRMS (EI)** calc. for $[C_{19}H_{21}NO_3S, M]^+$ 343.1242, found 343.1240.



(2i) Pale yellow solid; **mp**: 183−190 °C (decomp.); **IR** (Neat) 3310, 2968, 2857, 1738, 1620, 1519 cm^{-1}; **^{1}H NMR** (400 MHz, acetone) δ 8.01 (s, 1 H), 6.57 (s, 1 H), 4.96 (d, *J* = 1.9 Hz, 2 H), 4.93 (d, *J* = 2.1 Hz, 2 H), 2.09 (s, 3 H), 2.03 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, acetone) δ 155.6, 140.3, 129.3, 129.3, 115.7, 115.6, 73.6, 73.4, 18.4, 12.0 ppm. **HRMS (EI)** calc. for $[C_{10}H_{12}O_2, M]^+$ 164.0837, found 164.0839.

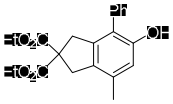


(2j) White solid; **mp**: 113−116 °C; **IR** (Neat) 3311, 2969, 2858, 1739, 1620, 1521 cm^{-1}; **^{1}H NMR** (400 MHz, acetone) δ 8.00 (s, 1 H), 7.42 – 7.36 (m, 4 H), 7.33 – 7.25 (m, 1 H), 6.74 (s, 1 H), 4.98 (t, *J* = 2.0 Hz, 2 H), 4.87 (t, *J* = 1.9 Hz, 2 H), 2.18 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, acetone) δ 154.6, 140.0, 137.5, 131.8, 130.2, 128.9, 127.7, 121.1, 116.8, 116.7, 73.9, 73.3, 18.5 ppm. **HRMS (EI)** calc. for $[C_{15}H_{14}O_2, M]^+$ 226.0994, found 226.0996.

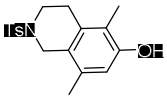


(2k) White solid; **mp**: 114−117 °C; **IR** (Neat) 3502, 2982, 2360, 2339, 1724, 1675, 1656 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.43 (s, 1 H), 4.70 (s, 1 H), 4.21 (q, *J* = 7.1 Hz, 4 H), 3.51 (s, 2 H), 3.45 (s, 2 H), 2.15 (s, 3 H), 2.10 (s, 3 H), 1.26

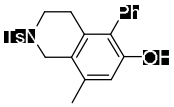
(t, *J* = 7.1 Hz, 6 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.1, 153.0, 140.2, 131.5, 130.6, 116.7, 114.9, 61.8, 60.0, 39.8, 39.1, 18.8, 14.1, 11.9 ppm. **HRMS (EI)** calc. for $[C_{17}H_{22}O_5, M]^+$ 306.1467, found 306.1465.



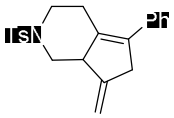
(2l) Pale yellow solid; **mp**: 101–104 °C; **IR** (Neat) 3449, 2970, 2360, 2340, 1741, 1718, 1617 cm^{-1}; **^{1}H NMR** (400 MHz, acetone) δ 7.73 (s, 1 H), 7.45 – 7.27 (m, 5 H), 6.66 (s, 1 H), 4.15 (q, *J* = 7.2 Hz, 4 H), 3.45 (s, 2 H), 3.35 (s, 2 H), 2.20 (s, 3 H), 1.19 (t, *J* = 7.1 Hz, 6 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.8, 152.0, 139.3, 135.0, 134.4, 130.9, 129.9, 129.5, 128.1, 122.1, 115.3, 61.8, 60.2, 40.2, 39.0, 19.1, 14.1 ppm. **HRMS (EI)** calc. for $[C_{22}H_{24}O_5, M]^+$ 368.1624, found 368.1620.



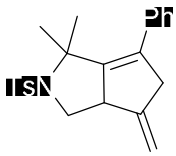
(2m) Pale yellow solid; **mp**: 175–180 °C (decomp.); **IR** (Neat) 3540, 3469, 2971, 2942, 1921, 1739 cm^{-1}; **^{1}H NMR** (400 MHz, acetone) δ 7.94 (s, 1 H), 7.76 (d, *J* = 8.0 Hz, 2 H), 7.44 (d, *J* = 8.0 Hz, 2 H), 6.58 (s, 1 H), 3.99 (s, 2 H), 3.27 (t, *J* = 6.0 Hz, 2 H), 2.76 (t, *J* = 6.0 Hz, 2 H), 2.42 (s, 3 H), 2.08 (s, 3 H), 2.02 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, acetone) δ 154.0, 144.4, 134.4, 133.7, 132.9, 130.5, 128.6, 122.1, 120.2, 115.5, 46.7, 44.4, 27.9, 21.4, 18.4, 10.8 ppm. **HRMS (EI)** calc. for $[C_{18}H_{21}NO_3S, M]^+$ 331.1242, found 331.1239.



(2n) Yellow solid; **mp**: 65−70 °C; **IR** (Neat) 3624, 3592, 3031, 2970, 2942, 2809, 1738 cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2 H), 7.51 – 7.40 (m, 3 H), 7.32 (d, *J* = 8.0 Hz, 2 H), 7.22 – 7.14 (m, 2 H), 6.72 (s, 1 H), 4.63 (s, 1 H), 4.12 (s, 2 H), 3.19 (t, *J* = 5.9 Hz, 2 H), 2.52 (t, *J* = 5.8 Hz, 2 H), 2.43 (s, 3 H), 2.20 (s, 3 H) ppm. **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.1, 143.7, 135.7, 134.4, 133.3, 132.2, 130.4, 129.8, 129.7, 128.5, 127.8, 125.1, 122.5, 115.2, 45.8, 43.3, 28.4, 21.6, 18.9 ppm. **HRMS (EI)** calc. for $[C_{23}H_{23}NO_3S, M]^+$ 393.1399, found 393.1397.



(4n) Yellow solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 2 H), 7.38 – 7.29 (m, 4 H), 7.25 – 7.11 (m, 3 H), 5.10 (d, *J* = 2.2 Hz, 1 H), 5.03 (d, *J* = 2.2 Hz, 1 H), 4.14 (ddd, *J* = 10.8, 6.1, 1.6 Hz, 1 H), 3.88 (dd, *J* = 11.2, 5.5 Hz, 1 H), 3.59 – 3.50 (m, 1 H), 3.50 – 3.35 (m, 2 H), 2.77 (d, *J* = 13.9 Hz, 1 H), 2.50 – 2.42 (m, 1 H), 2.41 (s, 3 H), 2.09 (dd, *J* = 18.3, 7.2 Hz, 2 H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.9, 143.6, 136.4, 134.7, 133.8, 133.6, 129.8, 128.4, 127.8, 127.6, 127.2, 108.3, 52.2, 49.8, 46.7, 42.7, 26.7, 21.6 ppm. **HRMS (EI)** calc. for $[C_{22}H_{23}NO_2S, M]^+$ 365.1449, found 365.1449.



(4o) Yellow solid; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71

(d, J = 8.2 Hz, 2 H), 7.36 – 7.22 (m, 5 H), 7.19 (d, J = 6.7 Hz, 2 H), 4.99 (d, J = 1.4 Hz, 1 H), 4.87 (d, J = 2.0 Hz, 1 H), 4.06 (dd, J = 10.3, 8.1 Hz, 1 H), 3.90 (t, J = 8.2 Hz, 1 H), 3.62 (ddd, J = 48.3, 25.3, 11.3 Hz, 2 H), 2.86 (dd, J = 10.2, 8.3 Hz, 1 H), 2.39 (s, 3 H), 1.81 (s, 3 H), 1.24 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 147.0, 142.7, 138.3, 136.6, 132.3, 129.5, 128.3, 128.1, 127.7, 127.3, 108.4, 65.6, 52.5, 51.1, 49.0, 30.4, 24.1, 21.6 ppm. HRMS (EI) calc. for $[C_{23}H_{25}NO_2S, M]^+$ 379.1606, found 379.1609.

X-ray analysis

Diffraction data were measured by a Bruker-Nonius CCD single-crystal X-ray diffractometer at room temperature by using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Preliminary orientation matrices and unit cell parameters were obtained from the peaks of the first 10 frames and then refined using the whole data set. Frames were integrated and corrected for Lorentz and polarization effects using DENZO. The structure was solved by direct methods using SHELXS-97, and refined by full-matrix least-squares with SHELXL-97. All non-hydrogen atoms were refined anisotropically and hydrogen atoms except some were treated as idealized contributions.

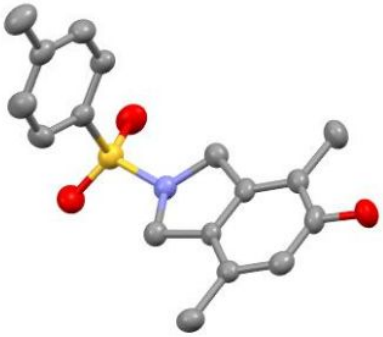


Figure 1. An Mercury drawing of **2a** with 30% probability of thermal ellipsoids.

CCDC reference numbers CCDC 1003519 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

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국문초록

알카인이 연결된 알킬리딘사이클로프로페인으로부터 두고리 페놀이 높은 수득률로 합성되는 로듐 촉매하에 카보닐화 [3+2+1] 고리화 첨가반응이 연구되었다. 이 반응은 탄소와 헤테로원자로 치환된 반응에 대해서도 유효했다.

주요어: 로듐 촉매, 카보닐화, [3+2+1] 고리화 첨가, 알킬리딘사이클로프로페인, 페놀, 일산화탄소

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