学位論文

Development of a Novel Palladium-catalyzed Synthetic Approach to Vinyl-substituted Heterocycles using Propargylic Compounds

(パラジウム触媒によるプロパルギル化合物を用いた
ビニル基置換複素環式化合物類の新規合成法の開発)

2021 年 3 月

佐藤　　和哉

Preface

The studies presented in this thesis have carried out under the direction of Professor Norio Sakai at the Department of Pure and Applied Chemistry, Faculty of Science and Technology, Tokyo University of Science (RIKADAI) during 2016-2021.

The objects of this thesis are “Development of a Novel Palladium-catalyzed Synthetic Approach to Vinyl-substituted Heterocycles using Propargylic Compounds”. The author hopes that this basic work described in this thesis contributes to broader application of propargylic compounds in organic synthetic chemistry and seeking functional materials in engineering field.

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contents

Abbreviations

Ac	acetyl; $COCH_3$
Me	methyl; CH_3
M	Metal
Bz	benzoyl; C_6H_5CO
Ts	tosyl; *p*-$H_3C(C_6H_4)SO_2$
dba	dibenzylideneacetone
tol	tolyl; *p*-$H_3C(C_6H_4)$
COD	1,5-cyclooctadiene
DPEphos	Bis[2-(diphenylphosphino)phenyl]ether
DCE	dichloromethane; CH_2ClCH_2Cl
COE	cyclooctene
DPPP	1,3-Bis(diphenylphosphino)propane
THF	tetrahydrofuran
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
NiXantphos	4,6-Bis(diphenylphosphino)phenoxazine
JohnPhos	2-(Di-*tert*-butylphosphino)biphenyl
CyJohnPhos	2-(Dicyclohexylphosphino)biphenyl
XPhos	2-Dicyclohexylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl
^{t}BuXPhos	2-Di-*tert*-butylphosphino-2',4',6'-triisopropyl-1,1'-biphenyl
Ph	phenyl; C_6H_5
GC	gas chromatography
NMR	Nuclear Magnetic Resonance
ORTEP	Oak Ridge Thermal Ellipsoid Plot Program
Bu	*n*-butyl; $CH_3CH_2CH_2CH_2$

D	deuterium
Cy	cyclohexyl; C_6H_{11}
δ	chemical sift
Hz	hertz
ppm	parts per million
Et	ethyl; CH_3CH_2
Ar	aryl
HRMS	High Resolution Mass Spectrometry
EI	Electron ionization
FAB	Fast Atom Bombardment
Pr	*n*-propyl; $CH_3CH_2CH_2$
LRMS	Low Resolution Mass Spectrometry
DMF	*N*, *N*-dimethylformamide
DPPE	1,2-Bis(diphenylphosphino)ethane
DPPB	1,4-Bis(diphenylphosphino)butane
MW	microwave

General Introduction

1-1. Vinyl-substituted heterocycles

Substituted heterocycles are a structural component of a vast number of organic compounds.[1] Among them, vinyl-substituted heterocycles have been found in some natural products and physiologically active compounds[2] (**Figure 1**), and furthermore, they have been used as synthetic intermediates of complex molecules in total syntheses[3] since the vinyl moiety can be transformed into various functional groups via Mizoroki-Heck reaction, olefin metathesis, Wacker oxidation,[4] etc. (**Scheme 1**). Therefore, it is important to develop novel synthetic methodologies for these useful heterocycles in organic synthesis.

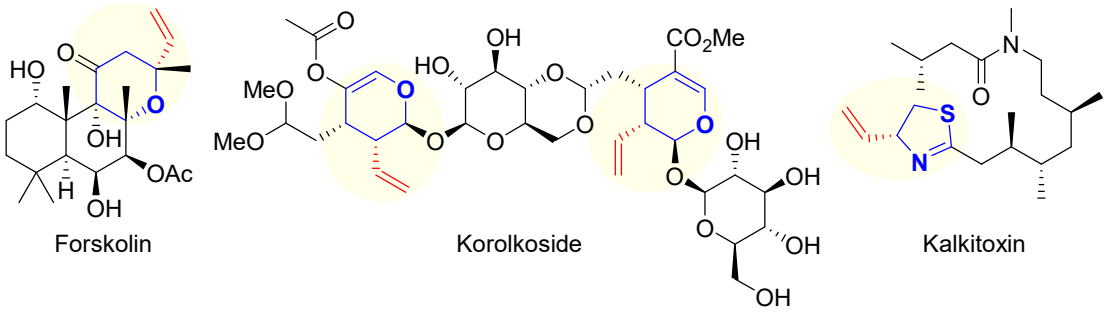
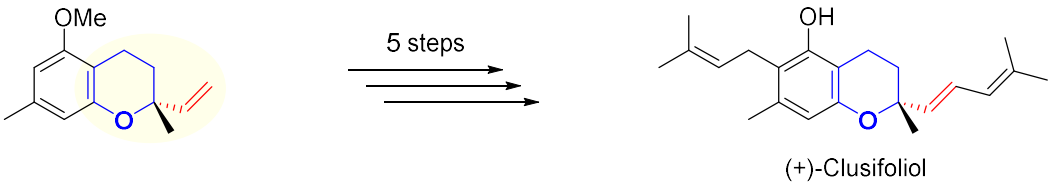


Figure 1. Vinyl-substituted heterocyclic systems in some natural products

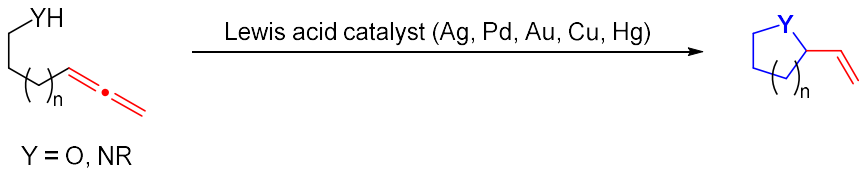


Scheme 1. A vinyl-substituted heterocycle as a reaction intermediate in total synthesis

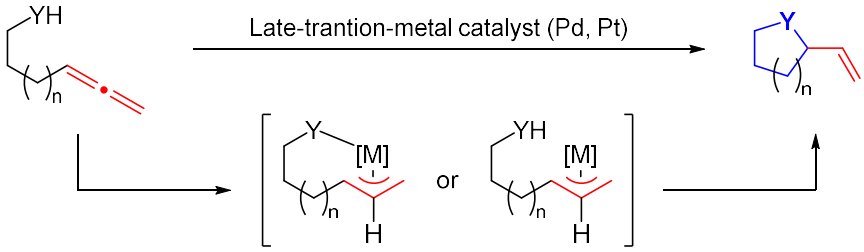
1-2. Transition-metal-catalyzed intramolecular cyclizations using unsaturated compounds to furnish vinyl-substituted heterocycles

Transition-metal-catalyzed intramolecular cyclizations via formation of a carbon-heteroatom bond are one of powerful strategies for syntheses of the vinyl-substituted heterocycles because it is possible to form a vinyl group and construct a heterocyclic system at once. Among these reactions, allenes and alkenes are utilized for various synthetic approaches.

Intramolecular hydrofunctionalization of allenes are mentioned as a traditional approach for the heterocycles bearing a vinyl group. Lewis-acid-catalyzed cyclizations of allenyl alcohols or amines produce vinyl-tetrahydrofurans, pyrrolidines, etc. via activation of a carbon-carbon double bond[5] (**Scheme 2**). Alternatively, transition-metal-catalyzed cyclizations through formation of π-allyl intermediates are also reported[6] (**Scheme 3**).

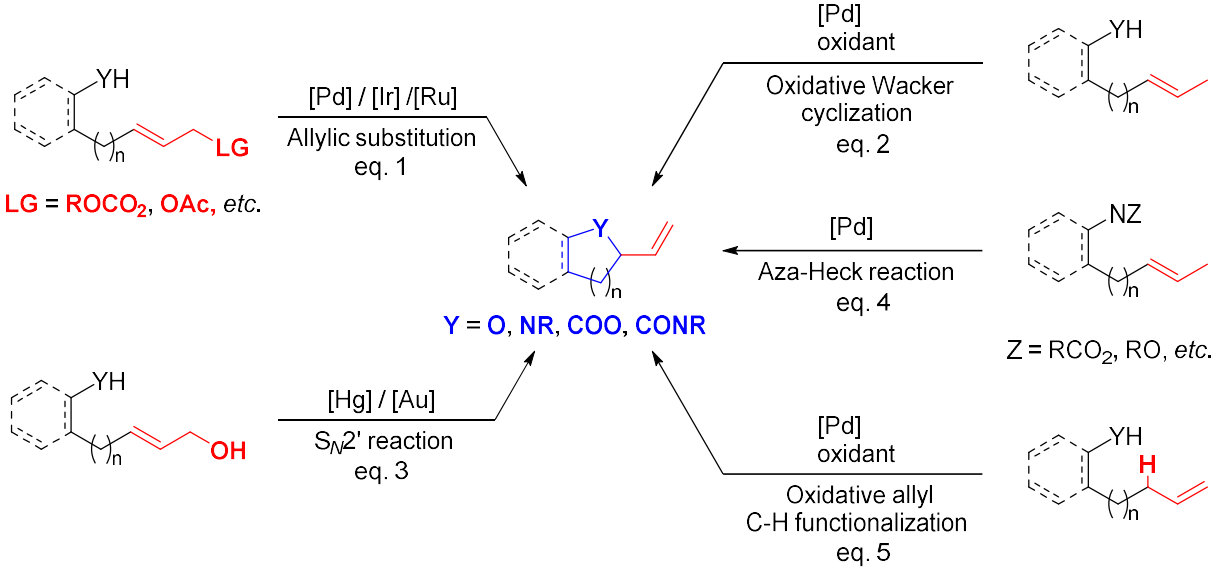


Scheme 2. Lewis-acid-catalyzed hydrofunctionalization of allnes



Scheme 3. Transition-metal-catalyzed hydrofunctionalization of allnes via allylpalladium

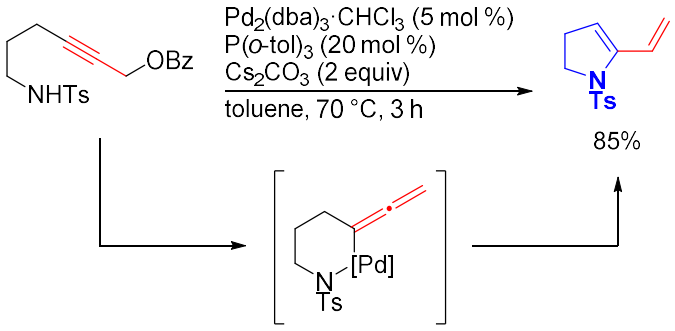
Transition-metal-catalyzed intramolecular cyclizations using substituted alkenes are wide variety of approaches to vinyl-substituted heterocycles. As a synthetic methodology, transition-metal-catalyzed intramolecular allylic alkylations of allyl compounds bearing a leaving group ($ROCO_2$, RCO_2, etc.) are studied[7] (**Scheme 4**, **eq 1**). On the other hand, oxidative Wacker cyclization of alkyl substituted alkenes are published to synthesize the heterocycles[8] (**Scheme 4**, **eq 2**). Other synthetic approaches, such as intramolecular S_N2' reactions, aza-Heck reactions, and oxidative allyl C-H functionalizations, are also known and applied in this field.[9-11] (**Scheme 4**, **eq 3-5**).



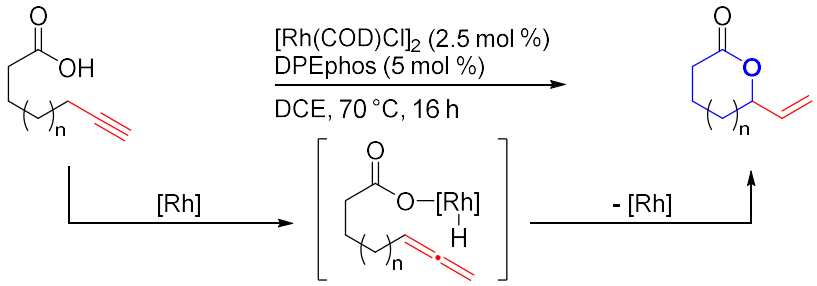
Scheme 4. Trantition-metal-catalyzed intramolecular cyclization using substituted alkenes to construct vinyl-substituted heterocyclic system

Although allenes or substituted alkenes have been utilized for construction of various heterocyclic systems bearing a vinyl group, few studies have focused on the synthetic methods using alkynes. Mori and co-workers reported a palladium-catalyzed synthesis of vinyl-dihydrof1pyrroles from propargyl benzoate derivatives (**Scheme 5**). In this proposal mechanism, it is thought that allenyl

palladium intermediate would be generated by a reaction of propargylic benzoate and a palladium catalyst *in situ*.[12] Breit *et al.* reported rhodium-catalyzed intramolecular cyclization to gain vinyl lactones[13] (**Scheme 6**). Their mechanistic studies revealed that the terminal alkyne moiety was converted into allenyl group in this rhodium-catalyst system.[14]



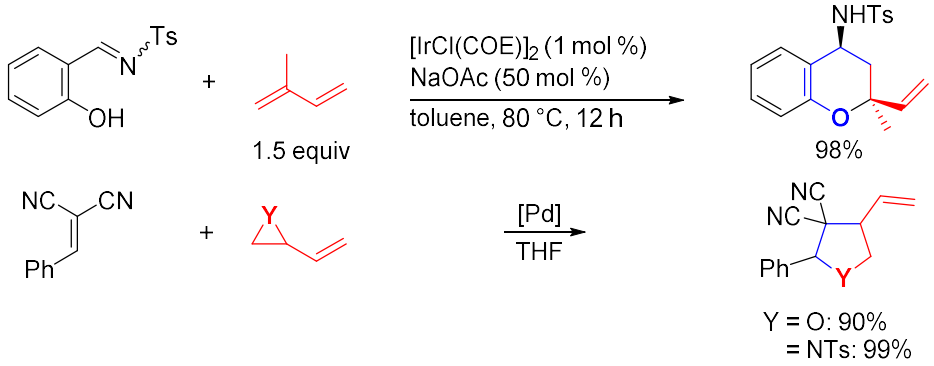
Scheme 5. Palladium-catalyzed cyclization of propargyl derivatives



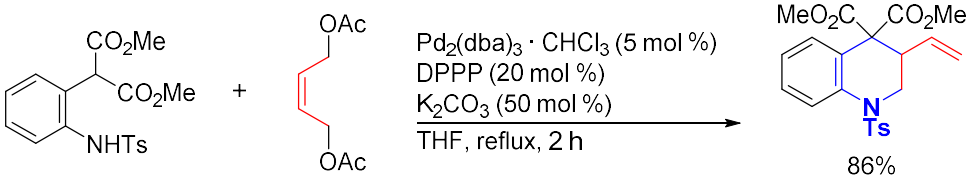
Scheme 6. Rhodium-catalyzed lactonization via a redox-neutral propargylic C-H oxidation reaction

1-3. Transition-metal-catalyzed intermolecular cyclizations using carbon component with vinyl group or its synthetic equivalent

While various intramolecular cyclizations to access vinyl-substituted heterocycles have been used widely, intermolecular cyclizations using carbon components including a vinyl group, such as diene,

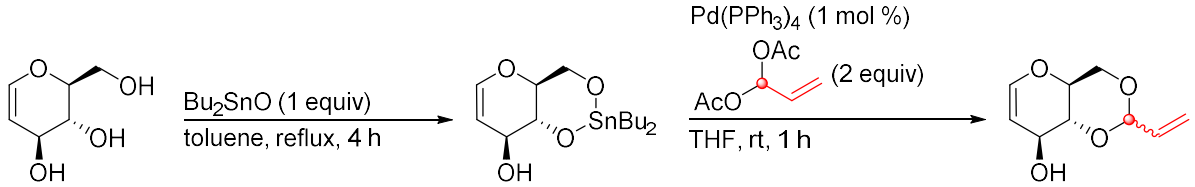


Scheme 7. Transition-metal-catalyzed intermolecular cyclizations using carbon component with a vinyl group

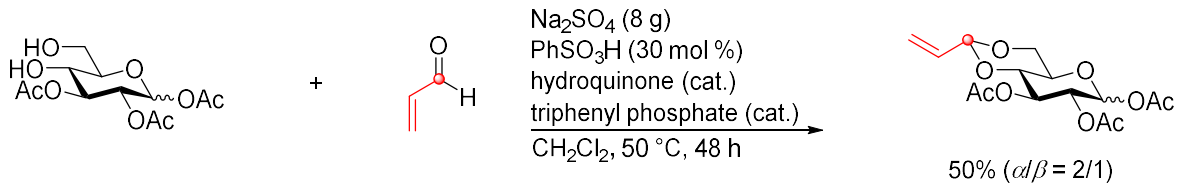


Scheme 8. Palladium-catalyzed intermolecular cyclizations using bis-acetate

vinyl aziridines or epoxides, etc., are also effective methodologies[15-17] (**Scheme 7**). Besides, allylic bis-acetate or bis-carbonate derivatives function as a synthetic equivalent of their carbon components to produce corresponding cyclic products bearing a vinyl group[18-19] (**Scheme 8**). On the other hands, synthetic methodologies using C1 components with a vinyl group or their synthetic equivalents are few reported. Holzapfel and van Heerden reported palladium-catalyzed construction of vinyl-substituted cyclic acetal system using a vinyl diacetate in two steps (**Scheme 9**). Since the vinyl acetal protecting group can be removed by treatment of Wilkinson catalyst, it has been proposed this vinyl acetal can be used as a protecting group of two hydroxy group in sugar analogues.[20] Additionally, it was also reported that acrolein was used for introducing of vinyl substituted carbon atom in a ring system[21] (**Scheme 10**).



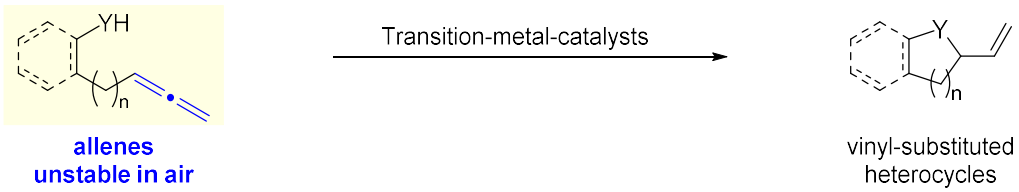
Scheme 9. Palladium-catalyzed selective protection of two hydroxyl groups in sugar analogues



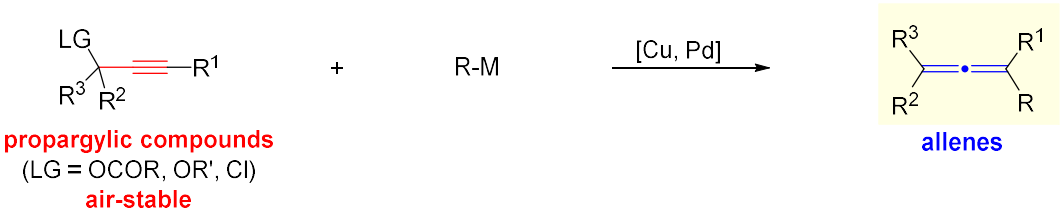
Scheme 10. Synthesis of vinyl acetals of D-glucose

1-4. This work

Transition-metal-catalyzed intramolecular cyclizations using allene derivatives containing an alcohol or amine have been established as one of synthetic approaches of vinyl-substituted heterocycles (**Scheme 11**). However, allenes are unstable in air, and difficult to handle.[22]



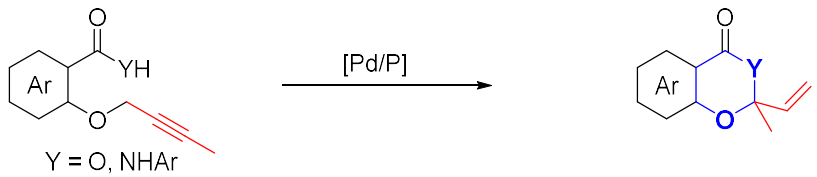
Scheme 11. Syntheses of vinyl-substituted heterocycles using allenes with transition-metal-catalysts



Scheme 12. Transformations of propargylic compounds into allenes

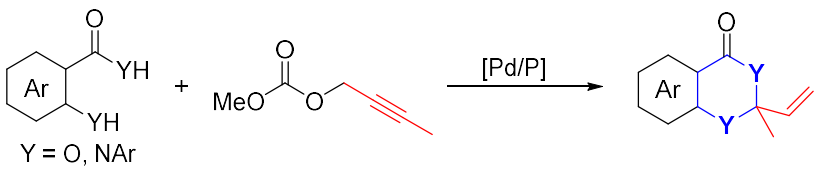
On the other hands, propargyl alcohols and their derivatives are not only stable and useful building blocks in organic synthetic chemistry, and they can be easily converted into allenes with appropriate transition-metal catalyst (**Scheme 12**). From this reason, the author attempted to develop a novel transition-metal-catalyzed intramolecular cyclization using propargylic compounds.

In **chapter 2**, palladium-catalyzed intramolecular cyclization of salicylic acid or salicylamide derivatives bearing a propargyl group at a phenol site was described (**Scheme 13**). The novel intramolecular cyclization of alkynoic acid derivatives produce vinyl dioxanone derivatives bearing a fully substituted allylic carbon.



Scheme 13. Intramolecular cyclization of salicylic acids with a propargyl group (chapter 2)

In **chapter 3**, the palladium-catalyzed intermolecular cyclization of propargylic carbonates and bis-nucleophiles including salicylic acid derivatives was described (**Scheme 14**). Based on the mechanistic study of novel intramolecular cyclization with alkynoic acid derivatives, intermolecular cyclization using propargylic carbonates as a synthetic equivalent of vinyl substituted C1 component was developed to afford various vinyl-substituted heterocycles.



Scheme 14. Intermolecular cyclization of bis-nucleophiles and propargylic carbonates (chapter 3)

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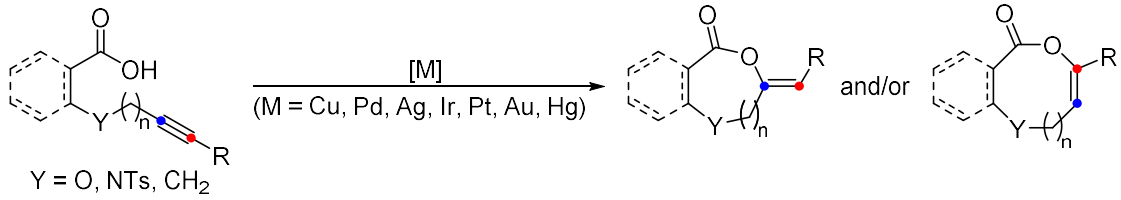
Chapter 2.

Palladium-catalyzed intramolecular cyclization of salicylic acid or salicylamide derivatives bearing a propargyl group at phenol site

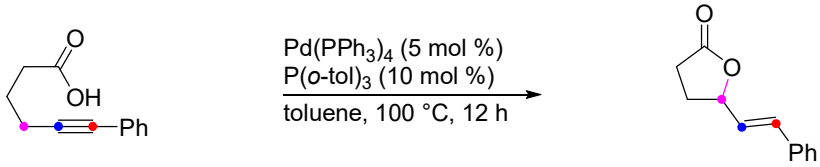
Introduction

Alkynoic acids are utilized for synthesizing various heterocyclic compounds. Transition-metal-catalyzed intramolecular addition of carboxylic acid to alkyne is one of the most common approaches to heterocycles using alkynoic acids. Generally, this type of reaction can occur in either *exo*- or *endo*-cyclization manner to provide corresponding cyclic products in accordance with the structure of substrates and catalysts.[1] (**Scheme 1**).

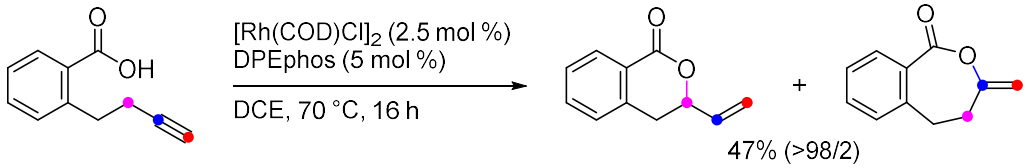


Scheme 1. Transition-metal-catalyzed intramolecular cyclization of alkynoic acids via addition of carboxylic acid to alkyne

Meanwhile, Yamamoto *et al*. developed a palladium-catalyzed intramolecular cyclization of alkynoic acids to furnish alkenyl-substituted lactones in a different cyclization pattern from common approach of alkynoic acids[2] (**Scheme 2**). In 2012, Briet and co-workers reported a synthetic method of vinyl-lactones with a rhodium catalyst in analogous to Yamamoto's cyclization manner[3] (**Scheme 3**). These Yamamoto/Breit's cyclizations of alkynoic acids show a complementary methodology for the synthesis of heterocycles to traditional cyclizations of alkynoic acids.

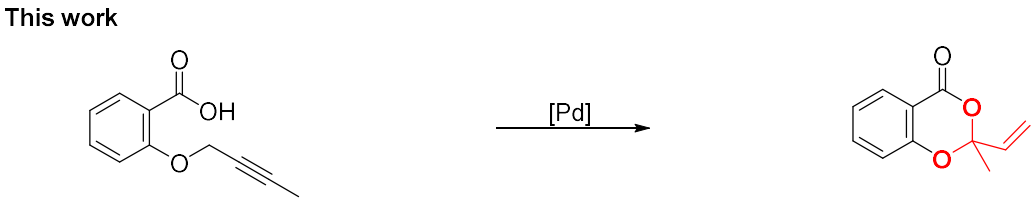


Scheme 2. Palladium-catalyzed intramolecular cyclization to furnish alkenyl-substituted lactones



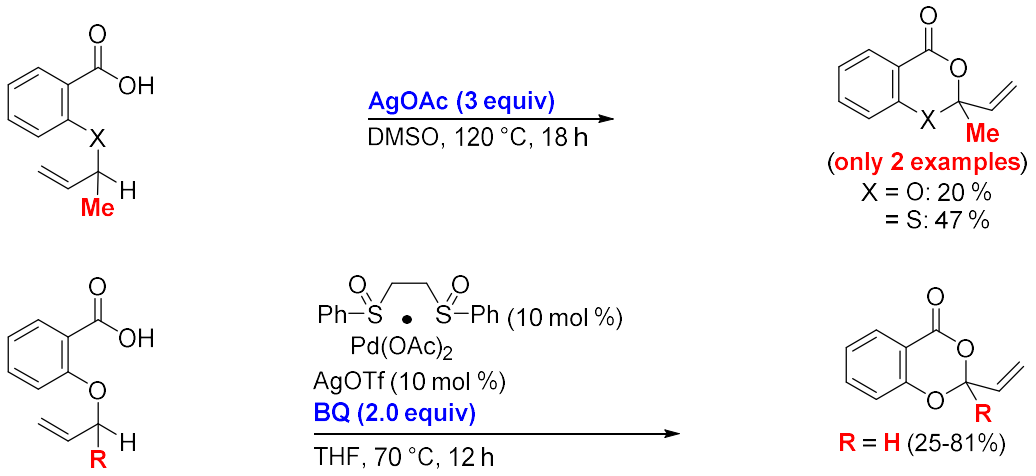
Scheme 3. Rhodium-catalyzed synthesis of macrolactones using alkynoic acids

Herein, the author found palladium-catalyzed intramolecular cyclization of alkynoic acids derived from salicylic acids to produce vinyl dioxanone derivatives bearing a fully substituted



Scheme 4. The novel intramolecular cyclization of alkynoic acids to produce vinyl-dioxanone compounds

carbon (**Scheme 4**). The reaction is a novel cyclization mode with alkynoic acids, in which vinyl dioxanone compounds that cannot be obtained by the aforementioned cyclization reactions are synthesized. Although the heterocyclic compounds called "4*H*-benzo[*d*][1,3]dioxin-4-ones" are generally obtained from salicylic acid derivatives and aldehydes or ketones[4], synthetic examples of the vinyl dioxanone derivatives are quite limited. In recent years, silver-promoted or palladium-catalyzed cyclization of alkenoic acids were reported as one of the synthetic approaches[5] (**Scheme 5**). Nevertheless, necessity of stoichiometric additives or narrow substrate scope of the vinyl dioxanone derivatives bearing a fully substituted carbon are task for synthesizing vinyl-dioxanones in these cases. In contrast, this cyclization can be an efficient method for the synthesis of such vinyl dioxanone derivatives. From this reason, the author has studied the unprecedented cyclization of alkynoic acid and developed a novel synthetic method.

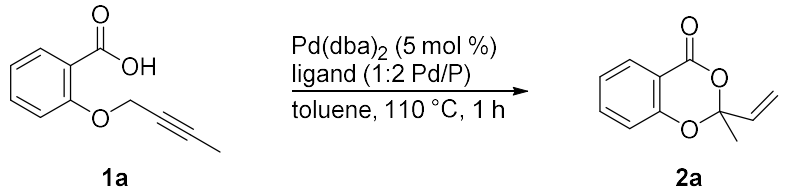


Scheme 5. Cyclizations of alkenoic acids to produce vinyl dioxanone derivatives

Results and discussion

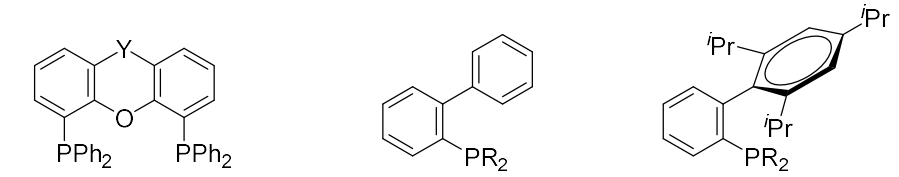
2-1. Palladium-catalyzed intramolecular cyclization of alkynoic acids

Table 1. Ligand screening for the palladium-catalyzed cyclization of an alkynoic acid **1a**[a]



1a **2a**

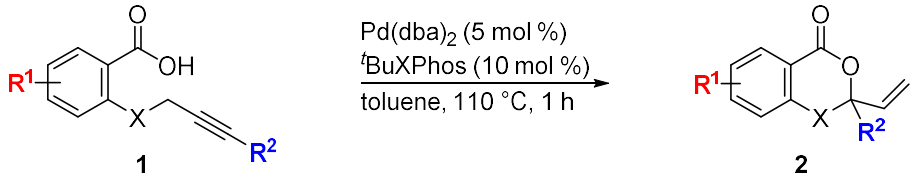
entry	ligand	GC yield / %
1	PPh_3	9
2	PCy_3	0
3	P^tBu_3	2
4	Xantphos[c]	51
5	NiXantphos[c]	70
6	JohnPhos	80 (68)[b]
7	CyJohnPhos	13
8	XPhos	50
9	**^{t}BuXPhos**	**95 (86)[b]**

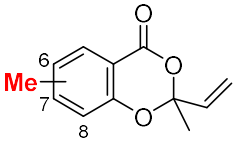


[a]Reaction conditions: **1a** (0.5 mmol), $Pd(dba)_2$ (0.025 mmol), ligand (0.05 mmol), toluene (1 mL), 110 °C, 1 h. [b]Isolated yield (1 mmol scale). [c]Ligand (0.025 mmol).

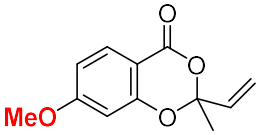
To evaluate the cyclization of alkynoic acid **1a**, which is derived from salicylic acid, the reactions in the presence of a catalytic amount of $Pd(dba)_2$ and several phosphine ligands (1:2 Pd/P) were conducted in toluene at 110 °C for 1 h (**Table 1**). When 2-(Di-*tert*-butylphosphino)biphenyl (JohnPhos) was used as a ligand, the formation of 6-membered cyclization product vinyl dioxanone **2a** was accomplished in an 80% GC yield, and then the product was isolated in a 68% yield (entry 6).[6] After the screening of a series of dialkylbiarylphosphines (Buchwald-type ligands), such as CyJohnPhos, XPhos, and ^{t}BuXPhos (entries 7−9), ^{t}BuXPhos proved to be the most effective ligand, as shown in entry 9 (95% GC yield, 86% isolated yield). However, triaryl- or trialkylphosphines were less effective for this transformation (entries 1−3). The bidentate ligands Xantphos and NiXantphos were also found to be applicable and resulted in 51% and 70% yields, respectively (entries 4 and 5).

Table 2. Scope of alkynoic acids **1**[a]

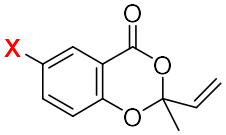




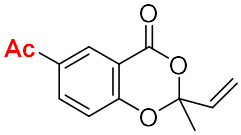
2b: 8-Me: 80%
2c: 7-Me: 82%
2d: 6-Me: 79%



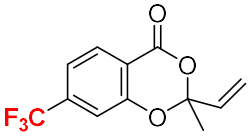
2e: 80%



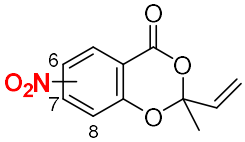
2f: X = Cl: 88%
2g: = Br: 8%[c,d]



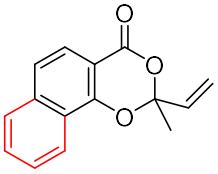
2h: 86%



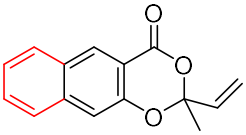
2i: 60%



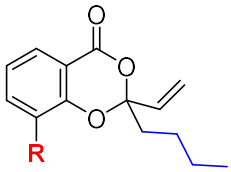
2j: 8-NO_2: 47%[c,d]
2k: 6-NO_2: 30%[d]



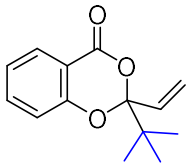
2l: 72%



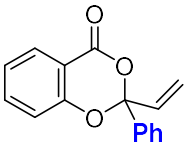
2m: 75%



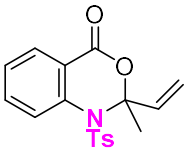
2n: R = H: 47%[d]
2o: = Me: 55%[d]



2p: 28%[d,e]



2q: 33%[d]



2r: 64%[d]

[a]Reaction conditions: **1** (1 mmol), $Pd(dba)_2$ (0.05 mmol), ^{t}BuXPhos (0.1 mmol), toluene (2 mL), 110 °C, 1 h. [b]Isolated yield. [c]JohnPhos was used as a ligand instead of ^{t}BuXPhos. [d]12 h. [e]20 mol % of $Pd(dba)_2$ (0.2 mmol) and 40 mol % of ^{t}BuXPhos (0.4 mmol) were used.

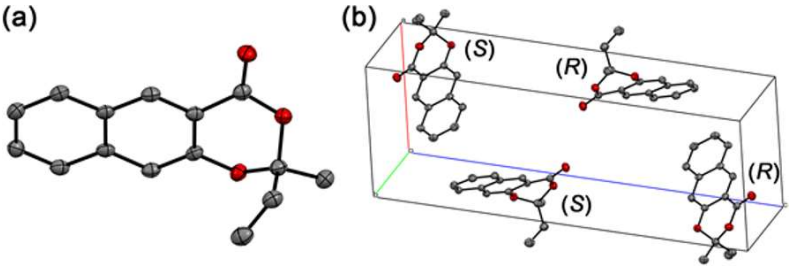


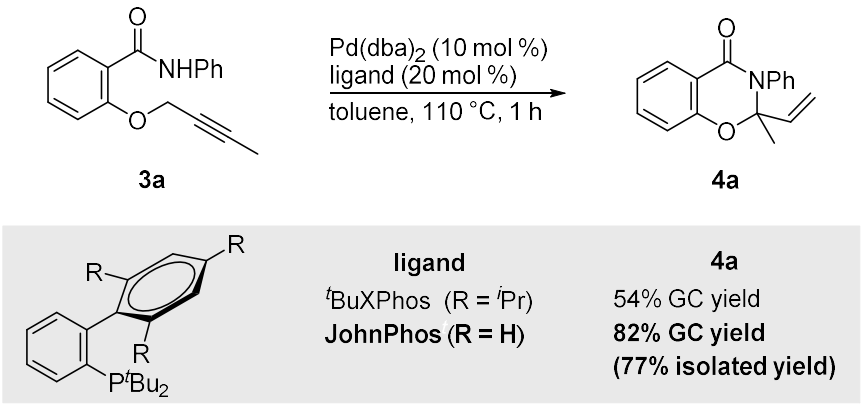
Figure 2. ORTEP drawings of the X-ray crystal structure of (a) (*S*)-**2m** and (b) the packing structure. H-atoms are omitted for clarity.

Conversion of various alkynoic acids **1** into **2** was then conducted in the presence of $Pd(dba)_2$/^{t}BuXPhos (**Table 2**). The reactions of methyl-substituted versions at the 3-, 4-, and 5-position of the benzene ring, **1b**−**1d**, afforded the expected cyclization products **2b**−**2d** in 79−82%

yields. Substrates bearing a methoxy- and a chlorine-substituent, **1e** and **1f**, provided the products, **2e** and **2f**, in good yields, whereas with the bromine-substituted **1g**, the yield of **2g** was 8%. Electron-withdrawing substituents, such as an acetyl, a trifluoromethyl, and nitro groups, **1h**−**1k**, were also suitable for the reaction and provided the corresponding heterocycles **2h**−**2k**. Naphthoic acid derivatives **1l** and **1m** afforded **2l** and **2m** in 72% and 75% yields. The molecular structure of **2m** was confirmed by single crystal X-ray diffraction analysis, and the ORTEP drawings of **2m** are illustrated in Figure 2.[7] Intramolecular reactions of a carboxylic acid with an internal alkyne substituted by a *n*butyl, a *t*butyl, or a phenyl group, **1n**−**1q**, also proceeded in the same cyclization manner, to form **2n**−**2q**. The anthranilic acid derivative **1r** was available for this cyclization, giving *N*-containing heterocycle **2r** in a 64% yield. On the other hand, the expected cyclization was not observed in the case of an alkynoic acid bearing a methyl substituent at the propargylic position as a starting substrate.

2-2. Palladium-catalyzed intramolecular cyclization of salicylamide derivatives 3a

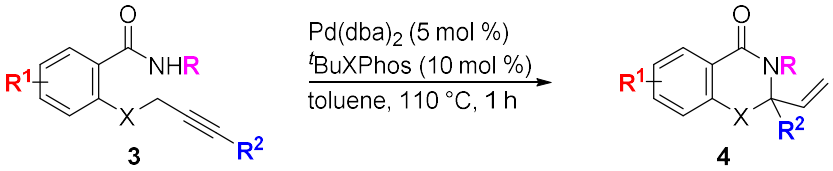
To expand the generality of the unprecedented intramolecular cyclization of alkynoic acids, the author also attempted to apply this protocol for salicylamide derivatives. Initially, we chose the salicylamide derivative *N*-phenyl-benzamide **3a**, which bears a propargyl ether moiety at the *ortho*-position, as the starting substrate for the ligand screening (**Scheme 5**). The salicylamide derivative **3a** was stirred for 1 h in toluene at 110 °C in the presence of $Pd(dba)_2$ (10 mol %) and ^{t}BuXPhos (20 mol %). Under these conditions, the expected intramolecular cyclization afforded *N*-heterocyclic **4a** with a tetrasubstituted allylic carbon atom in 54% GC yield. After screening the reaction conditions[8], the GC yield of **4a** was improved to 82% when JohnPhos was used as the ligand, and **4a** was isolated in 77% yield.

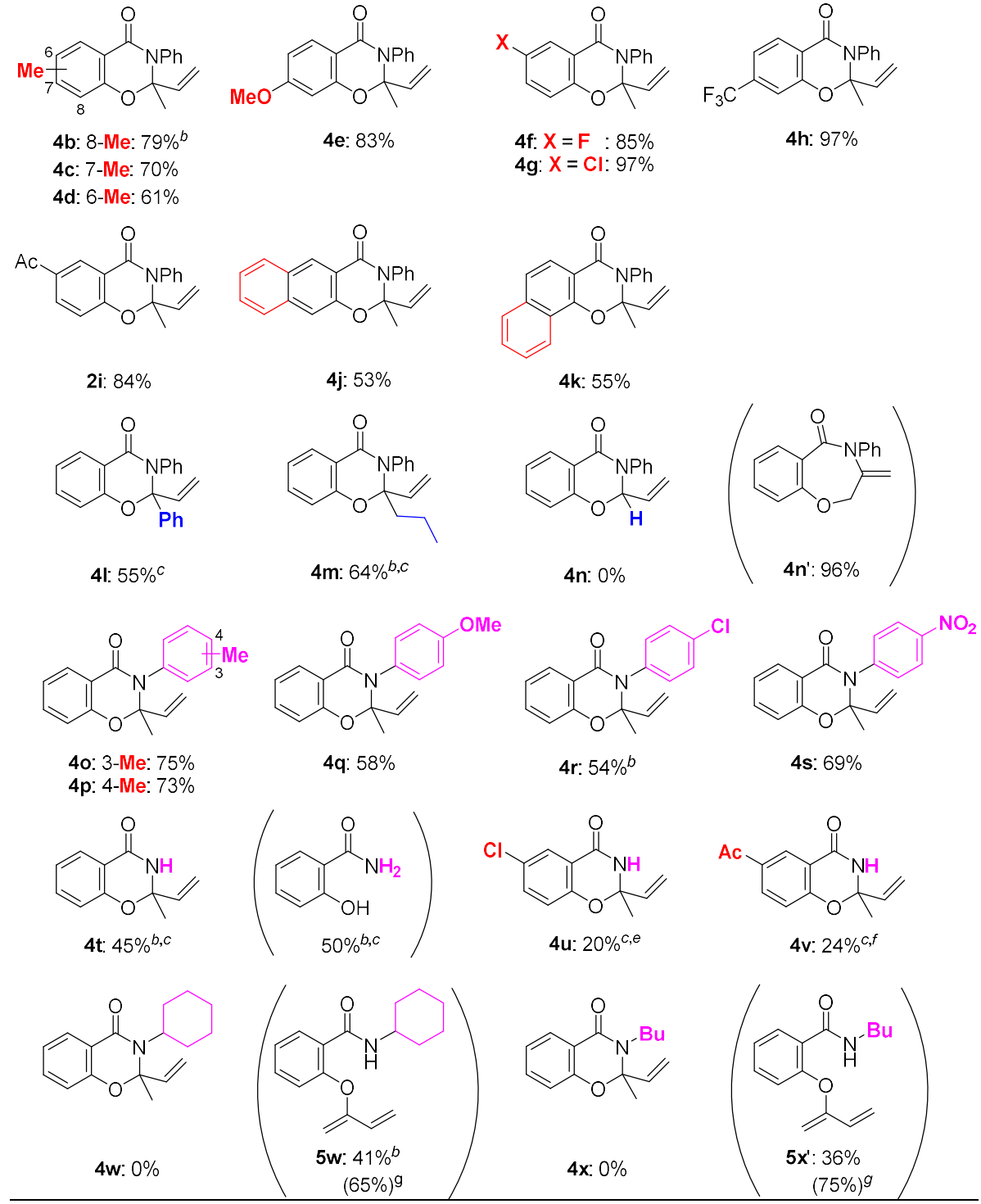


Scheme 5. Ligand screening for the palladium-catalyzed cyclization of a salicylamide derivative

The scope of this cyclization reaction was then explored using the $Pd(dba)_2$/JohnPhos system. As shown in **Table 3**, a variety of substrates **3** underwent cyclization to produce the corresponding products **4** in high yield. Substrates bearing electron-donating and electron-withdrawing substituents on the benzene ring (R^1) or fused-aromatic rings (**3b**−**k**) efficiently provided the corresponding products (**4b**−**k**). Internal alkynes that bear an aryl or an alkyl substituent at their alkynyl carbon atom (R^2) (**3l** and **3m**) also underwent the present cyclization to afford **4l** and **4m**. In contrast, **4n** was

Table 3. Scope of salicylamide derivatives





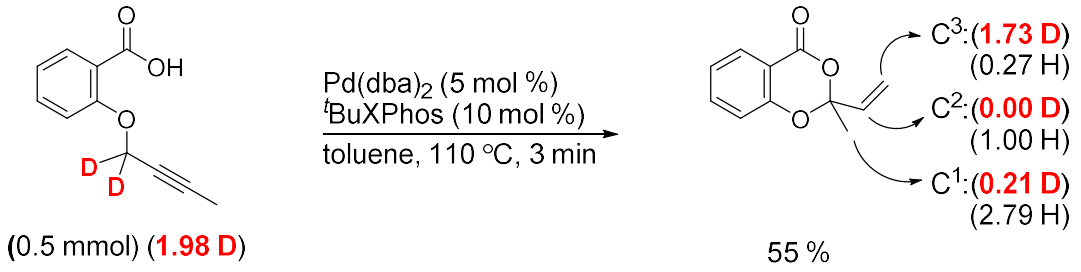
[a]Reaction conditions: **3** (1.0 mmol), $Pd(dba)_2$ (0.1 mmol), and JohnPhos (0.2 mmol) in toluene (1 mL) at 110 °C for 1 h. Isolated yields are shown. [b]0.5 mmol scale. [c]12 h. [d]ORTEP drawing of **3s** with thermal ellipsoids set to 50% probability; hydrogen atoms are omitted for clarity. [e]0.5 mmol scale, toluene (1 mL). [f]0.4 mmol scale, toluene (0.8 mL). [g]^{1}H NMR yield.

not detected using terminal alkyne **3n**; instead, the formation of **4n′** with a seven-membered ring, which is a typical 7-*exo-dig* adduct, was observed in 96% yield.[9] The conversion of several *N*-arylbenzamide derivatives (**3o**–**s**; R^3 = Ar) afforded a series of *N*-aryl heterocycles (**4o**–**s**). The unequivocal structural characterization of **4s** was accomplished by a single-crystal X-ray diffraction analysis.[10] Notably, primary amides (**3t**–**v**; R^3 = H) were also transformed into the corresponding products (**4t**–**v**) that contain an unprotected nitrogen atom. On the other hand, *N*-alkylbenzamide derivatives **3w** (R^3 = cyclohexyl) and **3x** (R^3 = butyl) did not provide the corresponding cyclization products **4w** and **4x**, but predominantly generated 1,3-dienes **5w** and **5x**.[11]

2-3. Mechanistic studies of palladium-catalyzed intramolecular cyclization

2-3-1. Deuterium labeling experiment of an alkynoic acid-d^2

A deuterium-labeling experiment was performed as a preliminary mechanistic study (**Scheme 6**). The reaction of **1a-d²**, deuterated at the propargylic carbon, was carried out under the standard conditions in short time (3 min). The reaction gave the cyclization product **2a-d²** in a 55% yield and the starting substrate was recovered. Then a significant incorporation of deuterium was observed at the terminal vinylic carbon (C3) of **2a-d²** (1.73 D with 0.27 H) by ^{1}H and ^{2}H NMR analyses, along with a small amount of the deuterium incorporation at the methyl carbon (C1) (0.21 D with 2.79 H). This result indicated that deuterium is transferred from the propargylic carbon of **1a-d²** into the terminal vinylic carbon (C3) of **2a-d²** in the essential conversion process from **1a-d²** into **2a-d²**.

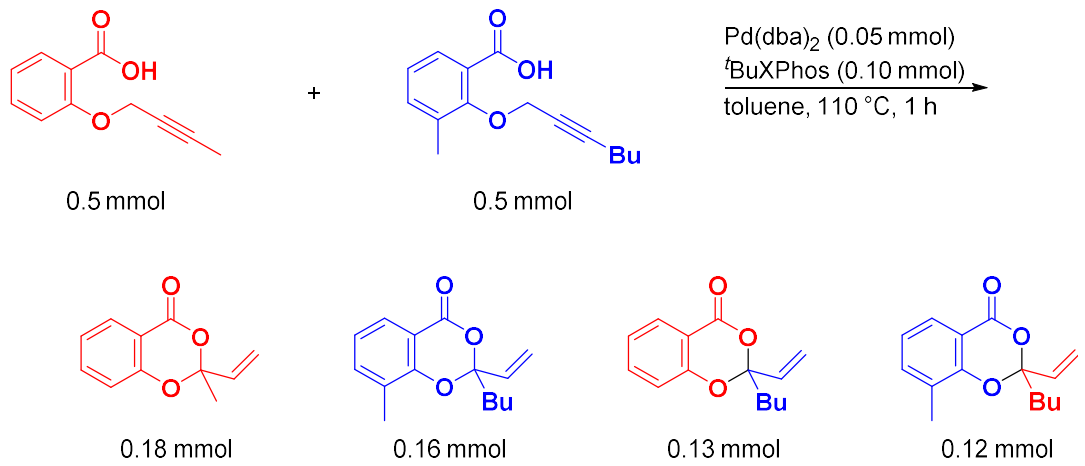


(0.5 mmol) (1.98 D) 55 %

Scheme 6. Deuterium labeling experiment of alkynoic acid-d^2

2-3-2. Cross over experiment of alkynoic acids 1a and 1o

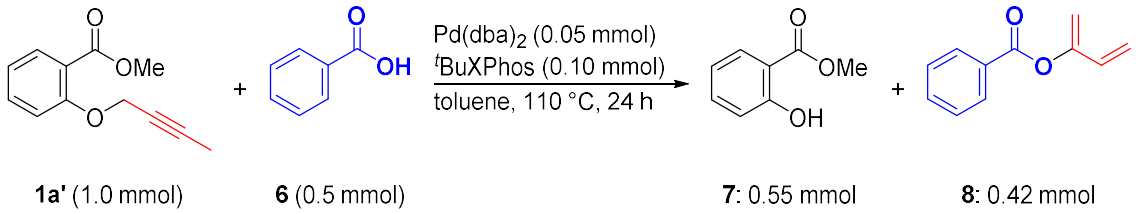
A crossover experiment using different alkynoic acids, **1a** and **1o**, as starting substrates was then examined (**Scheme 7**). The reaction of 1 equiv (0.5 mmol) each of **1a** and **1o** afforded four kinds of products: the standard intermolecular cyclization products **2a** (0.18 mmol) and **2o** (0.16 mmol), **2n** (0.13 mmol) and **2b** (0.12 mmol), produced by annulation via the exchange of the propargyl fragments.



Scheme 7. Crossover experiment using different alkynoic acids

2-3-3. Reaction of methylated alkynoic acid and benzoic acid

A migration of the propargyl fragment was also observed when methyl ester **1a′** (1 mmol) was treated with benzoic acid (**6**, 0.5 mmol) under the standard conditions (**Scheme 8**). Along with the production of methyl salicylate (**7**, 0.55 mmol) formed via propargylic C−O bond cleavage of **1a′**, it was determined that the cleaved propargyl unit was transferred into benzoic acid (**6**) to form 1,3-butadien-2-yl benzoate (**8**, 0.42 mmol).

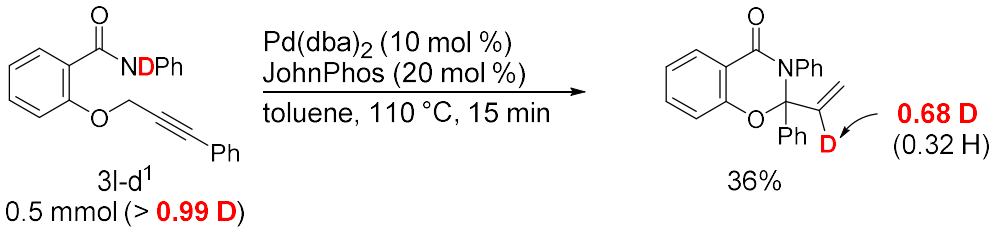


Scheme 8. Reaction of methylated alkynoic acid and benzoic acid

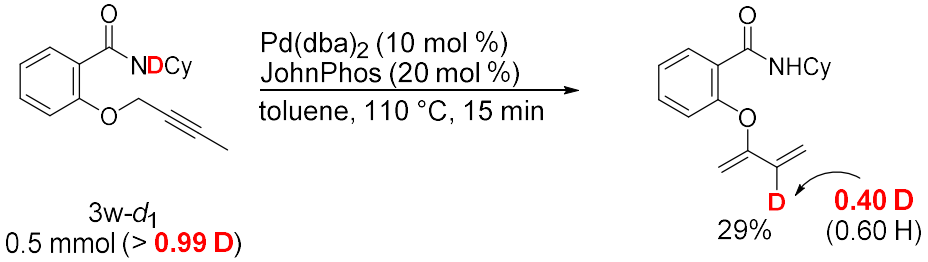
2-3-4. Deuterium labeling experiment of salicylamide derivatives

We conducted deuterium-labeling experiments employing **3l-d^1**, **3w-d^1**, and **3h-d^1** as the starting substrates, which were deuterated at the nitrogen atom of their amide moieties (**Scheme 9-11**). At the initial stage (15 min) of the reaction of **3l-d^1** under standard conditions, cyclization product **4l-d^1** was isolated in 36% yield and the starting substrate was recovered (**Scheme 9**). ^{1}H and ^{2}H NMR spectral analyses of the product revealed deuterium incorporation only at the internal vinylic carbon atom of **4l-d** (0.68 D, 0.32 H). The reaction of deuterated *N*-alkylbenzamide derivative **3w-d^1**, which did not afford the cyclization product, proceeded to form 1,3-diene **5w-d** in 29% isolated yield with selective deuterium incorporation at the internal diene carbon atom and the starting substrate was recovered, although the deuterium content was moderate (0.40 D, 0.60 H) (**Scheme 10**). When the reaction of **3h-d^1** was carried out for 5 min, both the cyclization product **4h-d** and 1,3-diene **5h-d** were isolated in 79% and 9% yield, respectively (**Scheme 11**). For the cyclization product **4h-d**, deuteration of the

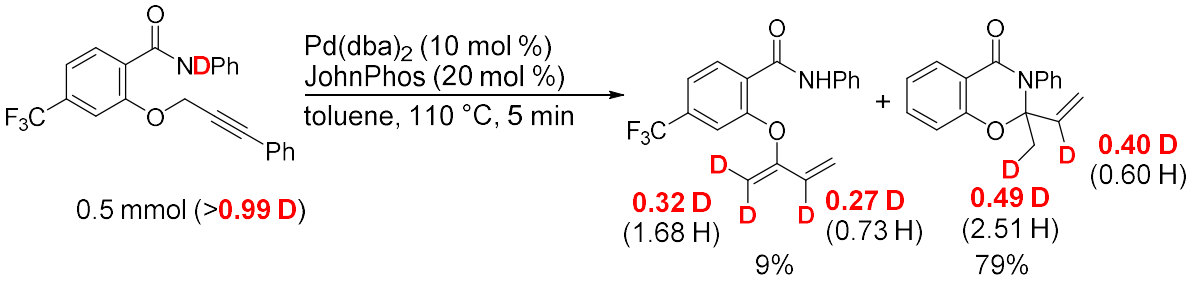
methyl carbon atom next to the tetrasubstituted carbon atom was also observed (0.49 D, 2.51 H), in addition to that at the internal vinylic carbon atom (0.32 D, 0.68 H). Furthermore, the deuterium incorporation in diene **5h-d** occurred at the internal diene carbon atom (0.27 D, 0.73 H) and at the terminal diene carbon atom (0.16 D, 0.84 H) next to the oxygen-substituted carbon atom.



Scheme 9. Deuterium labeling experiment of salicylamide **3l-d[1]**



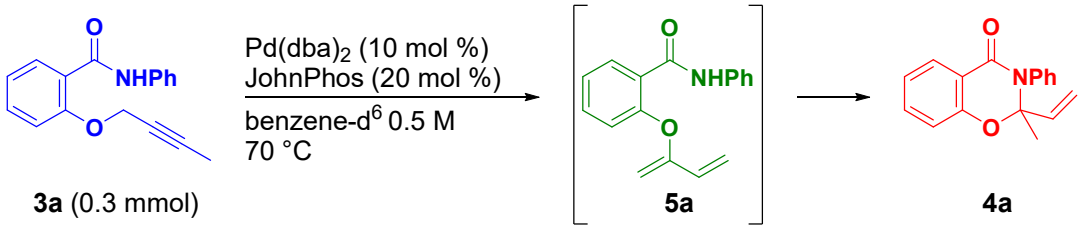
Scheme 10. Deuterium labeling experiment of salicylamide **3w-d[1]**



Scheme 11. Deuterium labeling experiment of salicylamide **3h-d[1]**

2-3-5. ^{1}H NMR monitoring for the detection of intermediate 5a

The formation of 1,3-dienes **5** was also observed in the case of the model substrate, i.e., *N*-phenylbenzamide derivative **3a**. When the reaction of **3a** with catalytic amounts of $Pd(dba)_2$/ JohnPhos in C_6D_6 at 70 °C was monitored by ^{1}H NMR spectroscopy, the transient formation of 1,3-diene **5a** was observed (**Scheme 12**). The plots for the concentrations of the starting substrate [**3a**], cyclization product [**4a**], and 1,3-diene [**5a**] as a function of time are shown in Figure 3. At the initial stage of the reaction (0−30 min), **5a** is generated predominantly. Subsequently, cyclization product **4a** is formed as diene **5a** is consumed.



Scheme 12. ^{1}H NMR monitoring for the detection of intermediate **5a**

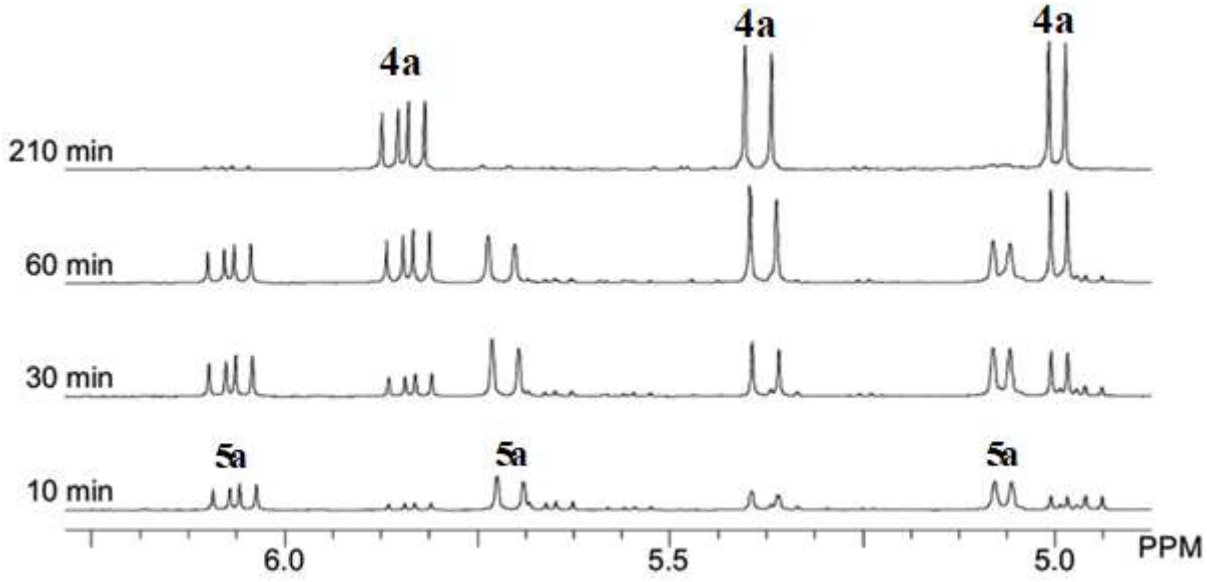


Figure 3. ^{1}H NMR spectra

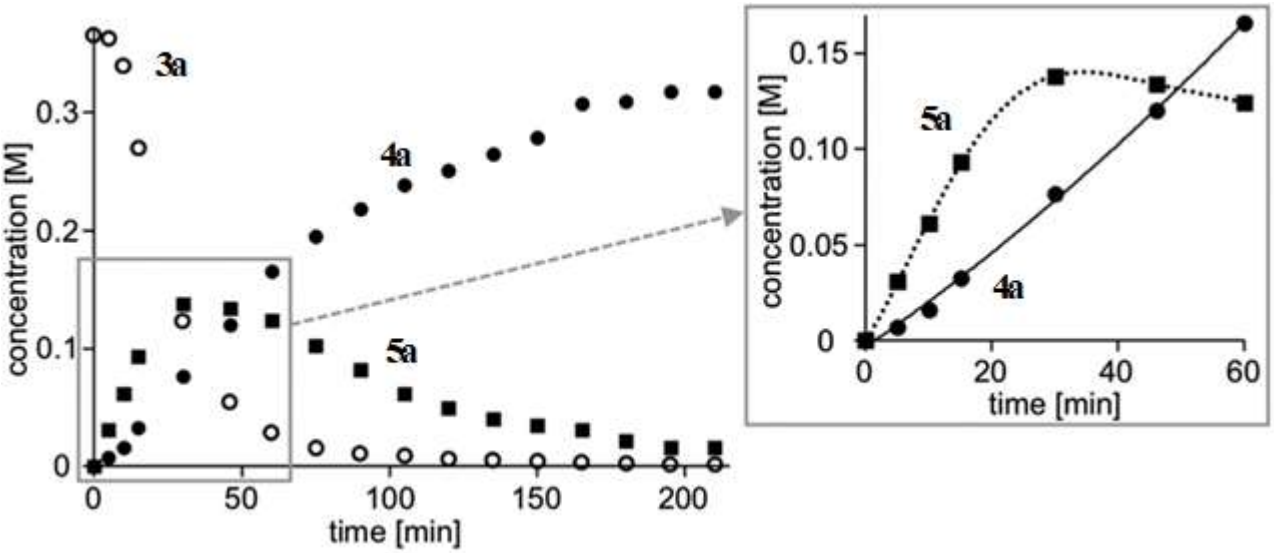
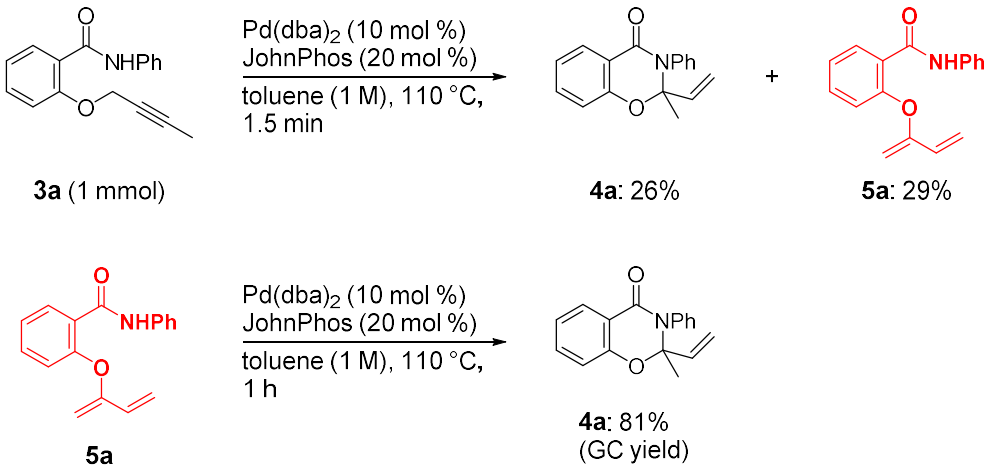


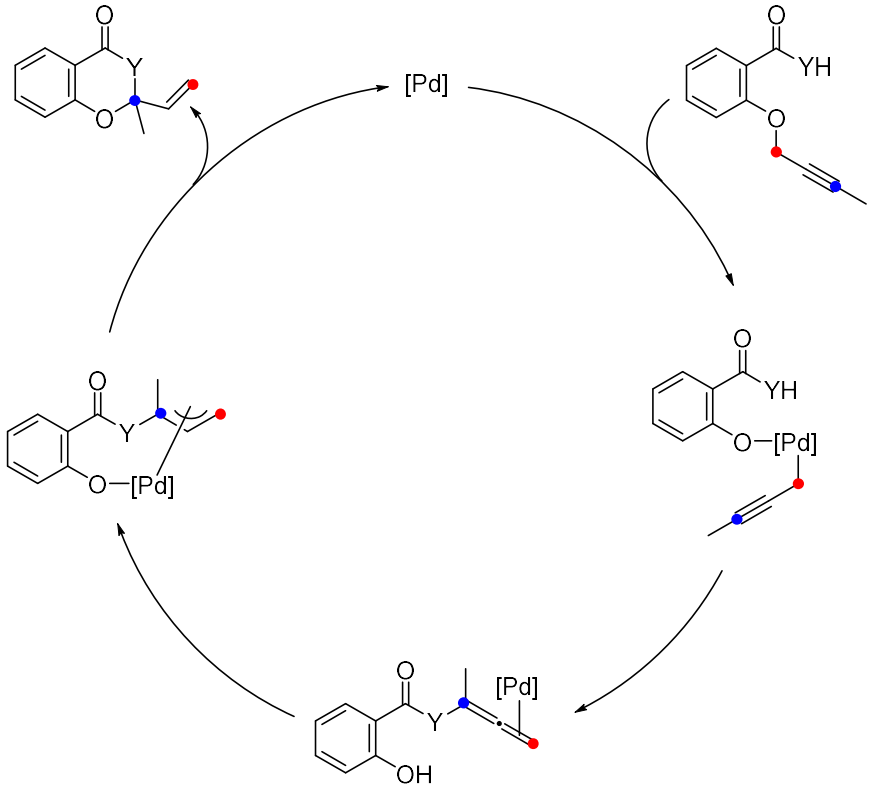
Figure 4. The kinetic profiles of cyclization with salicylamide **3a**. Reaction conditions: **3a** (0.3 mmol), $Pd(dba)_2$ (0.03 mmol), and JohnPhos (0.06 mmol) in C_6D_6 (0.6 mL) at 70 °C. The concentrations of **3a** (○), **4a** (●), and **5a** (■) were calculated from the ^{1}H NMR spectra using 1,3,5-trimethoxybenzene as the internal standard.

The isolation of 1,3-diene **5a** was possible by shortening the reaction time to 1.5 min (**Scheme 13**). Then isolated diene **5a** was used as the starting substrate and catalyzed using $Pd(dba)_2$/JohnPhos to furnish the expected cyclization product **4a** in 81% GC yield. In their entirety, the kinetic profiles and control experiments suggest that **3a** is initially converted into intermediate **5a**, which subsequently undergoes cyclization into **4a**.



Scheme 13. Isolation and reaction of diene **5a**

2-3-6. Proposal mechanism



Scheme 14. Proposed reaction mechanism of the intermolecular cyclization

Based on these mechanistic investigations and literature by several research group[12], employing carboxylic acid or salicylamide derivatives, a possible mechanism is proposed in Scheme 14. Oxidative addition of the propargylic C–O bond of **1** or **3** to Pd (0) would form η^1-propargyl palladium[13]. Next, an intramolecular S_N2'-type attack could occur at the methyl-substituted alkyne carbon to generate allene intermediate. The formation of π-allylpalladium species from allene intermediate and the subsequent C–O reductive elimination of the cyclization product would then

proceed under regeneration of the palladium catalyst. As shown in Figure 5, DFT calculations were performed by selecting Pd^0(JohnPhos) and a salicylamide as the starting point. The energy profile diagram of the reaction pathway is presented as Gibbs free energy changes (ΔG) obtained at 383.15 K and 1 atm pressure. This computational result support this proposed mechanism is probable.

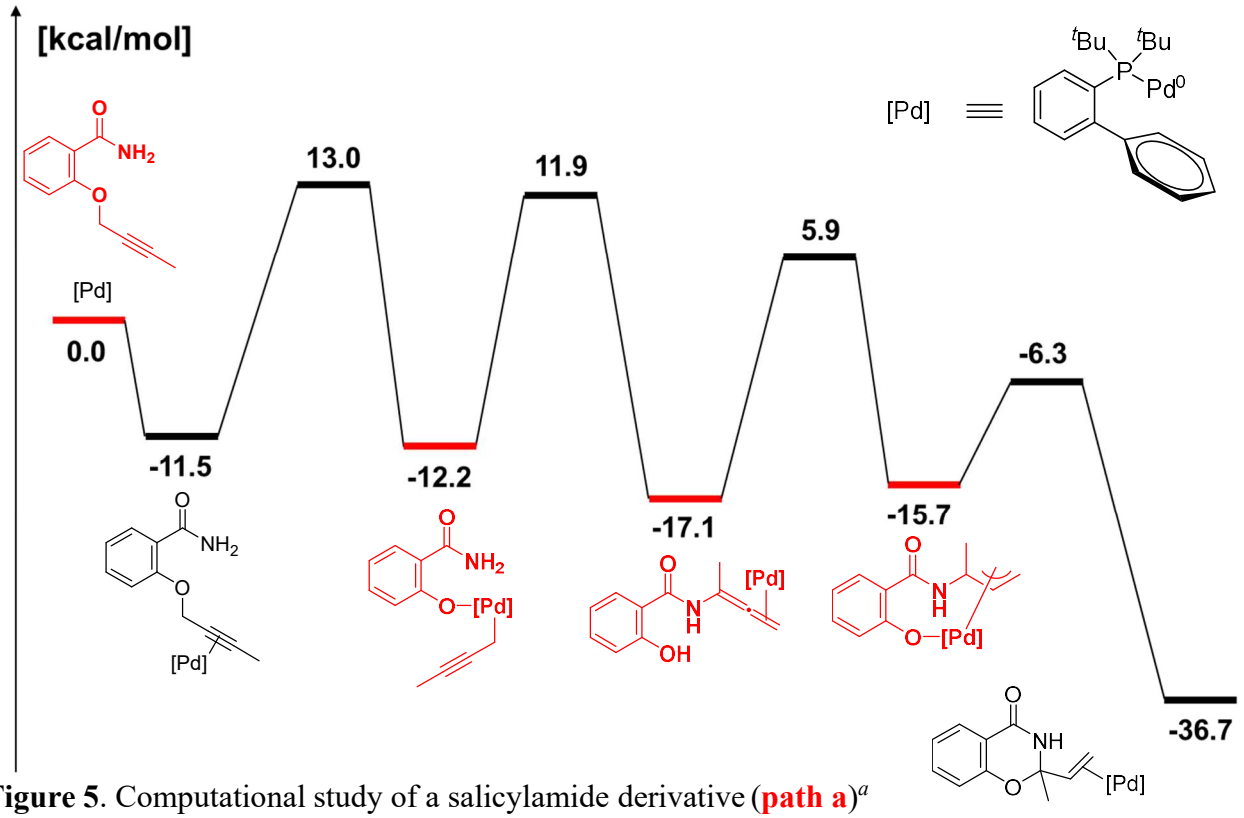


Figure 5. Computational study of a salicylamide derivative (**path a**)[a]

[a]DFT calculation by Prof. Hatanaka, M. (Keio Univ.) B3LYP+D3/6-31+G(d,p)/B3LYP+D3/6-31, Gibbs free energy, 383.15 K, kcal/mol.

On the other hands, computational study also has provided another reasonable pathway (**Figure 6**). In this path, propargyl palladium complex is formed from the substrate **3** and the palladium catalyst as well as path A. Subsequently, cumulene intermediate and salicylamide are generated from the propargyl palladium complex. Next, a reaction of phenol site and cumulene under palladium catalysis leads to the formation of diene product. The formation of π-allylpalladium species from diene product and the subsequent C-N reductive elimination proceed to afford cyclic product. It has also been suggested that hydrogen atoms on amide and phenol can be exchanged when cumulene intermediate is obtained. Considering this exchange process, results of deuterium labeling experiments support the path b. Additionally, the calculation of path b shows formation of allylpalladium species is rate-determining step, and isolation of diene product can support this. However, since ΔG of the rate-limiting steps in two pathways (**11.9** and **12.0** [kcal/mol]) are close, it is thought that more reasonable pathway is different depending on the substrate (**figure 7**). Note that the reaction proceeds via the formation of propargyl palladium in either pathway.

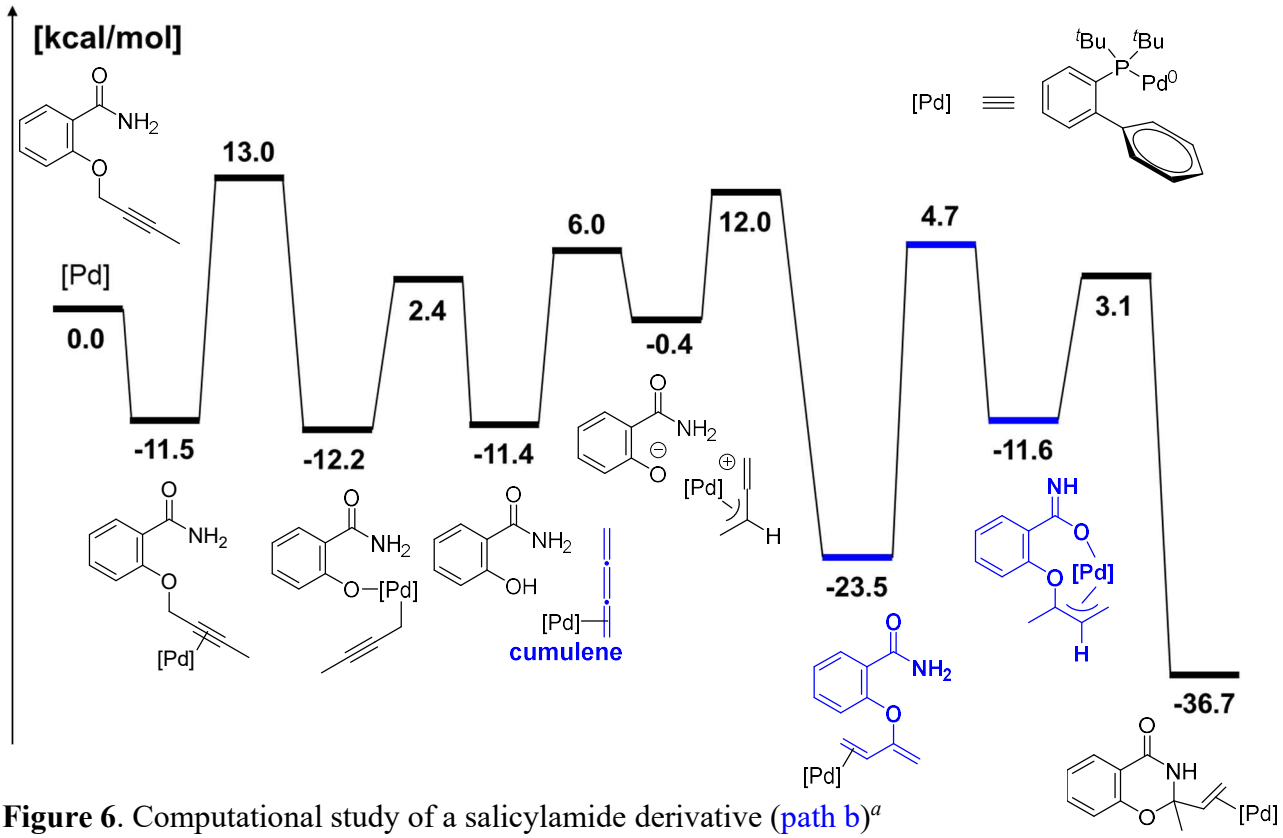


Figure 6. Computational study of a salicylamide derivative (path b)[a]

[a]DFT calculation by Prof. Hatanaka, M. (Keio Univ.) B3LYP+D3/6-31+G(d,p)/B3LYP+D3/6-31, Gibbs free energy, 383.15 K, kcal/mol.

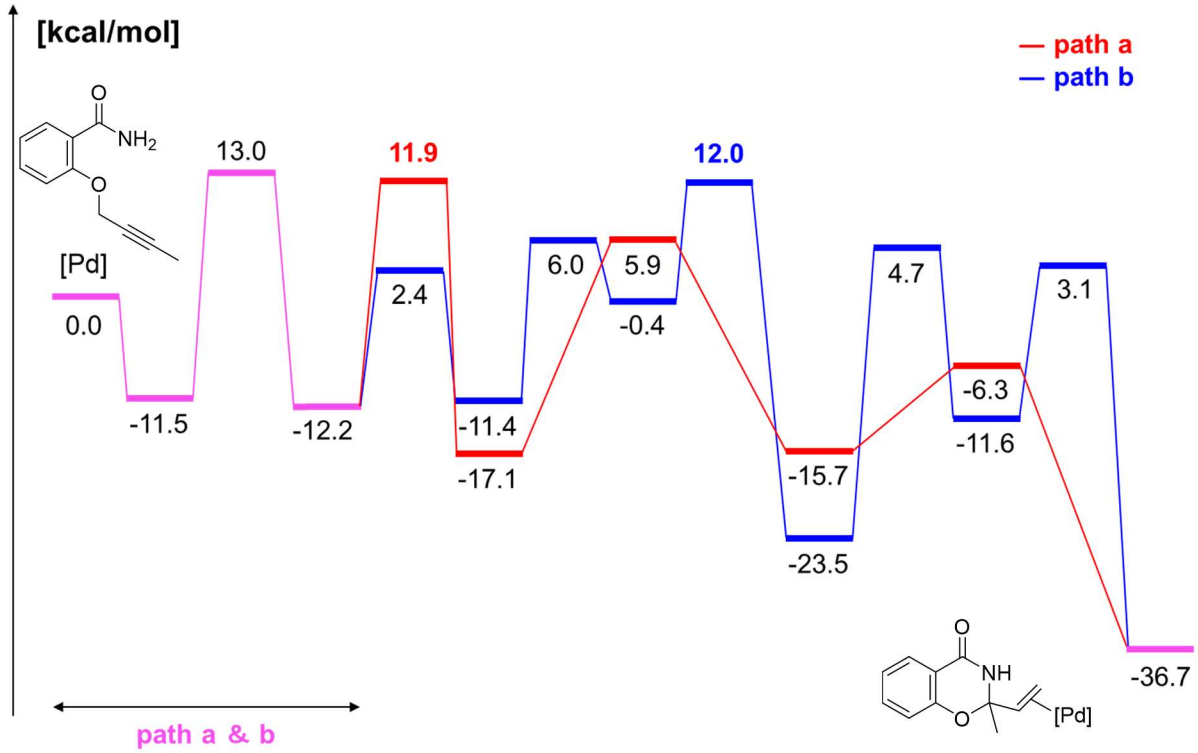


Figure 7. Computational study of a salicylamide derivative (comparing **a** with **b**)[a]

[a]DFT calculation by Prof. Hatanaka, M. (Keio Univ.) B3LYP+D3/6-31+G(d,p)/B3LYP+D3/6-31, Gibbs free energy, 383.15 K, kcal/mol.

2-4. Conclusion

The author has developed a palladium-catalyzed intramolecular cyclization to furnish vinyl-dioxanone derivatives bearing a fully substituted allylic carbon. Various types of alkynoic acids were available for this transformation, and this protocol could be also applied to diverse salicylamide derivatives. As a result, manifold vinyl-dioxanone derivatives bearing a fully substituted allylic carbon, which is one of vinyl-substituted heterocycles, are synthesized in this research. Additionally, mechanistic studies suggest that the unprecedented cyclization starts with the cleavage of a propargylic C-O bond.

2-5. Experimental section

General Information

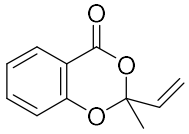
^{1}H, ^{2}H, ^{13}C, ^{19}F, and 2D NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts in the ^{1}H, ^{13}C NMR spectra were reported in ppm relative to residual solvent peaks such as those of chloroform (δ 7.26 for ^{1}H, and δ 77.0 for ^{13}C) and methanol (δ 3.30 for ^{1}H, and δ 49.0 for ^{13}C), or of the internal reference tetramethylsilane (δ 0.00 for both ^{1}H and ^{13}C). Chemical shifts in the ^{19}F NMR spectra were reported in ppm relative to residual solvent peaks of the external reference α,α,α-trifluorotoluene (δ −62.6). GC analyses were performed using a DB-5 capillary column (30 m × 0.25 mm, film thickness = 0.25 μm). Toluene was distilled from Na/benzophenone ketyl. $Pd(dba)_2$, and ligands were purchased and used without further purification. All alkynoic acids **1** described in this manuscript, **1a**−**1r** and **1a-*d*₂** were prepared by hydrolysis of the corresponding alkynoic acid methyl esters and these esters, except **3q** and **3r**, were synthesized from the corresponding methyl salicylate derivatives via the following procedures (A and B). Esters **3q** and **3r** were also synthesized from methyl salicylate or methyl anthranilate in two steps, respectively (procedures C and D). The starting methyl salicylate and anthranilate derivatives were purchased or prepared by esterification of the corresponding commercial salicylic acids. All salicylamide derivatives **3a**−**s** and **3w**−**y** were prepared from the corresponding carboxylic acids **1** via the following procedure A. Primary amides **3t**, **3u** and **3v** were synthesized from the corresponding salicylamide derivatives via the following procedure B.

General Procedure for the Palladium-Catalyzed Cyclization of Alkynoic Acids 1

To a screw-capped vial in a glovebox, alkynoic acid **1** (1 mmol), $Pd(dba)_2$ (28.8 mg, 0.05 mmol), ^{t}BuXPhos (42.5 mg, 0.1 mmol), and toluene (2 mL) were added in this order. The vial was sealed and removed from the glovebox, then the mixture was heated at 110 °C for 1 h. After the reaction, H_2O was added to the mixture, which was then extracted with EtOAc. The organic layer was dried over Na_2SO_4, and the volatile materials were removed by rotary evaporation. The crude material was purified by silica gel column chromatography.

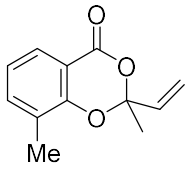
Spectral data of vinyl dioxanone derivatives 2

cyclization product 2a[1]



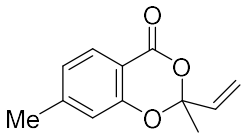
General procedure was followed with **1a** (190.2 mg). Column chromatography (50/1 to 30/1 hexane/EtOAc) afforded **2a** (163.6 mg, 86%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.82 (s, 3 H, C*H*$_3$), 5.32 (d, J = 10.5 Hz, 1 H, C*H*), 5.52 (d, J = 17.0 Hz, 1 H, C*H*), 5.90 (dd, J = 17.0, 10.5 Hz, 1 H, C*H*), 6.99 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.10 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.52−7.56 (m, 1 H, Ar*H*), 7.92 (dd, J = 8.0, 1.5 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.6, 105.1, 114.4, 116.9, 119.6, 122.7, 129.5, 136.2, 136.3, 156.2, 161.3; HRMS (EI) calcd for $[M]^+$ ($C_{11}H_{10}O_3$) m/z 190.0630, found 190.0626.

cyclization product 2b



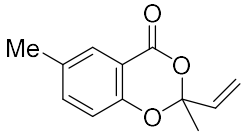
General procedure was followed with **1b** (204.2 mg). Column chromatography (50/1 to 20/1 hexane/EtOAc) afforded **2b** (163.4 mg, 80%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.84 (s, 3 H, C*H*$_3$), 2.26 (s, 3 H, C*H*$_3$), 5.29 (d, J = 10.5 Hz, 1 H, C*H*), 5.47 (d, J = 17.5 Hz, 1 H, C*H*), 5.88 (dd, J = 17.5, 10.5 Hz, 1 H, C*H*), 6.99 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.38 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.76 (d, J = 7.0 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.0, 26.8, 105.0, 114.1, 119.1, 122.1, 126.3, 127.1, 136.6, 137.2, 154.4, 161.7; HRMS (EI) calcd for $[M]^+$ ($C_{12}H_{12}O_3$) m/z 204.0786, found 204.0786.

cyclization product 2c



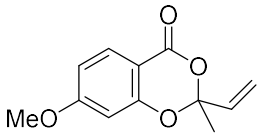
General procedure was followed with **1c** (204.2 mg). Column chromatography (50/1 to 20/1 hexane/EtOAc) afforded **2c** (167.5 mg, 82%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.81 (s, 3 H, C*H*$_3$), 2.38 (s, 3 H, C*H*$_3$), 5.31 (d, J = 11.0 Hz, 1 H, C*H*), 5.51 (d, J = 17.5 Hz, 1 H, C*H*), 5.89 (dd, J = 17.5, 11.0 Hz, 1 H, C*H*), 6.79 (s, 1 H, Ar*H*), 6.91 (d, J = 7.5 Hz, 1 H, Ar*H*), 7.79 (d, J = 7.5 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 22.0, 26.6, 105.0, 111.8, 117.1, 119.4, 123.9, 129.4, 136.5, 147.9, 156.2, 161.4; HRMS (EI) calcd for $[M]^+$ ($C_{12}H_{12}O_3$) m/z 204.0786, found 204.0792.

cyclization product 2d



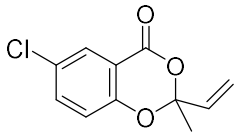
General procedure was followed with **1d** (204.2 mg). Column chromatography (50/1 to 20/1 hexane/EtOAc) afforded **2d** (161.3 mg, 79%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.81 (s, 3 H, C*H*$_3$), 2.32 (s, 3 H, C*H*$_3$), 5.31 (d, J = 11.0 Hz, 1 H, C*H*), 5.51 (d, J = 17.5 Hz, 1 H, Ar*H*), 7.71 (s, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.5, 26.7, 105.1, 114.1, 116.7, 119.5, 129.4, 132.4, 136.5, 137.2, 154.1, 161.6; HRMS (EI) calcd for $[M]^+$ ($C_{12}H_{12}O_3$) m/z 204.0786, found 204.0796.

cyclization product 2e



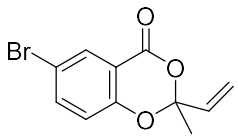
General procedure was followed with **1e** (220.2 mg). Column chromatography (40/1 hexane/EtOAc) afforded **2e** (176.2 mg, 80%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.80 (s, 3 H, C*H*$_3$), 3.85 (s, 3 H, OC*H*$_3$), 5.31 (d, J = 10.5 Hz, 1 H, C*H*), 5.52 (d, J = 17.0 Hz, 1 H, C*H*), 5.91 (dd, J = 17.0, 10.5 Hz, 1 H, C*H*), 6.45 (s, 1 H, Ar*H*), 6.63 (d, J = 8.5 Hz, 1 H, Ar*H*), 7.82 (d, J = 8.5 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.6, 55.7, 100.8, 105.1, 107.1, 110.3, 119.2, 131.1, 136.4, 158.1, 161.1, 166.2; HRMS (EI) calcd for $[M]^+$ ($C_{12}H_{12}O_4$) m/z 220.0736, found 220.0733.

cyclization product 2f



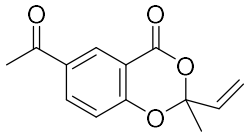
General procedure was followed with **1f** (224.6 mg). Column chromatography (50/1 hexane/EtOAc) afforded **2f** (197.7 mg, 88%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.82 (s, 3 H, C*H*$_3$), 5.35 (d, J = 11.0 Hz, 1 H, C*H*), 5.51 (d, J = 17.0 Hz, 1 H, C*H*), 5.87 (dd, J = 17.0, 11.0 Hz, 1 H, C*H*), 6.96 (d, J = 8.5 Hz, 1 H, Ar*H*), 7.49 (dd, J = 8.5, 2.0 Hz, 1 H, Ar*H*), 7.88 (d, J = 2.0 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.4, 105.4, 115.4, 118.5, 119.9, 127.8, 128.7, 135.9, 136.1, 154.5, 160.0; HRMS (EI) calcd for $[M]^+$ ($C_{11}H_9O_3Cl$) m/z 224.0240, found 224.0238.

cyclization product 2g



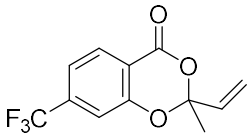
General procedure was followed with **1g** (269.1 mg), and the reaction was carried out for 12 h. Column chromatography (50/1 hexane/EtOAc) afforded **2g** (21.5 mg, 8%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.82 (s, 3 H, C*H*$_3$), 5.35 (d, J = 11.0 Hz, 1 H, C*H*), 5.51 (d, J = 17.5 Hz, C*H*), 5.89 (dd, J = 17.5, 11.0 Hz, 1 H, C*H*), 6.88 (d, J = 8.5 Hz, 1 H, Ar*H*), 7.34 (d, J = 8.5 Hz, 1 H, 2.5 Hz, 1 H, Ar*H*), 8.03 (d, J = 2.5 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.6, 105.6, 115.0, 116.0, 118.9, 120.1, 132.0, 136.0, 139.0, 155.2, 160.1; HRMS (EI) calcd for $[M]^+$ ($C_{11}H_9O_3Br$) m/z 267.9735, found 267.9742.

cyclization product 2h



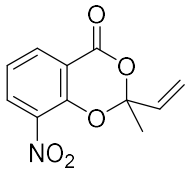
General procedure was followed with **1h** (232.2 mg). Column chromatography (30/1 hexane/EtOAc) afforded **2h** (199.7 mg, 86%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.86 (s, 3 H, C*H*$_3$), 2.61 (s, 3 H, C*H*$_3$), 5.36 (d, J = 11.0 Hz, 1 H, C*H*), 5.54 (d, J = 17.0 Hz, 1 H, C*H*), 5.90 (dd, J = 17.0, 11.0 Hz, 1 H, C*H*), 7.09 (d, J = 8.5 Hz, 1 H, Ar*H*), 8.21 (dd, J = 8.5, 2.5 Hz, 1 H, Ar*H*), 8.50 (d, J = 2.5 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.4, 26.6, 105.8, 113.7,117.6, 120.1, 130.7, 132.0, 135.8, 135.9, 159.6, 160.5, 195.6; HRMS (EI) calcd for $[M]^+$ ($C_{13}H_{12}O_4$) m/z 232.0736, found 232.0731.

cyclization product 2i



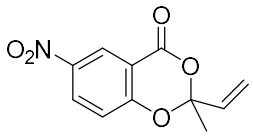
General procedure was followed with **1i** (258.2 mg). Column chromatography (50/1 hexane/EtOAc) afforded **2i** (154.9 mg, 60%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.86 (s, 3 H, C*H*$_3$), 5.37 (d, J = 11.0 Hz, 1 H, C*H*), 5.54 (d, J = 17.5 Hz, 1 H, C*H*), 5.90 (dd, J = 17.5, 11.0 Hz, 1 H, C*H*), 7.27 (s, 1 H, Ar*H*), 7.35 (d, J = 8.0 Hz, 1 H, Ar*H*), 8.05 (d, J = 8.0 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.6, 105.9, 114.5 (q, J_{C-F} = 3.8 Hz), 117.2, 119.3 (q, J_{C-F} = 3.8 Hz), 120.4, 122.8 (q, J_{C-F} = 272.9 Hz), 130.5, 135.8, 137.6 (q, J_{C-F} = 32.7 Hz), 156.2, 160.1; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −63.5 (s); HRMS (EI) calcd for $[M]^+$ ($C_{12}H_9O_3F_3$) m/z 258.0504, found 258.0507.

cyclization product 2j



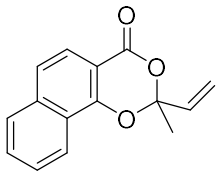
General procedure was followed with **1j** (235.2 mg), except that JohnPhos (29.8 mg, 0.1 mmol was used as a ligand, and the reaction was carried out for 12 h. Column chromatography (30/1 hexane/EtOAc) afforded **2j** (110.5 mg, 47%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.92 (s, 3 H, C*H*$_3$), 5.40 (d, J = 11.0 Hz, 1 H, C*H*), 5.62 (d, J = 17.5 Hz, 1 H, C*H*), 5.94 (dd, J = 17.5, 11.0 Hz, 1 H, C*H*), 7.24 (t, J = 8.0 Hz, 1 H, Ar*H*), 8.20−8.23 (m, 2 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.5, 74.8, 120.5, 123.4, 124.9, 129.2, 136.4, 142.9, 143.6, 148.8, 164.8; HRMS (EI)calcd for $[M]^+$ ($C_{11}H_9NO_5$) m/z 235.0481, found 235.0472.

cyclization product 2k



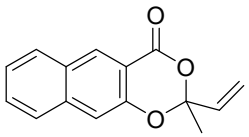
General procedure was followed with **1k** (235.2 mg), and the reaction was carried out for 12 h. Column chromatography (50/1 hexane/EtOAc) afforded **2k** (70.6 mg, 30%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.89 (s, 3 H, C*H*$_3$), 5.41 (d, J = 11.0 Hz, 1 H, C*H*), 5.55 (d, J = 17.5 Hz, 1 H, C*H*), 5.90 (dd, J = 17.5, 11.0 Hz, 1 H, C*H*), 7.17 (d, J = 8.5 Hz, 1 H, Ar*H*), 8.43 (d, J = 8.5 Hz, 1 H, Ar*H*), 8.83 (s, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.5, 106.4, 114.4, 118.3, 120.7, 125.9, 131.0, 135.3, 142.8, 159.2, 160.4; HRMS (EI) calcd for $[M]^+$ ($C_{11}H_9NO_5$) m/z 235.0481, found 235.0487.

cyclization product 2l



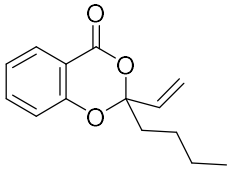
General procedure was followed with **1l** (240.3 mg). Column chromatography (70/1 hexane/EtOAc) afforded **2l** (173.0 mg, 72%) as a colorless solid: mp 92−93 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.96 (s, 3 H, C*H*$_3$), 5.28 (d, J = 11.0 Hz, 1 H, C*H*), 5.56 (d, J = 17.0 Hz, 1 H, C*H*), 5.96 (dd, J = 17.0, 11.0 Hz, 1 H, C*H*), 7.50 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.58 (t, J = 8.0 Hz, 1 H, Ar*H*), 7.65 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.83−7.86 (m, 2 H, Ar*H*), 8.25 (d, J = 8.0 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.8, 105.7, 108.6, 119.2, 122.2, 122.7, 123.4, 123.6, 126.7, 128.1, 129.8, 136.2, 137.5, 154.4, 161.6; HRMS (EI) calcd for $[M]^+$ ($C_{15}H_{12}O_3$) m/z 240.0786, found 240.0791.

cyclization product 2m



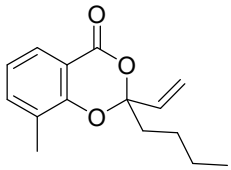
General procedure was followed with **1m** (240.3 mg). Column chromatography (70/1 afforded **2m** (180.2 mg, 75%) as a colorless solid: mp 79−80 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.87 (s, 3 H, CH_3), 5.29 (d, J = 11.0 Hz, 1 H, CH), 5.55 (d, J = 17.5 Hz, 1 H, CH), 5.94 (dd, J = 17.5, 11.0 Hz, 1 H, CH), 7.37 (s, 1 H, ArH), 7.42−7.45 (m, 1 H, ArH), 7.55−7.59 (m, 1 H,ArH), 7.76 (d, J = 8.5 Hz, 1 H, ArH), 7.90 (d, J = 8.5 Hz, 1 H, ArH), 8.56 (s, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.8, 105.2, 112.6, 114.9, 119.7, 125.4, 126.9, 129.1, 129.5, 129.7, 132.1,136.8, 137.6, 151.4, 161.8; HRMS (EI) calcd for $[M]^+$ ($C_{15}H_{12}O_3$) m/z 240.0786, found 240.0785.

cyclization product 2n



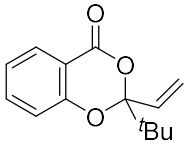
General procedure was followed with **1n** (232.3 mg), and the reaction was carried out for 12 h. Column chromatography (90/1 to 50/1 hexane/EtOAc) afforded **2n** (109.2 mg, 47%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (t, J = 7.5 Hz, 3 H, CH_3), 1.39 (sext, J = 7.5 Hz, 2 H, CH_2), 1.53−1.59 (m, 2 H, CH_2), 2.00−2.04 (m, 2 H, CH_2), 5.34 (d, J = 11.0 Hz, 1 H, CH), 5.48 (d, J = 17.5 Hz, 1 H, CH), 5.82 (dd, J = 17.5, 11.0 Hz, 1 H, CH), 6.98 (d, J = 8.5 Hz, 1 H, ArH), 7.09 (td, J = 7.5, 1.0 Hz, 1 H, ArH), 7.51−7.55 (m, 1 H, ArH), 7.91 (dd, J = 7.5, 1.5 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 22.5, 24.7, 39.2, 106.8, 114.6, 116.9, 120.3, 122.6, 129.6, 135.9, 136.2, 156.3, 161.6; HRMS (EI) calcd for $[M]^+$ ($C_{14}H_{16}O_3$) m/z 232.1099, found 232.1105.

cyclization product 2o



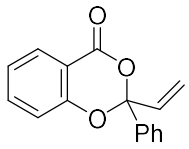
General procedure was followed with **1o** (246.3 mg), and the reaction was carried out for 12 h. Column chromatography (50/1 hexane/EtOAc) afforded **2o** (135.5 mg, 55%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.94 (t, J = 7.5 Hz, 3 H, CH_3), 1.40 (sext, J = 7.5 Hz, 2 H, CH_2), 1.53−1.61 (m, 2 H, CH_2), 2.03−2.06 (m, 2 H, CH_2), 2.27 (s, 3 H, CH_3), 5.32 (d, J = 11.0 Hz, 1 H, CH), 5.43 (d, J = 17.5 Hz, 1 H, CH), 5.80 (dd, J = 17.5, 11.0 Hz, 1 H, CH), 6.98 (t, J = 7.5 Hz, 1 H, ArH), 7.37−7.39 (m, 1 H, ArH), 7.75 (d, J = 8.0 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 15.0, 22.5, 24.7, 39.2, 106.7, 114.2, 119.8, 122.0, 126.3, 127.1, 136.0, 137.1, 154.5, 161.9; HRMS (FAB) calcd for $[M+H]^+$ ($C_{15}H_{19}O_3$) m/z 247.1334, found 247.1335.

cyclization product 2p



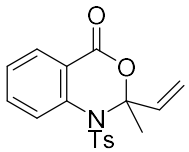
General procedure was followed with **1p** (232.3 mg), except that $Pd(dba)_2$ (115.2 mg, 0.2 mmol) and ^{t}BuXPhos (170.0 mg, 0.4 mmol) were used, and the reaction was carried out for 12 h. Column chromatography (90/1 to 50/1 hexane/EtOAc) afforded **2p** (65.0 mg, 28%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.14 (s, 9 H, C*H*$_3$), 5.41 (d, J = 11.0, 1 H, C*H*), 5.43 (d, J = 17.0 Hz, 1 H, C*H*), 5.79 (dd, J = 17.0, 11.0 Hz, 1 H, C*H*), 6.99 (d, J = 7.5 Hz, 1 H, Ar*H*), 7.06 (t, J = 8.0 Hz, 1 H, Ar*H*), 7.52 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.90 (d, J = 8.0 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.2, 38.7, 110.1, 114.6, 116.9, 122.29, 122.33, 129.4, 133.4, 136.0, 156.5, 161.8; HRMS (EI) calcd for $[M]^+$ ($C_{14}H_{16}O_3$) m/z 232.1099, found 232.1100.

cyclization product 2q



General procedure was followed with **1q** (252.3 mg), and the reaction was carried out for 12 h. Column chromatography (50/1 hexane/EtOAc) afforded **2q** (83.2 mg, 33%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.42 (d, J = 11.0 Hz, 1 H, C*H*), 5.56 (d, J = 17.0 Hz, 1 H, C*H*), 6.16 (dd, J = 17.0, 11.0 Hz, 1 H, C*H*), 7.06 (td, J = 7.5, 1.0 Hz, 1 H, Ar*H*), 7.10 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.31−7.38 (m, 3 H, Ar*H*), 7.52−7.55 (m, 1 H, Ar*H*), 7.57−7.59 (m, 2 H, Ar*H*), 7.87 (dd, J = 8.0, 1.5 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 105.5, 114.9, 117.2, 119.2, 122.9, 126.4, 128.6, 129.3, 129.7, 136.37, 136.44, 138.1, 156.2, 161.0; HRMS (EI) calcd for $[M]^+$ ($C_{16}H_{12}O_3$) m/z 252.0786, found 252.0790.

cyclization product 2r



General procedure was followed with **1r** (343.4 mg), and the reaction was carried out for 12 h. Column chromatography (50/1 to 10/1 hexane/EtOAc) afforded **2r** (220.0 mg, 64%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.95 (s, 3 H, C*H*$_3$), 2.38 (s, 3 H, C*H*$_3$), 5.09 (d, J = 10.5 Hz, 1 H, C*H*), 5.28 (d, J = 17.0 Hz, 1 H, C*H*), 5.92 (dd, J = 17.0, 10.5 Hz, 1 H, C*H*), 7.18 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.28 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.42−7.45 (m, 1 H, Ar*H*), 7.67−7.70 (m, 1 H,

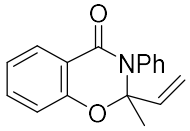
Ar*H*), 27.8, 93.9, 116.6, 123.3, 127.6, 128.0, 128.9, 129.0, 129.8, 134.3, 135.1, 139.2, 140.0, 145.0, 161.8; HRMS (FAB) calcd for $[M+H]^+$ ($C_{18}H_{18}NO_4S$) *m*/*z* 344.0957, found 344.0949.

General Procedure for the Palladium-Catalyzed Cyclization of 3

A screw-capped vial in a glovebox was charged with **3** (1 mmol), $Pd(dba)_2$ (57.5 mg, 0.1 mmol), JohnPhos (59.7 mg, 0.2 mmol), and toluene (1 mL) (added in this order). The vial was sealed and removed from the glovebox, and the mixture was heated to 110 °C for 1 h. After the reaction, the volatile materials were removed under reduced pressure, and the crude material was purified by column chromatography on silica gel, followed by gel permeation chromatography (if necessary), to give the corresponding product.

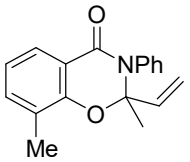
Spectral Data of 4

cyclization product 4a



General procedure was followed with **3a**, except that the reaction was performed on a half scale (**3a**, 131.5 mg, 0.5 mmol; $Pd(dba)_2$, 28.8 mg, 0.05 mmol; JohnPhos, 29.8 mg, 0.1 mmol; toluene, 0.5 mL). Column chromatography (50/1 to 10/1 hexane/EtOAc) afforded **4a** (101.8 mg, 77%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 3 H, CH_3), 5.30 (d, 1 H, J = 11.0 Hz, C=C*H*), 5.48 (d, 1 H, J = 17.0 Hz, C=C*H*), 6.01 (dd, 1 H, J = 17.0, 11.0 Hz, C=C*H*), 6.95 (d, 1 H, J = 8.5 Hz, Ar*H*), 7.06 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.25 (d, 2 H, J = 7.5 Hz, Ar*H*), 7.33–7.46 (m, 4 H, Ar*H*), 7.97 (d, 1 H, J = 8.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.0, 92.3, 116.6, 118.0, 118.4, 122.0, 128.0, 128.1, 129.1, 134.2, 137.5, 137.8, 155.1, 162.1; HRMS (FAB) calcd for $[M+H]^+$ ($C_{17}H_{16}NO_2$) *m*/*z* 266.1181, found 266.1187.

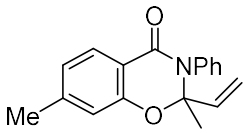
cyclization product 4b



General procedure was followed with **3b**, except that the reaction was performed on a half scale (**3b**, 140.8 mg, 0.5 mmol; $Pd(dba)_2$, 28.8 mg, 0.05 mmol; JohnPhos, 29.8 mg, 0.1 mmol; toluene, 0.5 mL). Column chromatography (50/1 to 5/1 hexane/EtOAc) afforded **4b** (111.4 mg, 79%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60 (s, 3 H, CH_3), 2.26 (s, 3 H, CH_3), 5.28 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.46 (d, 1 H, J = 17.0 Hz, C=C*H*), 6.00 (dd, 1 H, J = 17.0, 10.5 Hz, Ar*H*), 6.98 (t, 1 H, J = 8.0 Hz, Ar*H*), 7.26 (d, 2 H, J = 8.0 Hz, Ar*H*), 7.31 (d, 1 H, J = 7.0 Hz, Ar*H*), 7.35–7.44 (m, 3 H, Ar*H*), 7.81 (d, 1 H, J = 7.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.2, 26.3, 92.2, 117.7,

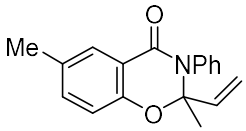
118.2, 121.6, 125.8, 125.9, 128.1, 129.2, 135.3, 137.9, 138.0, 153.4, 162.5; HRMS (EI) calcd for $[M]^+$ ($C_{18}H_{17}NO_2$) *m*/*z* 279.1259, found 279.1260.

cyclization product 4c



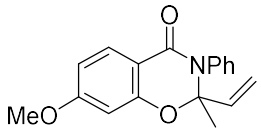
General procedure was followed with **3c** (276.3 mg). Column chromatography (50/1 to 10/1 hexane/EtOAc) afforded **4c** (192.6 mg, 70%) as a colorless solid: mp 67–69 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 3 H, C*H*$_3$), 2.37 (s, 3 H, C*H*$_3$) 5.30 (d, 1 H, *J* = 10.5 Hz, C=C*H*), 5.48 (d, 1 H, *J* = 17.5 Hz, C=C*H*), 6.02 (dd, 1 H, *J* = 17.5, 10.5 Hz, C=C*H*), 6.77 (s, 1 H, Ar*H*), 6.89 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.25 (d, 2 H, *J* = 7.0 Hz, Ar*H*), 7.34–7.43 (m, 3 H, Ar*H*), 7.84 (d, 1 H, *J* = 8.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.8, 26.1, 92.3, 115.9, 116.9, 118.0, 123.2, 128.05, 128.08, 129.2, 137.7, 138.0, 145.5, 155.2, 162.4; HRMS (EI) calcd for $[M]^+$ ($C_{18}H_{17}NO_2$) *m*/*z* 279.1259, found 279.1257.

cyclization product 4d



General procedure was followed with **3d** (281.5 mg). Column chromatography (50/1 to 3/1 hexane/EtOAc) afforded **4d** (171.3 mg, 61%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.56 (s, 3 H, C*H*$_3$), 2.33 (s, 3 H, C*H*$_3$), 5.31 (d, 1 H, *J* = 11.0 Hz, C=C*H*), 5.48 (d, 1 H, *J* = 17.0 Hz, C=C*H*), 6.01 (dd, 1 H, *J* = 17.0, 11.0 Hz, C=C*H*), 6.85 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 7.26 (s, 3 H, Ar*H*), 7.35–7.44 (m, 3 H, Ar*H*), 7.75 (s, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 20.6, 26.2, 92.3, 116.5, 118.1, 118.2, 128.10, 128.14, 129.2, 131.6, 135.1, 137.8, 138.0, 153.1, 162.4; HRMS (EI) calcd for $[M]^+$ ($C_{18}H_{17}NO_2$) *m*/*z* 279.1259, found 279.1253.

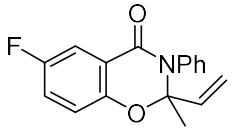
cyclization product 4e



General procedure was followed with **3e** (295.3 mg). Column chromatography (50/1 to 4/1 hexane/EtOAc) afforded **4e** (245.0 mg, 83%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 3 H, C*H*$_3$), 3.84 (s, 3 H, OC*H*$_3$), 5.31 (d, 1 H, *J* = 10.5 Hz, C=C*H*), 5.49 (d, 1 H, *J* = 17.0 Hz, C=C*H*), 6.04 (dd, 1 H, *J* = 17.0, 10.5 Hz, C=C*H*), 6.45 (d, 1 H, *J* = 2.0 Hz, Ar*H*), 6.63 (dd, 1 H, *J* = 8.5, 2.0 Hz, Ar*H*), 7.24–7.26 (m, 2 H, Ar*H*), 7.34– 7.43 (m, 3 H, Ar*H*), 7.88 (d, 1 H, *J* = 9.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 55.5, 92.6, 101.0, 109.2, 111.6, 117.9, 128.0, 129.1, 129.8, 137.7, 138.0, 156.9, 162.2, 164.8; HRMS (FAB) calcd for $[M+H]^+$ ($C_{18}H_{18}NO_3$) *m*/*z* 296.1287, found

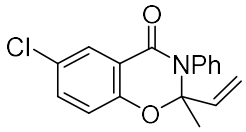
296.1283.

cyclization product 4f



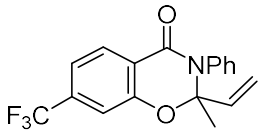
General procedure was followed with **3f** (277.2 mg). Column chromatography (50/1 to 5/1 hexane/EtOAc) afforded **4f** (236.8 mg, 85%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 3 H, C*H*$_3$), 5.34 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.49 (d, 1 H, J = 17.5 Hz, C=C*H*), 5.99 (dd, 1 H, J = 17.0, 11.0 Hz, C=C*H*), 6.93 (dd, 1 H, J = 9.0, 4.5 Hz, Ar*H*), 7.15–7.19 (m, 1 H, Ar*H*), 7.24–7.26 (m, 2 H, Ar*H*), 7.36–7.40 (m, 1 H, Ar*H*), 7.42–7.45 (m, 2 H, Ar*H*), 7.64 (dd, 1 H, J = 8.5, 3.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 92.7, 114.1 (d, $J_{C–F}$ = 25.0 Hz), 118.2 (d, $J_{C–F}$ = 7.7 Hz), 118.5, 119.5 (d, $J_{C–F}$ = 8.2 Hz), 121.4 (d, $J_{C–F}$ = 24.5 Hz), 128.3, 129.3, 137.5, 137.6, 151.3, 157.7 (d, $J_{C–F}$ = 240.9 Hz), 161.4; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −120.2 (s); HRMS (EI) calcd for $[M]^+$ ($C_{17}H_{14}NO_2F$) *m*/*z* 283.1009, found 283.1001.

cyclization product 4g



General procedure was followed with **3g** (297.8 mg). Column chromatography (50/1 to 3/1 hexane/EtOAc) afforded **4g** (289.5 mg, 97%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.57 (s, 3 H, C*H*$_3$), 5.34 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.48 (d, 1 H, J = 17.0 Hz, C=C*H*), 5.98 (dd, 1 H, J = 17.0, 10.5 Hz, C=C*H*), 6.91 (d, 1 H, J = 8.5 Hz, Ar*H*), 7.24 (d, 2 H, J = 7.5 Hz, Ar*H*), 7.35–7.44 (m, 4 H, Ar*H*), 7.92 (d, 1 H, J = 2.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 92.8, 118.3, 118.5, 119.7, 127.4, 127.7, 128.3, 129.3, 134.2, 137.3, 137.5, 153.7, 161.2; HRMS (EI) calcd for $[M]^+$ ($C_{17}H_{14}NO_2Cl$) *m*/*z* 299.0713, found 299.0732.

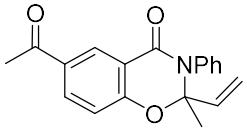
cyclization product 4h



General procedure was followed with **3h** (334.2 mg). Column chromatography (50/1 to 5/1 hexane/EtOAc) afforded **4h** (323.0 mg, 97%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.60 (s, 3H, C*H*$_3$), 5.37 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.52 (d, 1 H, J = 17.0 Hz, C=C*H*), 6.00 (dd, 1 H, J = 17.0, 10.5 Hz, C=C*H*), 7.24–7.26 (m, 3 H, Ar*H*), 7.33 (dd, 1 H, J = 8.0, 1.0 Hz, Ar*H*), 7.37–7.41 (m, 1 H, Ar*H*), 7.43–7.46 (m, 2 H, Ar*H)*, 8.09 (d, 1 H, J = 8.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 93.1, 114.3 (q, $J_{C–F}$ = 3.8 Hz), 118.7 (q, $J_{C–F}$ = 3.8 Hz), 118.8, 121.3, 123.2 (q, $J_{C–F}$ = 272.5 Hz), 128.4, 129.1, 129.4, 135.8 (q, $J_{C–F}$ = 32.7 Hz), 137.2, 137.4, 155.2, 161.2; ^{19}F NMR

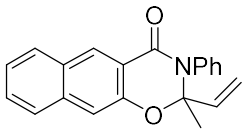
($CDCl_3$, 470 MHz) δ −63.1 (s); HRMS (EI) calcd for $[M]^+$ ($C_{18}H_{14}NO_2F_3$) *m/z* 333.0977, found 333.0977.

cyclization product 4i



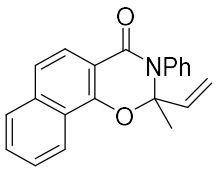
General procedure was followed with **3i** (305.4 mg). Column chromatography (50/1 to 4/1 hexane/EtOAc) afforded **4i** (256.9 mg, 84%) as a colorless solid: mp 191–193 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.61 (s, 3 H, C*H*$_3$), 2.60 (s, 3 H, C*H*$_3$), 5.35 (d, 1 H, *J* = 10.5 Hz, C=C*H*), 5.50 (d, 1 H, *J* = 17.0 Hz, C=C*H*), 6.01 (dd, 1 H, *J* = 17.0, 10.5 Hz, C=C*H*), 7.04 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 7.25 (d, 2 H, *J* = 7.0 Hz, Ar*H*), 7.39–7.45 (m, 3 H, Ar*H*), 8.14 (dd, 1 H, *J* = 8.5, 2.0 Hz, Ar*H*), 8.54 (d, 1 H, *J* = 2.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.2, 26.5, 93.2, 117.4, 117.9, 118.6, 121.5, 128.5, 129.3, 129.6, 131.6, 134.1, 137.2, 137.5, 158.9, 161.7, 196.3; HRMS (FAB) calcd for $[M+H]^+$ ($C_{19}H_{18}NO_3$) *m/z* 308.1287, found 308.1286.

cyclization product 4j



General procedure was followed with **3j** (314.7 mg). Column chromatography (50/1 to 3/1 hexane/EtOAc), followed by gel permeation chromatography, afforded **4j** (166.7 mg, 53%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.62 (s, 3 H, C*H*$_3$), 5.28 (d, 1 H, *J* = 10.5 Hz, C=C*H*), 5.52 (d, 1 H, *J* = 17.0 Hz, C=C*H*), 6.04 (dd, 1 H, *J* = 17.0, 10.5 Hz, C=C*H*), 7.25–7.31 (m, 2 H, Ar*H*), 7.34 (s, 1 H, Ar*H*), 7.38–7.47 (m, 4 H, Ar*H*), 7.50–7.53 (m, 1 H, Ar*H*), 7.75 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.90 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 8.56 (s, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.3, 92.3, 112.3, 118.3, 119.2, 124.8, 126.7, 128.2, 128.5, 129.2, 129.3, 129.5, 129.9, 136.8, 138.00, 138.03, 151.5, 162.4; HRMS (FAB) calcd for $[M+H]^+$ ($C_{21}H_{18}NO_2$) *m/z* 316.1338, found 316.1333.

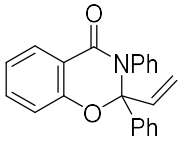
cyclization product 4k



General procedure was followed with **3k** (313.3 mg). Column chromatography (50/1 to 5/1 hexane/EtOAc) afforded **4k** (172.3 mg, 55%) as a colorless solid: mp 109–110 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.72 (s, 3 H, C*H*$_3$), 5.27 (d, 1 H, *J* = 11.0 Hz, C=C*H*), 5.54 (d, 1 H, *J* = 17.0 Hz, C=C*H*), 6.08 (dd, 1 H, *J* = 17.0, 11.0 Hz, C=C*H*), 7.31 (d, 2 H, *J* = 7.5 Hz, Ar*H*), 7.37–7.40 (m, 1 H, Ar*H*), 7.43–7.46 (m, 2 H, Ar*H*), 7.51 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 7.53–7.56 (m, 1 H, Ar*H*), 7.58–7.62 (m, 1

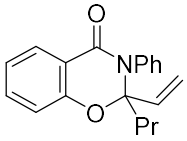
H, Ar*H*), 7.84 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.97 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 8.25 (d, 1 H, *J* = 8.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.3, 93.1, 112.8, 118.0, 121.5, 122.5, 123.3, 124.1, 126.2, 127.9, 128.2, 128.7, 129.3, 136.8, 137.4, 138.0, 152.5, 162.6; HRMS (FAB) calcd for $[M+H]^+$ ($C_{21}H_{18}NO_2$) *m/z* 316.1338, found 316.1338.

cyclization product 4l



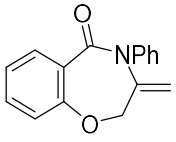
General procedure was followed with **3l** (327.1 mg), except that the reaction was performed for 12 h. Column chromatography (50/1 to 5/1 hexane/EtOAc), followed by gel permeation chromatography, afforded **4l** (181.5 mg, 55%) as a colorless solid: mp 152–154 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.49 (d, 1 H, *J* = 10.5 Hz, C=C*H*), 5.64 (d, 1 H, *J* = 17.0 Hz, C=C*H*), 6.04 (dd, 1 H, *J* = 17.0, 10.5 Hz, C=C*H*), 6.95 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.02 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.12–7.14 (m, 2 H, Ar*H*), 7.15–7.18 (m, 1 H, Ar*H*), 7.20–7.25 (m, 5 H, Ar*H*), 7.38–7.41 (m, 1 H, Ar*H*), 7.53–7.55 (m, 2 H, Ar*H*), 7.96 (dd, 1 H, *J* = 8.0, 2.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 95.5, 117.0, 119.2, 120.0, 122.3, 127.3, 128.0, 128.1, 128.2, 128.6, 128.9, 129.6, 134.3, 136.6, 138.2, 138.7, 155.1, 162.7; HRMS (FAB) calcd for $[M+H]^+$ ($C_{22}H_{18}NO_2$) *m/z* 328.1338, found 328.1335.

cyclization product 4m



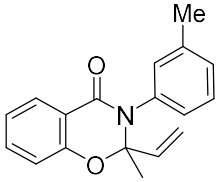
General procedure was followed with **3m**, except that the reaction was performed on a half scale (**3m**, 146.6 mg, 0.5 mmol; $Pd(dba)_2$, 28.8 mg, 0.05 mmol; JohnPhos, 29.8 mg, 0.1 mmol; toluene, 0.5 mL) for 12 h. Column chromatography (50/1 to 3/1 hexane/EtOAc), followed by gel permeation chromatography, afforded **4m** (94.4 mg, 64%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.77 (t, 3 H, *J* = 7.5 Hz, CH_3), 1.45 (qt, 2 H, *J* = 7.5, 7.5 Hz, CH_2), 1.68–1.74 (m, 1 H, CH_2), 1.98–2.04 (m, 1 H, CH_2), 5.34 (d, 1 H, *J* = 10.5 Hz, C=C*H*), 5.50 (d, 1 H, *J* = 17.0 Hz, C=C*H*), 5.83 (dd, 1 H, *J* = 17.0, 10.5 Hz, C=C*H*), 6.98 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 7.08 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.27 (brs, 2 H, Ar*H*), 7.35–7.38 (m, 1 H, Ar*H*), 7.41–7.44 (m, 2 H, Ar*H*), 7.45–7.49 (m, 1 H, Ar*H*), 7.97 (dd, 1 H, *J* = 7.5, 1.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.9, 16.3, 39.9, 94.2, 116.7, 118.5, 118.6, 122.0, 128.0, 128.2, 129.0, 134.3, 136.4, 137.7, 155.2, 162.4; HRMS (FAB) calcd for $[M+H]^+$ ($C_{19}H_{20}NO_2$) *m/z* 294.1494, found 294.1491.

cyclization product 4n'



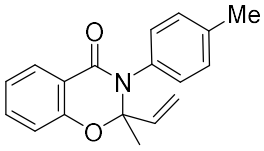
General procedure was followed with **3n** (252.8 mg). Column chromatography (50/1 to 3/1 hexane/EtOAc) afforded **4n'** (242.1 mg, 96%) as a colorless solid: mp 82–84 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.44 (s, 1 H, C=C*H*), 4.78 (s, 1 H, C=C*H*), 4.84 (s, 2 H, CH_2), 7.06 (d, 1 H, J = 8.0 Hz, Ar*H*), 7.11–7.14 (m, 1 H, Ar*H*), 7.24–7.26 (m, 2 H, Ar*H*), 7.33–7.36 (m, 1 H, Ar*H*), 7.42–7.47 (m, 3 H, Ar*H*), 8.24 (dd, 1 H, J = 8.0, 1.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 74.3, 107.7, 119.8, 122.4, 122.6, 127.57, 127.58, 129.6, 133.5, 133.9, 142.2, 144.3, 158.0, 165.2; HRMS (EI) calcd for $[M]^+$ ($C_{16}H_{13}NO_2$) *m/z* 251.0946, found 251.0953.

cyclization product 4o



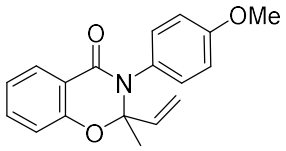
General procedure was followed with **3o** (272.4 mg). Column chromatography (50/1 to 25/1 hexane/EtOAc) afforded **4o** (204.4 mg, 75%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.58 (s, 3 H, CH_3), 2.37 (s, 3 H, CH_3), 5.31 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.49 (d, 1 H, J = 17.0 Hz, C=C*H*), 6.02 (dd, 1 H, J = 17.0, 10.5 Hz, C=C*H*), 6.95 (d, 1 H, J = 8.0 Hz, Ar*H*), 7.05–7.09 (m, 3 H, Ar*H*), 7.18 (d, 1 H, J = 7.5 Hz, Ar*H*), 7.31 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.44–7.48 (m, 1 H, Ar*H*), 7.96 (dd, 1 H, J = 7.5, 1.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.3, 26.2, 92.4, 116.7, 118.1, 118.6, 122.1, 128.3, 129.01, 129.02, 134.3, 137.7, 137.8, 139.2, 155.3, 162.3; HRMS (FAB) calcd for $[M+H]^+$ ($C_{18}H_{18}NO_2$) *m/z* 280.1338, found 280.1331.

cyclization product 4p



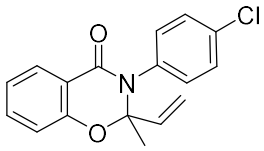
General procedure was followed with **3p** (279.1 mg). Column chromatography (50/1 to 10/1 hexane/EtOAc) afforded **4p** (203.7 mg, 73%) as a colorless solid: mp 89–91 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ1.58 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 5.30 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.48 (d, 1 H, J = 17.0 Hz, C=C*H*), 6.01 (dd, 1 H, J = 17.0, 10.5 Hz, C=C*H*), 6.95 (d, 1 H, J = 8.0 Hz, Ar*H*), 7.07 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.13 (d, 2 H, J = 8.0 Hz, Ar*H*), 7.22 (d, 2 H, J = 8.0 Hz, Ar*H*), 7.44–7.47 (m, 1 H, Ar*H*), 7.96 (dd, 1 H, J = 8.0, 1.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1, 26.2, 92.4, 116.7, 118.0, 118.6, 122.1, 128.3, 129.9, 134.3, 135.2, 137.7, 138.1, 155.2, 162.4; HRMS (EI) calcd for $[M+H]^+$ ($C_{18}H_{18}NO_2$) *m/z* 280.1338, found 280.1339.

cyclization product 4q



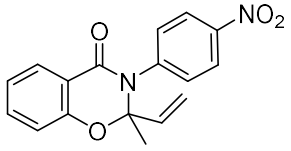
General procedure was followed with **3q** (292.9 mg). Column chromatography (50/1 to 10/1 hexane/EtOAc) afforded **4q** (169.1 mg, 58%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.58 (s, 3 H, C*H*$_3$), 3.82 (s, 3 H, OC*H*$_3$), 5.29 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.46 (d, 1 H, J = 17.0 Hz, C=C*H*), 6.01 (dd, 1 H, J = 17.0, 10.5 Hz, C=C*H*), 6.92–6.96 (m, 3 H, Ar*H*), 7.07 (td, 1 H, J = 7.5, 1.0 Hz, Ar*H*), 7.16 (d, 2 H, J = 8.5 Hz, Ar*H*), 7.43– 7.46 (m, 1 H, Ar*H*), 7.96 (dd, 1 H, J = 8.0, 2.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.1, 55.3, 92.4, 114.4, 116.6, 117.9, 118.5, 122.0, 128.2, 130.4, 134.2, 137.6, 155.2, 159.1, 162.4; HRMS (FAB) calcd for $[M+H]^+$ ($C_{18}H_{18}NO_3$) m/z 296.1287, found 296.1282.

cyclization product 4r



General procedure was followed with **3r**, except that the reaction was performed on a half scale (**3r**, 149.5 mg, 0.5 mmol; $Pd(dba)_2$, 28.8 mg, 0.05 mmol; JohnPhos, 29.8 mg, 0.1 mmol; toluene, 0.5 mL). Column chromatography (50/1 to 3/1 hexane/EtOAc) afforded **4r** (80.2 mg, 54%) as a colorless solid: mp 68–70 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.59 (s, 3 H, C*H*$_3$), 5.32 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.47 (d, 1 H, J = 17.0 Hz, C=C*H*), 6.00 (dd, 1 H, J = 17.0, 10.5 Hz, C=C*H*), 6.96 (d, 1 H, J = 8.5 Hz, Ar*H*), 7.09 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.21 (d, 2 H, J = 8.5 Hz, Ar*H*), 7.40 (d, 2 H, J = 9.0 Hz, Ar*H*), 7.46–7.49 (m, 1 H, Ar*H*), 7.95 (dd, 1 H, J = 7.5, 1.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.0, 92.3, 116.8, 118.2, 118.4, 122.2, 128.2, 129.4, 134.0, 134.5, 136.4, 137.4, 155.1, 162.2; HRMS (FAB) calcd for $[M+H]^+$ ($C_{17}H_{15}NO_2Cl$) m/z 300.0791, found 300.0793.

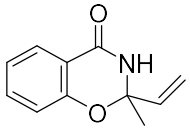
cyclization product 4s



General procedure was followed with **3s** (311.4 mg). Column chromatography (10/1 to 1/1 hexane/EtOAc) afforded **4s** (214.3 mg, 69%) as a colorless solid: mp 193–194 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.64 (s, 3 H, C*H*$_3$), 5.39 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.50 (d, 1 H, J = 17.0 Hz, C=C*H*), 6.03 (dd, 1 H, J = 17.0, 10.5 Hz, C=C*H*), 6.98 (d, 1 H, J = 8.0 Hz, Ar*H*), 7.12 (td, 1 H, J = 7.5, 1.0 Hz, Ar*H*), 7.46 (d, 2 H, J = 9.0 Hz, Ar*H*), 7.49–7.52 (m, 1 H, Ar*H*), 7.96 (dd, 1 H, J = 7.5, 1.5 Hz, Ar*H*), 8.29 (d, 2 H, J = 9.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.0, 92.5, 117.0, 117.9, 119.0,

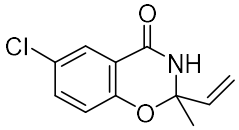
122.5, 124.4, 128.2, 130.5, 135.0, 137.2, 144.0, 147.0, 155.1, 162.1; HRMS (FAB) calcd for $[M+H]^+$ ($C_{17}H_{15}N_2O_4$) *m/z* 311.1032, found 311.1026. Colorless crystals of **4s** were obtained by recrystallization from methanol for a single-crystal Xray diffraction analysis.

cyclization product 4t



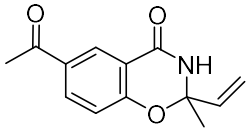
General procedure was followed with **3t**, except that the reaction was performed on a half scale (**3t**, 89.5 mg, 0.5 mmol; $Pd(dba)_2$, 28.8 mg, 0.05 mmol; JohnPhos, 29.8 mg, 0.1 mmol; toluene, 0.5 mL) for 12 h. Column chromatography (10/1 to 2/1 hexane/EtOAc) afforded **4t** (40.0 mg, 45%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.74 (s, 3 H, CH_3), 5.24 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.43 (d, 1 H, J = 17.0 Hz, C=C*H*), 5.91 (dd, 1 H, J = 17.0, 10.5 Hz, C=C*H*), 6.67 (brs, 1 H, N*H*), 6.93 (d, 1 H, J = 8.0 Hz, Ar*H*), 7.05 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.44 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.90 (d, 1 H, J = 7.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.0, 87.9, 116.9, 117.46, 117.48, 122.0, 127.6, 134.6, 138.7, 156.0, 163.5; HRMS (FAB) calcd for $[M+H]^+$ ($C_{11}H_{12}NO_2$) *m/z* 190.0868, found 190.0873.

cyclization product 4u



General procedure was followed with **3u**, except that the reaction was performed on a half scale (**3u**, 112.4 mg, 0.5 mmol; $Pd(dba)_2$, 28.8 mg, 0.05 mmol; JohnPhos, 29.8 mg, 0.1 mmol; toluene, 1 mL) for 12 h. Column chromatography (50/1 to 4/1 hexane/EtOAc), followed by gel permeation chromatography, afforded **4u** (22.0 mg, 20%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.76 (s, 3 H, CH_3), 5.25 (d, 1 H, J = 10.5 Hz, C=C*H*), 5.42 (d, 1 H, J = 17.0 Hz, C=C*H*), 5.89 (dd, 1 H, J = 17.0, 10.5 Hz, C=C*H*), 6.88 (d, 1 H, J = 8.5 Hz, Ar*H*), 7.38 (dd, 1 H, J = 8.5, 2.5 Hz, Ar*H*), 7.85 (d, 1 H, J = 2.5 Hz, Ar*H*), 7.92 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.0, 88.2, 117.9, 118.5, 118.6, 127.3, 134.5, 138.3, 154.4, 162.3; HRMS (FAB) calcd for $[M+H]^+$ ($C_{11}H_{11}NO_2Cl$) *m/z* 224.0478, found 224.0473.

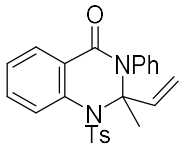
cyclization product 4v



General procedure was followed with **3v**, except that the reaction was performed on a 0.4 mmol scale (**3v**, 92.0 mg, 0.4 mmol; $Pd(dba)_2$, 23.0 mg, 0.04 mmol; JohnPhos, 23.5 mg, 0.08 mmol; toluene, 0.8 mL) for 12 h. Column chromatography (50/1 to 10/1 hexane/EtOAc) afforded **4v** (22.1 mg, 24%)

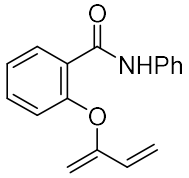
as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.82 (s, 3 H, CH_3), 2.61 (s, 3 H, CH_3), 5.27 (d, 1 H, J = 10.5 Hz, C=CH), 5.45 (d, 1 H, J = 17.5 Hz, C=CH), 5.93 (dd, 1 H, J = 17.5, 10.5 Hz, C=CH), 7.01 (d, 1 H, J = 9.0 Hz, ArH), 8.08 (brs, 1 H, NH), 8.11 (dd, 1 H, J = 8.5, 2.0 Hz, ArH), 8.48 (d, 1 H, J = 2.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 26.5, 27.0, 88.7, 116.8, 117.6, 118.0, 129.0, 131.4, 134.4, 138.2, 159.6, 162.7, 196.3; HRMS (FAB) calcd for $[M+H]^+$ ($C_{13}H_{14}NO_3$) m/z 232.0974, found 232.0979.

cyclization product 4y



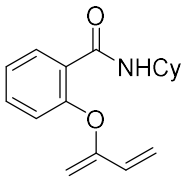
General procedure was followed with **3y** (416.8 mg). Column chromatography (50/1 to 5/1 hexane/EtOAc), followed by gel permeation chromatography, afforded **4y** (116.7 mg, 28%) as a colorless solid: mp 148–149 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.66 (s, 3 H, CH_3), 2.47 (s, 3 H, CH_3), 5.06 (d, 1 H, J = 10.5 Hz, C=CH), 5.23 (d, 1 H, J = 17.0 Hz, C=CH), 5.59 (d, 1 H, J = 7.5 Hz, ArH), 5.87 (dd, 1 H, J = 17.0, 10.5 Hz, C=CH), 7.01 (d, 1 H, J = 6.5 Hz, ArH), 7.11–7.14 (m, 1 H, ArH), 7.23– 7.35 (m, 4 H, ArH), 7.42 (t, 1 H, J = 7.5 Hz, ArH), 7.48 (d, 2 H, J = 8.5 Hz, ArH), 7.59 (t, 1 H, J = 7.5 Hz, ArH), 7.71 (d, 1 H, J = 8.5 Hz, ArH), 8.00 (d, 1 H, J = 7.5 Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.6, 25.8, 79.4, 116.2, 126.7, 127.3, 127.7, 127.9, 128.1, 128.6, 128.8, 128.9, 129.7, 130.2, 132.4, 137.9, 138.1, 139.2, 140.8, 144.4, 163.1; HRMS (FAB) calcd for $[M+H]^+$ ($C_{24}H_{23}N_2O_3S$) m/z 419.1429, found 419.1430.

1,3-diene 5a



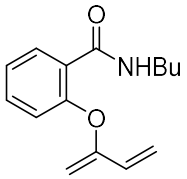
General procedure was followed with **3a** (265.1 mg), except that the reaction was performed for 1.5 min. Column chromatography (50/1 to 10/1 hexane/EtOAc), followed by gel permeation chromatography, afforded **5a** (77.9 mg, 29%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.45 (s, 1 H, C=CH), 4.72 (s, 1 H, C=CH), 5.36 (d, 1 H, J = 10.5 Hz, C=CH), 5.80 (d, 1 H, J = 17.0 Hz, C=CH), 6.41 (dd, 1 H, J = 17.0, 10.5 Hz, C=CH), 7.11– 7.13 (m, 2 H, ArH), 7.30 (t, 1 H, J = 7.5 Hz, ArH), 7.34 (t, 2 H, J = 8.0 Hz, ArH), 7.48–7.51 (m, 1 H, ArH), 7.63 (d, 2 H, J = 8.0 Hz, ArH), 8.30 (dd, 1 H, J = 8.0, 1.5 Hz, ArH), 9.42 (brs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 98.5, 116.2, 120.3, 124.3, 124.8, 125.0, 128.97, 128.98, 131.4, 132.3, 133.1, 138.2, 153.2, 156.9, 162.5; HRMS (EI) calcd for $[M]^+$ ($C_{17}H_{15}NO_2$) m/z 265.1103, found 265.1101.

1,3-diene 5w



General procedure was followed with **3w**, except that the reaction was performed on a half scale (**3w**, 135.3 mg, 0.5 mmol; $Pd(dba)_2$, 28.8 mg, 0.05 mmol; JohnPhos, 29.8 mg, 0.1 mmol; toluene, 0.5 mL). Column chromatography (50/1 to 10/1 hexane/EtOAc) afforded **5w** (55.5 mg, 41%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.18–1.26 (m, 3 H, C*H*$_3$), 1.35–1.43 (m, 2 H, C*H*$_2$), 1.58–1.62 (m, 1 H, C*H*), 1.67–1.71 (m, 2 H, C*H*$_2$), 1.93–1.96 (m, 2 H, C*H*$_2$), 3.94–4.00 (m, 1 H, C*H*), 4.27 (s, 1 H, C=C*H*), 4.58 (s, 1 H, C=C*H*), 5.30 (d, 1 H, J = 11.0 Hz, C=C*H*), 5.71 (d, 1 H, J = 17.5 Hz, C=C*H*), 6.35 (dd, 1 H, J = 17.5, 11.0 Hz, C=C*H*), 7.05 (d, 1 H, J = 8.0 Hz, Ar*H*), 7.25 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.34 (brs, 1 H, N*H*), 7.41–7.44 (m, 1 H, Ar*H*), 8.17 (dd, 1 H, J = 8.0, 2.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 24.6, 25.6, 32.8, 48.2, 96.9, 115.7, 120.7, 124.7, 125.9, 131.6, 131.9, 132.3, 152.9, 157.1, 163.5; HRMS (FAB) calcd for $[M+H]^+$ ($C_{17}H_{22}NO_2$) *m/z* 272.1651, found 272.1650.

1,3-diene 5x



General procedure was followed with **3x** (244.5 mg). Column chromatography (50/1 to 10/1 hexane/EtOAc) afforded **5x** (87.2 mg, 36%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.92 (t, 3 H, J = 7.5 Hz, C*H*$_3$), 1.37 (qt, 2 H, J = 7.5, 7.5 Hz, C*H*$_2$), 1.54 (tt, 2 H, J = 7.5, 7.5 Hz, C*H*$_2$), 3.41–3.45 (m, 2 H, C*H*$_2$), 4.35 (s, 1 H, C=C*H*), 4.64 (s, 1 H, C=C*H*), 5.29 (d, 1 H, J =11.0 Hz, C=C*H*), 5.68 (d, 1 H, J =17.0 Hz, C=C*H*), 6.35 (dd, 1 H, J =17.0, 11.0 Hz, C=C*H*), 7.05 (d, 1 H, J = 8.0 Hz, Ar*H*), 7.23 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.40–7.44 (m, 2 H, Ar*H*), 8.19 (dd, 1 H, J = 7.5, 1.5 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.7, 20.1, 31.4, 39.5, 97.9, 115.8, 120.2, 124.4, 125.1, 131.5, 132.0, 132.4, 153.3, 157.0, 164.6; HRMS (EI) calcd for $[M]^+$ ($C_{15}H_{19}NO_2$) *m/z* 245.1416, found 245.1442.

Procedure A for Synthesis of Alkynoic Acid Methyl Esters

To a DMF solution of a methyl salicylate derivative with K_2CO_3 (2 equiv) in a round-bottom flask, a DMF solution of 1.2 equiv of propargyl bromide derivative, which was prepared from the corresponding propargyl alcohol with PBr_3, was added dropwise at room temperature. The mixture was stirred continuously overnight, then H_2O was added to the resultant mixture, which was extracted with Et_2O. The organic layer was dried over Na_2SO_4, and the volatile materials were removed by rotary evaporation. The crude material was purified by silica gel column chromatography.

Procedure B for Synthesis of Alkynoic Acid Methyl Esters

A toluene solution of a methyl salicylate derivative, and 1.1 equiv each of a propargyl alcohol derivative with PPh3 in a round-bottom flask was cooled to 0 °C, a toluene solution of 1.1 equiv of DIAD (diisopropyl azodicarboxylate) was added dropwise. The mixture was gradually warmed to 50 °C and stirred for 1 h, the volatile materials were then removed by rotary evaporation. To the resultant mixture was added hexane and Et_2O (4/1) to form the phosphine oxide as a precipitate. After filtration to remove the precipitate, the filtrate was concentrated by rotary evaporation, and was purified by silica gel column chromatography.

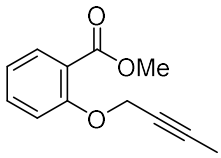
Procedure C for Synthesis of Alkynoic Acid Methyl Esters

Procedure A was followed with a methyl salicylate and a propargyl bromide to synthesize a methyl ester bearing a terminal alkyne, initially. To a 50 mL Schlenk tube, $PdCl_2(PPh_3)_2$ (3 mol %), CuI (5 mol %), the terminal alkyne, DMF, PhI (1.1 equiv), and NEt_3 (1.5 equiv) were added in this order. The mixture was then stirred at room temperature for 2 h. A saturated aqueous solution of NH_4Cl was added to the reaction mixture, which was then extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the volatile materials were removed by rotary evaporation. The crude material was purified by silica gel column chromatography (20/1 to 10/1 hexane/EtOAc).

Procedure D for Synthesis of Alkynoic Acid Methyl Esters

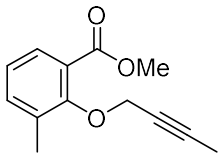
A $CHCl_3$ solution of methyl anthranilate and pyridine (1.2 equiv) in a 50 mL round-bottom flask was stirred at room temperature for 1 h, and then a $CHCl_3$ solution of 1.1 equiv of TsCl was added dropwise at room temperature. The mixture was stirred continuously overnight, then H_2O was added to the resultant mixture, which was then extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, and the volatile materials were removed by rotary evaporation, and recrystallization from $CHCl_3$ with hexane afforded the *N*-tosylation product. Procedure A was next followed using sulfonamide and a propargyl bromide derivative.

alkynoic acid methyl ester[2]



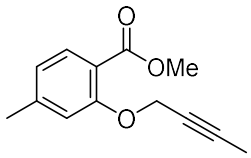
Procedure A was followed. Column chromatography (30/1 to 20/1 hexane/EtOAc) afforded as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.84 (t, J = 2.0 Hz, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 4.75 (q, J = 2.0 Hz, 2 H, CH_2), 7.01 (t, J = 7.5 Hz, 1 H, ArH), 7.12 (d, J = 8.5 Hz, 1 H, ArH), 7.45−7.48 (m, 1 H, ArH), 7.80 (d, J = 7.5 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 52.0, 57.3, 73.7, 84.2, 114.2, 120.75, 120.78, 131.6, 133.2, 157.3, 166.5; HRMS (EI) calcd for $[M]^+$ ($C_{12}H_{12}O_3$) m/z 204.0786, found, 204.0787.

3-methyl-alkynoic acid methyl ester



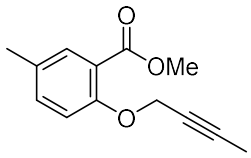
Procedure A was followed. Column chromatography (70/1 to 20/1 hexane/EtOAc) afforded as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.85 (t, J = 2.5 Hz, 3 H, CH_3), 2.36 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 4.59 (q, J = 2.5 Hz, 2 H, CH_2), 7.08 (t, J = 7.5 Hz, 1 H, ArH), 7.35 (d, J = 7.0 Hz, 1 H, ArH), 7.65 (d, J = 8.0 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 16.4, 52.1, 62.1, 74.5, 83.6, 124.0, 125.1, 129.1, 133.4, 135.1, 156.1, 166.8; HRMS (EI) calcd for $[M]^+$ ($C_{13}H_{14}O_3$) m/z 218.0943, found 218.0948.

4-methyl-alkynoic acid methyl ester



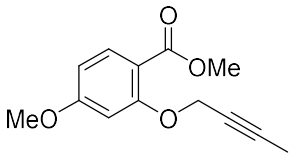
Procedure A was followed. Column chromatography (70/1 to 20/1 hexane/EtOAc) afforded as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.84 (t, J = 2.0 Hz, 3 H, CH_3), 2.38 (s, 3 H, CH_3), 3.86 (s, 3 H, CH_3), 4.73 (q, J = 2.0 Hz, 2 H, CH_2), 6.81 (d, J = 8.0, 1 H, ArH), 6.90 (s, 1 H, ArH), 7.72 (d, J = 8.0 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 21.7, 51.7, 57.3, 73.7, 83.9, 114.9, 117.7, 121.6, 131.7, 144.2, 157.4, 166.3; HRMS (EI) calcd for $[M]^+$ ($C_{13}H_{14}O_3$) m/z 218.0943, found 218.0942.

5-methyl-alkynoic acid methyl ester



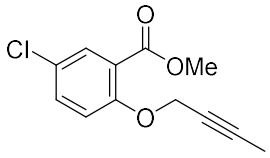
Procedure A was followed. Column chromatography (70/1 to 20/1 hexane/EtOAc) afforded as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.83 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 3.88 (s, 3 H, CH_3), 4.71 (s, 2 H, CH_2), 7.02 (d, J = 8.5 Hz, 1 H, ArH), 7.26 (d, J = 8.5 Hz, 1 H, ArH), 7.61 (s, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.5, 20.1, 51.8, 57.4, 73.8, 83.8, 114.4, 120.4, 130.2, 131.8, 133.6, 155.1, 166.5; HRMS (EI) calcd for $[M]^+$ ($C_{13}H_{14}O_3$) m/z 218.0943, found 218.0936.

4-MeO-alkynoic acid methyl ester



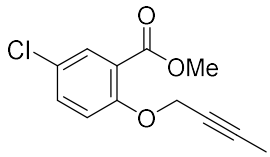
Procedure A was followed. Column chromatography (50/1 to 20/1 hexane/EtOAc) afforded as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.85 (t, J = 2.5 Hz, 3 H, CH_3), 3.84 (s, 3 H, CH_3), 3.85 (s, 3 H, CH_3), 4.74 (q, J = 2.5 Hz, 2 H, CH_2), 6.53 (dd, J = 8.5, 2.0 Hz, 1 H, ArH), 6.65 (d, J = 2.0 Hz, 1 H, ArH), 7.85 (d, J = 8.5 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 51.6, 55.4, 57.4, 73.6, 84.3, 100.9, 105.5, 112.9, 133.7, 159.4, 163.9, 165.9; HRMS (EI) calcd for $[M]^+$ ($C_{13}H_{14}O_4$) m/z 234.0892, found 234.0892.

5-Cl-alkynoic acid methyl ester[2]



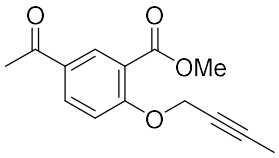
Procedure A was followed. Column chromatography (70/1 to 50/1 hexane/EtOAc) afforded as a colorless solid: mp 59−61 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.84 (s, 3 H, CH_3), 3.89 (s, 3 H, CH_3), 4.74 (s, 2 H, CH_2), 7.08 (dd, J = 8.0, 2.5 Hz, 1 H, ArH), 7.41 (d, J = 8.0 Hz, 1 H, ArH), 7.78 (t, J = 2.5 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 52.2, 57.6, 73.2, 84.6, 115.7, 121.9, 125.8, 131.3, 132.8, 155.8, 165.2; HRMS (EI) calcd for $[M]^+$ ($C_{12}H_{11}O_3Cl$) m/z 238.0397, found 238.0390.

5-Br-alkynoic acid methyl ester



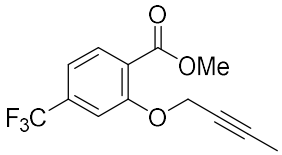
Procedure A was followed. Column chromatography (70/1 to 50/1 hexane/EtOAc) afforded as a colorless solid: mp 78−79 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.83 (t, J = 2.0 Hz, 3 H, CH_3), 3.88 (s, 3 H, CH_3), 4.73 (q, J = 2.0 Hz, 2 H, CH_2), 7.02 (d, J = 9.0 Hz, 1 H, ArH), 7.55 (dd, J = 9.0, 2.0 Hz, 1 H, ArH), 7.91 (d, J = 2.0 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 52.3, 57.6, 73.3, 84.8, 113.0, 116.2, 122.5, 134.3, 135.8, 156.4, 165.1; HRMS (EI) calcd for $[M]^+$ ($C_{12}H_{11}O_3Br$) m/z 281.9892; found 281.9890.

5-acethyl-alkynoic acid methyl ester



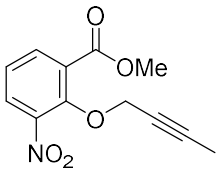
Procedure A was followed. Column chromatography (30/1 to 20/1 hexane/EtOAc) afforded as a colorless solid: mp 92−93 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.84 (s, 3 H, CH_3), 2.59 (s, 3 H, CH_3), 3.92 (s, 3 H, CH_3), 4.84 (s, 2 H, CH_2), 7.19 (d, J = 8.0 Hz, 1 H, ArH), 8.11 (d, J = 8.0 Hz, 1 H, ArH), 8.42 (s, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 26.3, 52.2, 57.3, 72.8, 85.1, 113.5, 120.3, 129.9, 132.6, 133.4, 160.7, 165.7, 196.0; HRMS (FAB) calcd for $[M+H]^+$ ($C_{14}H_{15}O_4$) m/z 247.0970, found 247.0970.

4-CF_3-alkynoic acid methyl ester



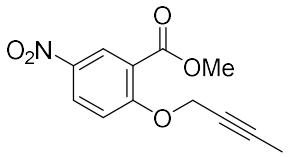
Procedure A was followed. Column chromatography (70/1 to 20/1 hexane/EtOAc) afforded as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.84 (t, J = 2.0 Hz, 3 H, CH_3), 3.92 (s, 3 H, CH_3), 4.80 (q, J = 2.0 Hz, 2 H, CH_2), 7.27 (d, J = 8.0 Hz, 1 H, ArH), 7.38 (s, 1 H, ArH), 7.87 (d, J = 8.0 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.5, 52.4, 57.7, 72.8, 85.3, 111.3 (q, J_{C-F} = 3.8 Hz), 117.4 (q, J_{C-F} = 3.8 Hz), 123.4 (q, J_{C-F} = 272.9 Hz), 124.2, 132.0, 134.6 (q, J_{C-F} = 32.7 Hz), 157.1, 165.6; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −63.1 (s); HRMS (EI) calcd for $[M]^+$ ($C_{13}H_{11}O_3F_3$) m/z 272.0660, found 272.0673.

3-NO_2-alkynoic acid methyl ester



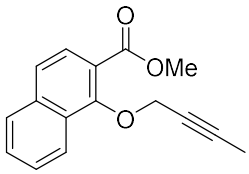
Procedure A was followed. Column chromatography (20/1 hexane/EtOAc) afforded as a pale yellow solid: mp 88−90 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.35 (s, 3 H, CH_3), 3.97 (s, 3 H, CH_3), 4.78 (s, 2H, CH_2), 7.31 (t, J = 8.0 Hz, 1 H, ArH), 7.93 (dd, J = 8.5, 2.0 Hz, 1 H, ArH), 8.10 (dd, J = 8.0, 2.0 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 52.8, 64.7, 72.9, 86,5, 124.4, 128.4, 128.6, 135.5, 146.3, 150.4, 164.9; HRMS (FAB) calcd for $[M+H]^+$ ($C_{12}H_{12}NO_5$) m/z 250.0715, found 250.0712.

5-NO_2-alkynoic acid methyl ester



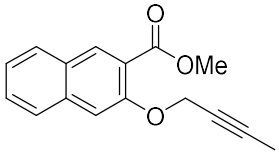
Procedure A was followed. Column chromatography (50/1 to 10/1 hexane/EtOAc) afforded as a colorless solid: mp 114−115°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.86 (s, 3H, CH_3), 3.94 (s, 3H, CH_3), 4.89 (s, 2H, CH_2), 7.26 (d, J = 8.0 Hz, 1H, ArH), 8.37 (dd, J = 8.0, 2.5 Hz, 1H, ArH), 8.71 (d, J = 2.5 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.5, 52.4, 57.7, 72.2, 85.7, 113.7, 120.7, 127.5, 128.4, 140.7, 161.6, 164.2; HRMS (FAB) calcd for $[M+H]^+$ ($C_{12}H_{12}NO_5$) m/z 250.0715, found 250.0719.

2-naphthalene-1-alkynoic acid methyl ester



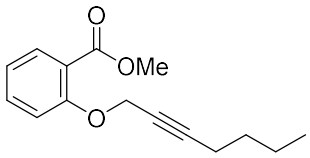
Procedure B was followed. Column chromatography (30/1 to 10/1 hexane/EtOAc) afforded as a pale orange oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.69 (t, J = 2.5 Hz, 3 H, CH_3), 3.82 (s, 3 H, CH_3), 4.68 (q, J = 2.5 Hz, 2 H, CH_2), 7.39−7.41 (m, 2 H, ArH), 7.46 (d, J = 8.5 Hz, 1 H, ArH), 7.65−7.67 (m, 1 H, ArH), 7.72 (d, J = 8.0 Hz, 1 H, ArH), 8.23−8.25 (m, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.5, 52.0, 63.7, 74.3, 84.3, 119.8, 123.8, 123.9, 126.2, 126.3, 127.5, 128.1, 128.7, 136.4, 155.8, 166.4; HRMS (EI) calcd for $[M]^+$ ($C_{16}H_{14}O_3$) m/z 254.0943, found 254.0937.

2-naphthalene-3-alkynoic acid methyl ester



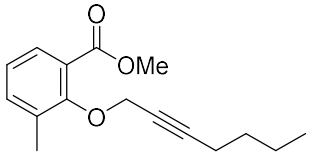
Procedure A was followed. Column chromatography (30/1 to 10/1 hexane/EtOAc) afforded as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.85 (t, J = 2.0 Hz, 3 H, CH_3), 3.95 (s, 3 H, CH_3), 4.84 (q, J = 2.0 Hz, 2 H, CH_2), 7.35 (s, 1 H, ArH), 7.38 (t, J = 7.5 Hz, 1 H, ArH), 7.51 (t, J = 7.5 Hz, 1 H, ArH), 7.76 (d, J = 8.0 Hz, 1 H, ArH), 7.81 (d, J = 8.0 Hz, 1 H, ArH), 8.32 (s, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 52.2, 57.3, 73.7, 84.2, 109.0, 122.0, 124.6, 126.6, 127.8, 128.3, 128.6, 132.8, 135.8, 153.7, 166.5; HRMS (EI) calcd for $[M]^+$ ($C_{16}H_{14}O_3$) m/z 254.0943, found 254.0948.

Butylated alkynoic acid methyl ester



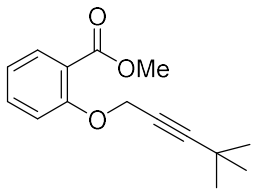
Procedure A was followed. Column chromatography (90/1 to 50/1 hexane/EtOAc) afforded as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H, CH_3), 1.33−1.40 (m, 2 H, CH_2), 1.43−1.49 (m, 2 H, CH_2), 2.20 (tt, J = 7.0, 2.0 Hz, 2 H, CH_2), 3.89 (s, 3 H, CH_3), 4.78 (t, J = 2.0 Hz, 2 H, CH_2), 7.00 (td, J = 8.0, 1.0 Hz, 1 H, ArH), 7.14 (d, J = 8.0 Hz, 1 H, ArH), 7.44−7.48 (m, 1 H, ArH), 7.80−7.81 (m, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.4, 18.4, 21.8, 30.3, 51.9, 57.4, 74.5, 88.8, 114.4, 120.75, 120.78, 131.6, 133.1, 157.3, 166.6; HRMS (EI) calcd for $[M]^+$ ($C_{15}H_{18}O_3$) m/z 246.1256, found 246.1261.

3-methyl-butylated alkynoic acid methyl ester



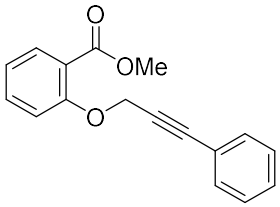
Procedure B was followed. Column chromatography (30/1 hexane/EtOAc) afforded as a colorless oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.79 (t, J = 7.0 Hz, 3 H, CH_3), 1.22−1.30 (m, 2 H, CH_2), 1.33−1.39 (m, 2 H, CH_2), 2.10 (tt, J = 7.0, 2.0 Hz, 2 H, CH_2), 2.27 (s, 3 H, CH_3), 3.81 (s, 3 H, CH_3), 4.55 (t, J = 2.0 Hz, 2 H, CH_2), 6.97 (t, J = 7.5 Hz, 1 H, ArH), 7.25 (d, J = 7.0 Hz, 1 H, ArH), 7.57 (t, J = 8.0 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.4, 16.4, 18.3, 21.7, 30.3, 52.0, 62.0, 75.1, 88.0, 123.8, 124.9, 129.0, 133.4, 134.9, 156.1, 166.6; HRMS (EI) calcd for $[M]^+$ ($C_{16}H_{20}O_3$) m/z 260.1412, found 260.1419.

***tert*-butylated alkynoic acid methyl ester**



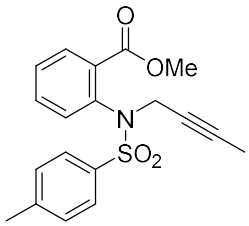
Procedure B was followed. Column chromatography (70/1 to 10/1 hexane/EtOAc) afforded as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.17 (s, 9 H, CH_3), 3.87 (s, 3 H, CH_3), 4.75 (s, 2 H, CH_2), 6.98−7.01 (m, 1 H, ArH), 7.14 (d, J = 8.5 Hz, 1 H, ArH), 7.43−7.45 (m, 1 H, ArH), 7.79 (d, J =8.0 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.4, 30.6, 51.9, 57.7, 73.2, 96.9, 114.8, 120.8, 120.9, 131.5, 133.0, 157.4, 166.6; HRMS (EI) calcd for $[M]^+$ ($C_{15}H_{18}O_3$) m/z 246.1256, found 246.1259.

phenylated alkynoic acid methyl ester[2]



Procedure C was followed. Column chromatography (30/1 hexane/EtOAc) afforded as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.88 (s, 3 H, C*H*$_3$), 5.00 (s, 2 H, C*H*$_2$), 7.02 (td, *J* = 7.5, 1.0 Hz, 1 H, Ar*H*), 7.21 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.25−7.31 (m, 3 H, Ar*H*), 7.39−7.41 (m, 2 H, Ar*H*), 7.45−7.48 (m, 1 H, Ar*H*), 7.82 (dd, *J* = 8.0, 2.0 Hz, 1 H, Ar*H*); ^{13}C NMR (CD_3OD, 125 MHz) δ 52.5, 58.3, 84.8, 88.3, 115.8, 122.16, 122.20, 123.5, 129.5, 129.8, 132.5, 132.7, 134.6, 158.5, 168.4; HRMS (EI) calcd for $[M]^+$ ($C_{17}H_{14}O_3$) *m*/*z* 266.0943, found 266.0942.

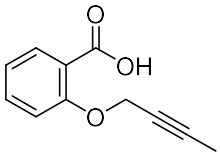
tosylated alkynoic acid methyl ester[2]



Procedure D was followed. Column chromatography (100/1 hexane/NEt_3) afforded as a colorless solid: mp 102−103 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.69 (s, 3 H, C*H*$_3$), 2.42 (s, 3 H, C*H*$_3$), 3.81 (s, 3 H, C*H*$_3$), 4.49 (s, 2 H, C*H*$_2$), 7.17−7.24 (m, 3 H, Ar*H*), 7.41−7.43 (m, 2 H, Ar*H*), 7.59 (d, *J* = 8.0 Hz, 2 H, Ar*H*), 7.83−7.85 (m, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.4, 21.5, 41.8, 52.2, 73.9, 81.5, 127.8, 128.7, 129.1, 131.0, 131.6, 131.9, 132.5, 137.2, 137.9, 143.1, 166.4; HRMS (FAB) calcd for $[M+H]^+$ ($C_{19}H_{20}NO_4S$) *m*/*z* 358.1113, found 358.1112.

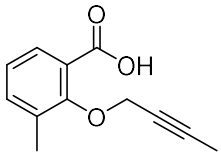
Spectral Data of alkynoic acid 1

alkynoic acid 1a[2]



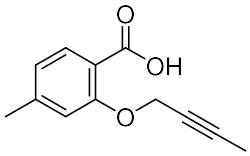
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1a** as a colorless solid: mp 95−96 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.88 (t, *J* = 2.0 Hz, 3 H, C*H*$_3$), 4.91 (q, *J* = 2.0 Hz, 2 H, C*H*$_2$), 7.14−7.18 (m, 2 H, Ar*H*), 7.56−7.59 (m, 1 H, Ar*H*), 8.20 (dd, *J* = 7.5, 1.5 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 58.4, 71.9, 86.4, 113.3, 118.2, 122.6, 133.8, 134.8, 156.5, 165.4; HRMS (EI) calcd for $[M]^+$ ($C_{11}H_{10}O_3$) *m*/*z* 190.0630, found 190.0633.

alkynoic acid 1b



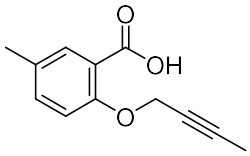
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1b** as a colorless solid: mp 107−108 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) 1 H, Ar*H*), 7.43 (d, *J* = 7.0 Hz, 1 H, Ar*H*), 7.91 (d, *J* = 8.0 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 16.2, 62.7, 73.0, 86.0, 123.6, 124.9, 130.2, 132.4, 136.5, 155.7, 168.3; HRMS (FAB) calcd for $[M-H]^-$ ($C_{12}H_{11}O_3$) *m*/*z* 203.0708, found 203.0711.

alkynoic acid 1c



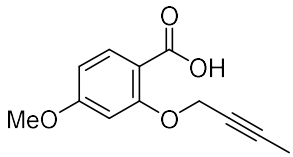
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1c** as a colorless solid: mp 123−124 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.88 (s, 3 H, C*H*$_3$), 2.43 (s, 3 H, C*H*$_3$), 4.88 (s, 2 H, C*H*$_2$), 6.92 (s, 1 H, Ar*H*), 6.97 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 8.07 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 10.68 (s, 1 H, O*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 22.0, 58.3, 72.0, 86.3, 113.8, 115.5, 123.6, 133.7, 146.3, 156.4, 165.3; HRMS (FAB) calcd for $[M-H]^-$ ($C_{12}H_{11}O_3$) *m*/*z* 203.0708, found 203.0700.

alkynoic acid 1d



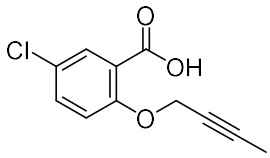
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1d** as a colorless solid: mp 104−105 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.87 (s, 3 H, C*H*$_3$), 2.34 (s, 3 H, C*H*$_3$), 4.87 (s, 2 H, C*H*$_2$), 7.04 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 7.36 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 7.98 (s, 1 H, Ar*H*), 10.84 (s, 1 H, O*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 20.2, 58.4, 72.1, 86.2, 113.3, 117.8, 132.2, 133.8, 135.4, 154.4, 165.6; HRMS (EI) calcd for $[M]^+$ ($C_{12}H_{12}O_3$) *m*/*z* 204.0786, found 204.0795.

alkynoic acid 1e



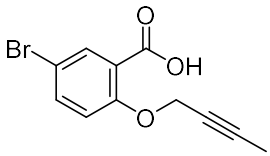
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1e** as a colorless solid: mp 127−128 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.89 (t, J = 2.5 Hz, 3 H, CH_3), 3.89 (s, 3 H, OCH_3), 4.87 (q, J = 2.5 Hz, 2 H, CH_2), 6.64 (d, J = 2.5 Hz, 1 H, ArH), 6.67 (dd, J = 9.0, 2.5 Hz, 1 H, ArH), 8.14 (d, J = 9.0 Hz, 1 H, ArH), 10.53 (s, 1 H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 55.7, 58.4, 71.8, 86.5, 100.0, 107.1, 110.9, 135.6, 157.8, 164.9, 165.1; HRMS (EI) calcd for $[M]^+$ ($C_{12}H_{12}O_4$) m/z 220.0736, found 220.0735.

alkynoic acid 1f[2]



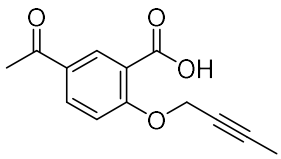
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1f** as a colorless solid: mp 126−128 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.87 (s, 3 H, CH_3), 4.90 (s, 2 H, CH_2), 7.12 (d, J = 9.0 Hz, 1 H, ArH), 7.52 (d, J = 9.0 Hz, 1 H, ArH), 8.15 (s, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 58.7, 71.6, 86.9, 115.0, 119.7, 128.0, 133.2, 134.5, 154.9, 164.3; HRMS (FAB) calcd for $[M+H]^+$ ($C_{11}H_{10}O_3Cl$) m/z 225.0318, found 225.0314.

alkynoic acid 1g



Hydrolysis of corresponding alkynoic acid methyl ester afforded **1g** as a colorless solid: mp 142−143 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.88 (t, J = 2.5 Hz, 3 H, CH_3), 4.90 (q, J = 2.5 Hz, 2 H, CH_2), 7.06 (d, J = 9.0 Hz, 1 H, ArH), 7.66 (dd, J = 9.0, 2.5 Hz, 1 H, ArH), 8.31 (d, J = 2.5 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 58.6, 71.6, 86.9, 115.0, 115.3, 120.0, 136.1, 137.4, 155.5, 164.4; HRMS (FAB) calcd for $[M+H]^+$ ($C_{11}H_{10}BrO_3$) m/z 268.9813, found 268.9820.

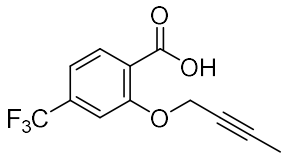
alkynoic acid 1h



Hydrolysis of corresponding alkynoic acid methyl ester afforded **1h** as a colorless solid: mp 167−169 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.88 (t, J = 2.0 Hz, 3 H, CH_3), 2.63 (s, 3 H, CH_3),

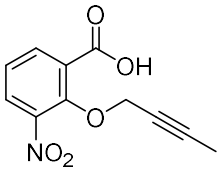
4.98 (q, *J* = 2.0 Hz, 2 H, C*H*$_2$), 7.25 (d, *J* = 9.0 Hz, 1 H, Ar*H*), 8.23 (dd, *J* = 9.0, 2.5 Hz, 1 H, Ar*H*), 8.74 (d, *J* = 2.5 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 26.5, 58.6, 71.4, 87.1, 113.5, 118.0, 131.5, 134.6, 134.7, 159.8, 164.9, 196.0; HRMS (EI) calcd for $[M]^+$ ($C_{13}H_{12}O_4$) *m*/*z* 232.0736, found 232.0741.

alkynoic acid 1i



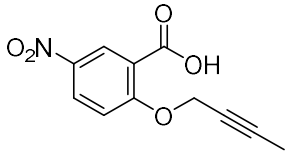
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1i** as a colorless solid: mp 121−122 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.89 (s, 3 H, C*H*$_3$), 4.97 (s, 2 H, C*H*$_2$), 7.41 (s, 1 H, Ar*H*), 7.43 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 8.32 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 10.44 (s, 1 H, O*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 58.5, 71.6, 86.9, 110.9 (q, J_{C-F} = 3.8 Hz), 118.6 (q, J_{C-F} = 3.8 Hz), 121.8, 123.1 (q, J_{C-F} = 273.4 Hz), 134.1, 136.0 (q, J_{C-F} = 32.7 Hz), 156.8, 166.1; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −63.3 (s); HRMS (FAB) calcd for $[M+H]^+$ ($C_{12}H_{10}F_3O_3$) *m*/*z* 259.0582, found 259.0573.

alkynoic acid 1j



Hydrolysis of corresponding alkynoic acid methyl ester afforded **1j** as a colorless solid: mp 120−121 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.80 (t, *J* = 2.5 Hz, 3 H, C*H*$_3$), 4.90 (q, *J* = 2.5 Hz, 2 H, C*H*$_2$), 7.40 (t, *J* = 8.0 Hz, 1 H, Ar*H*), 8.06 (dd, *J* = 8.0, 2.0 Hz, 1 H, Ar*H*), 8.27 (dd, *J* = 8.0, 2.0 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 65.1, 72.3, 88.0, 124.8, 127.1, 129.7, 136.5, 145.8, 150.7, 167.5; HRMS (FAB) calcd for $[M+H]^+$ ($C_{11}H_{10}NO_5$) *m*/*z* 236.0559, found 236.0560.

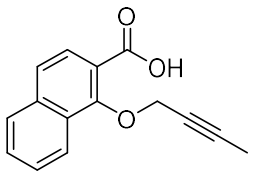
alkynoic acid 1k



Hydrolysis of corresponding alkynoic acid methyl ester afforded **1k** as a colorless solid: mp 121−122 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 1.83 (s, 3 H, C*H*$_3$), 4.92 (s, 2 H, C*H*$_2$), 7.39 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 8.39 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 8.63 (s, 1 H, Ar*H*); ^{13}C NMR (CD_3OD, 125

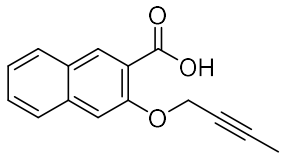
MHz) δ 3.0, 58.9, 73.8, 86.3, 115.7, 123.3, 128.2, 129.3, 142.5, 163.1, 167.4; HRMS (FAB) calcd for $[M+H]^+$ ($C_{11}H_{10}NO_5$) *m*/*z* 236.0559, found 236.0562.

alkynoic acid 1l



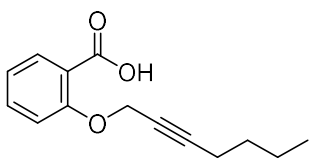
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1l** as a colorless solid: mp 122−123 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.85 (t, *J* = 2.0 Hz, 3 H, C*H*$_3$), 4.91 (q, *J* = 2.0 Hz, 2 H, C*H*$_2$), 7.60−7.66 (m, 2 H, Ar*H*), 7.74 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 7.90 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 8.09 (d, *J* = 8.5 Hz, 1 H, Ar*H*), 8.23 (d, *J* = 8.0 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 64.8, 73.0, 87.1, 119.2, 123.4, 125.1, 126.7, 126.9, 127.6, 128.2, 128.9, 137.4, 155.5, 167.9; HRMS (EI) calcd for $[M]^+$ ($C_{15}H_{12}O_3$) *m*/*z* 240.0786, found 240.0785.

alkynoic acid 1m



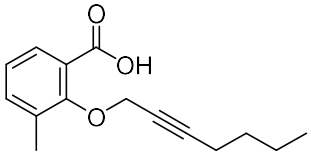
Hydrolysis of corresponding alkynoic acid methyl ester afforded 1m as a colorless solid: mp 142−143 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90 (t, *J* = 2.5 Hz, 3 H, C*H*$_3$), 5.00 (q, *J* = 2.5 Hz, 2 H, C*H*$_2$), 7.40 (s, 1 H, Ar*H*), 7.47 (t, *J* = 7.0 Hz, 1 H, Ar*H*), 7.59−7.62 (m, 1 H, Ar*H*), 7.80 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.92 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 8.81 (s, 1 H, Ar*H*), 10.89 (s, 1 H, O*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 58.3, 72.0, 86.2, 108.7, 118.3, 125.4, 126.6, 128.4, 129.28, 129.33, 136.0, 136.3, 152.6, 165.7; HRMS (FAB) calcd for $[M+H]^+$ ($C_{15}H_{13}O_3$) *m*/*z* 241.0865, found 241.0864.

alkynoic acid 1n



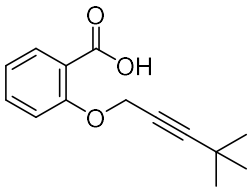
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1n** as a colorless solid: mp 62−63 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, J = 7.5 Hz, 3 H, CH_3), 1.36 (sext, J = 7.5 Hz, 2 H, CH_2), 1.48 (quin, J = 7.5 Hz, 2 H, CH_2), 2.23 (t, J = 7.5 Hz, 2 H, CH_2), 4.93 (s, 2 H, CH_2), 7.15−7.19 (m, 2 H, Ar*H*), 7.57 (t, J = 8.0 Hz, 1 H, Ar*H*), 8.19−8.21 (m, 1 H, Ar*H*), 10.74 (s, 1 H, O*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.5, 18.4, 21.8, 30.2, 58.5, 72.7, 91.1, 113.4, 118.3, 122.7, 133.8, 134.8, 156.4, 165.2; HRMS (FAB) calcd for $[M+H]^+$ ($C_{14}H_{17}O_3$) m/z 233.1178, found 233.1173.

alkynoic acid 1o



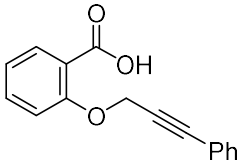
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1o** as a colorless solid: mp 78−79 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.88 (t, J = 7.0 Hz, 3 H, CH_3), 1.28−1.36 (m, 2 H, CH_2), 1.39−1.47 (m, 2 H, CH_2), 2.19 (tt, J = 7.0, 2.0 Hz, 2 H, CH_2), 2.38 (s, 3 H, CH_3), 4.72 (t, J = 2.0 Hz, 2 H, CH_2), 7.19 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.43 (d, J = 7.0 Hz, 1 H, Ar*H*), 7.96 (d, J = 8.0 Hz, 1 H, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.5, 16.3, 18.4, 21.8, 30.1, 62.9, 73.3, 91.1, 123.5, 125.0, 130.4, 132.1, 136.6, 155.5, 167.1; HRMS (FAB) calcd for $[M-H]^-$ ($C_{15}H_{17}O_3$) m/z 245.1178, found 245.1175.

alkynoic acid 1p



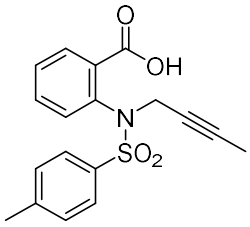
Hydrolysis of corresponding alkynoic acid methyl ester afforded **1p** as a colorless solid: mp 52−53 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.20 (s, 9 H, CH_3), 4.92 (s, 2 H, CH_2), 7.15−7.19 (m, 2 H, Ar*H*), 7.55−7.59 (m, 1 H, Ar*H*), 8.21 (dd, J = 8.0, 2.0 Hz, 1 H, Ar*H*), 10.78 (s, 1 H, O*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.5, 30.5, 58.8, 71.3, 99.2, 113.6, 118.4, 122.7, 133.7, 134.7, 156.5, 165.3; HRMS (EI) calcd for $[M]^+$ ($C_{14}H_{16}O_3$) m/z 232.1099, found 232.1095.

akynoic acid 1q[2]



Hydrolysis of corresponding alkynoic acid methyl ester afforded **1q** as a colorless solid: mp 110−111 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.18 (s, 2 H, CH_2), 7.19 (t, J = 7.5 Hz, 1 H, ArH), 7.25 (d, J = 8.5 Hz, 1 H, ArH), 7.31−7.36 (m, 3 H, ArH), 7.42−7.44 (m, 2 H, ArH), 7.60 (t, J = 8.0 Hz, 1 H, ArH), 8.22 (d, J = 7.5 Hz, 1 H, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.5, 81.3, 89.4, 113.4, 118.4, 121.3, 122.8, 128.4, 129.3, 131.8, 133.9, 134.9, 156.4, 165.3; HRMS (FAB) calcd for $[M-H]^-$ ($C_{16}H_{11}O_3$) m/z 251.0708, found 251.0706.

alkynoic acid 1r[2]



Hydrolysis of corresponding alkynoic acid methyl ester afforded **1r** as a colorless solid: mp 194−195 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 1.66 (s, 3 H, CH_3), 2.43 (s, 3 H, CH_3), 4.47 (s, 2 H, CH_2), 7.09−7.11 (m, 1 H, ArH), 7.33 (d, J = 7.5 Hz, 2 H, ArH), 7.41−7.47 (m, 2 H, ArH), 7.57 (d, J = 7.5 Hz, 2 H, ArH), 7.86 (dd, J = 7.0, 2.0 Hz, 1 H, ArH); ^{13}C NMR (CD_3OD, 125 MHz) δ 3.0, 21.5, 42.8, 74.7, 82.7, 129.1, 130.0, 130.4, 132.1, 132.6, 132.8, 134.9, 138.4, 139.2, 145.1, 169.3; HRMS (FAB) calcd for $[M-H]^-$ ($C_{18}H_{16}NO_4S$) m/z 342.0800, found 342.0793.

Procedures A for Synthesis of 3

An oven-dried round-bottom flask equipped with a reflux condenser was charged with a carboxylic acid, thionyl chloride (2 equiv), and chloroform. The mixture was stirred at 70 °C for 5 h. A chloroform solution of a primary amine (2 equiv) and triethylamine (2 equiv) was then added dropwise at 0 °C. The mixture was gradually warmed to rt and stirred for overnight. The reaction was quenched with a HCl aq (1 M) and was extracted with chloroform. The obtained organic portions were treated with an aqueous solution of NaOH and extracted with chloroform. The organic layer was dried over Na_2SO_4, and the volatile materials were removed by rotary evaporation. The crude material was purified by silica gel column chromatography, followed by recrystallization in some cases.

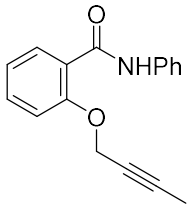
Procedures B for Synthesis of 3

To a DMF solution of a salicylamide derivative with K_2CO_3 (2 equiv) in a round-bottom flask, a DMF solution of 1.2 equiv of propargyl bromide derivative, which was prepared from the corresponding propargyl alcohol with PBr_3, was added dropwise at room temperature. The mixture was stirred continuously overnight, then H_2O was added to the resultant mixture, which was extracted

with Et_2O. The organic layer was dried over Na_2SO_4, and the volatile materials were removed by rotary evaporation. The crude material was purified by silica gel column chromatography.

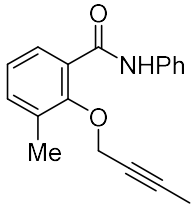
Spectral Data of 3

benzamide 3a



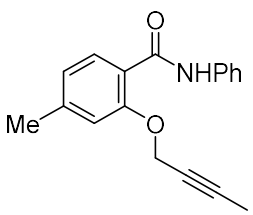
Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3a** as a colorless solid: mp 86–87 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.91 (t, 3 H, J = 2.5 Hz, CH_3), 4.85 (q, 2 H, J = 2.5 Hz, CH_2), 7.05 (d, 1 H, J = 8.0 Hz, ArH), 7.11–7.17 (m, 2 H, ArH), 7.36 (t, 2 H, J = 8.0 Hz, ArH), 7.46–7.50 (m, 1 H, ArH), 7.72 (d, 2 H, J = 8.0 Hz, ArH), 8.30 (dd, 1 H, J = 8.0, 2.0 Hz, ArH), 9.96 (brs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 58.1, 72.8, 85.4, 113.1, 120.2, 122.3, 122.4, 124.0, 128.9, 132.5, 133.0, 138.6, 155.7, 162.9; HRMS (FAB) calcd for $[M+H]^+$ ($C_{17}H_{16}NO_2$) m/z 266.1181, found 266.1187.

benzamide 3b



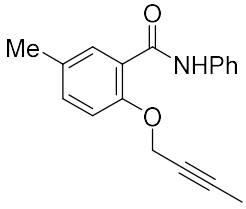
Procedure A was followed. Column chromatography (20/1 hexane/EtOAc) afforded **3b** as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.74 (t, 3 H, J = 2.5 Hz, CH_3), 2.37 (s, 3 H, CH_3), 4.56 (q, 2 H, J = 2.5 Hz, CH_2), 7.12 (t, 1 H, J = 7.5 Hz, ArH), 7.19 (t, 1 H, J = 7.5 Hz, ArH), 7.34–7.38 (m, 3 H, ArH), 7.75 (d, 2 H, J = 8.5 Hz, ArH), 8.00 (dd, 1 H, J = 8.0, 2.0 Hz, ArH), 9.77 (brs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.5, 16.2, 62.6, 73.1, 85.7, 120.1, 124.0, 125.2, 127.5, 128.8, 129.6, 131.8, 134.8, 138.4, 154.1, 163.4; HRMS (EI) calcd for $[M]^+$ ($C_{18}H_{18}NO_2$) m/z 280.1338, found 280.1346.

benzamide 3c



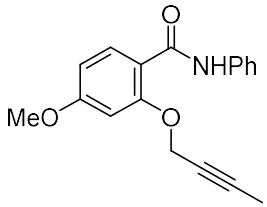
Procedure A was followed. Column chromatography (20/1 to 10/1 hexane/EtOAc), followed by recrystallization, afforded **3c** as a colorless solid: mp 107–108 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.92 (s, 3 H, C*H*$_3$), 2.41 (s, 3 H, C*H*$_3$), 4.83 (s, 2 H, C*H*$_2$), 6.83 (s, 1 H, Ar*H*), 6.97 (d, 1 H, J = 8.0 Hz, Ar*H*), 7.11 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.35 (t, 2 H, J = 7.5 Hz, Ar*H*), 7.72 (d, 2 H, J = 8.0 Hz, Ar*H*), 8.18 (d, 1 H, J = 8.0 Hz, Ar*H*), 9.96 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 21.7, 58.1, 72.9, 85.2, 113.7, 119.6, 120.1, 123.1, 123.8, 128.9, 132.4, 138.7, 144.0, 155.6, 163.0; HRMS (EI) calcd for $[M]^+$ ($C_{18}H_{17}NO_2$) *m*/*z* 279.1259, found 279.1260.

benzamide 3d



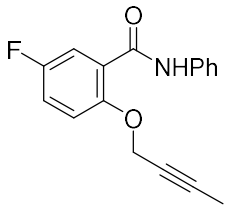
Procedure A was followed. Column chromatography (20/1 to 10/1 hexane/EtOAc), followed by recrystallization, afforded **3d** as a colorless solid: mp 108–109 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.90 (t, 3 H, J = 2.5 Hz, C*H*$_3$), 2.36 (s, 3 H, C*H*$_3$), 4.82 (q, 2 H, J = 2.5 Hz, C*H*$_2$), 6.95 (d, 1 H, J = 8.5 Hz, Ar*H*), 7.12 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.27 (dd, 1 H, J = 8.5, 2.5 Hz, Ar*H*), 7.36 (t, 2 H, J = 8.0 Hz, Ar*H*), 7.72 (d, 2 H, J = 7.5 Hz, Ar*H*), 8.10 (d, 1 H, J = 2.5 Hz, Ar*H*), 9.98 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 20.5, 58.3, 73.0, 85.3, 113.4, 120.2, 122.1, 123.9, 128.9, 131.8, 132.7, 133.5, 138.7, 153.7, 163.1; HRMS (EI) calcd for $[M]^+$ ($C_{18}H_{17}NO_2$) *m*/*z* 279.1259, found 279.1261.

benzamide 3e



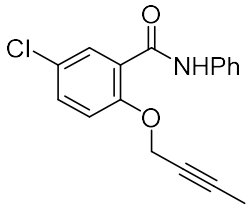
Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3e** as a colorless solid: mp 112–113 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.92 (t, 3 H, J = 2.5 Hz, C*H*$_3$), 3.87 (s, 3 H, OC*H*$_3$), 4.83 (q, 2 H, J = 2.5 Hz, C*H*$_2$), 6.57 (d, 1 H, J = 2.5 Hz, Ar*H*), 6.68 (dd, 1 H, J = 9.0, 2.0 Hz, Ar*H*), 7.10 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.35 (t, 2 H, J = 8.0 Hz, Ar*H*), 7.70 (d, 2 H, J = 7.5 Hz, Ar*H*), 8.27 (d, 1 H, J = 8.5 Hz, Ar*H*), 9.85 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 55.6, 58.1, 72.7, 85.5, 100.1, 106.4, 115.2, 120.1, 123.7, 128.9, 134.2, 138.8, 157.0, 162.9, 163.5; HRMS (FAB) calcd for $[M+H]^+$ ($C_{18}H_{18}NO_3$) *m*/*z* 296.1287, found 296.1295.

benzamide 3f



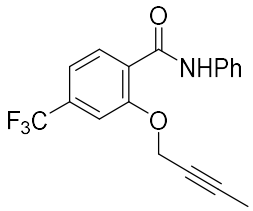
Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3f** as a colorless solid: mp 139–140 °C; ^{1}H NMR (CDCl3, 500 MHz) δ 1.90 (t, 3 H, J = 2.0 Hz, CH_3), 4.84 (q, 2 H, J = 2.0 Hz, CH_2), 7.02–7.05 (m, 1 H, Ar*H*), 7.12–7.20 (m, 2 H, Ar*H*), 7.37 (t, 2 H, J = 7.5 Hz, Ar*H*), 7.70 (d, 2 H, J = 8.0 Hz, Ar*H*), 8.00 (dd, 1 H, J = 9.5, 3.0 Hz, Ar*H*), 9.96 (brs, 1 H, N*H*); ^{13}C NMR (CDCl3, 125 MHz) δ 3.6, 58.9, 72.6, 85.8, 115.1 (d, $J_{C–F}$ = 7.7 Hz), 118.7 (d, $J_{C–F}$ = 25.0 Hz), 119.5 (d, $J_{C–F}$ = 23.0 Hz), 120.2, 124.2 (d, $J_{C–F}$ = 6.7 Hz), 124.3, 129.0, 138.2, 151.8 (d, $J_{C–F}$ = 1.9 Hz), 157.7 (d, $J_{C–F}$ = 241.8 Hz), 161.7; ^{19}F NMR (CDCl3, 470 MHz) δ −120.3 (s); HRMS (FAB) calcd for $[M+H]^+$ ($C_{17}H_{15}NO_2F$) *m*/*z* 284.1087, found 284.1087.

benzamide 3g



Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3g** as a colorless solid: mp 170–171 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.91 (s, 3 H, CH_3), 4.85 (s, 2 H, CH_2), 7.02 (d, 1 H, J = 9.0 Hz, Ar*H*), 7.14 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.37 (t, 2 H, J = 7.5 Hz, Ar*H*), 7.43 (dd, 1 H, J = 9.0, 3.0 Hz, Ar*H*), 7.70 (d, 2 H, J = 7.5 Hz, Ar*H*), 8.27 (d, 1 H, J = 3.0 Hz, Ar*H*), 9.84 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 58.6, 72.4, 86.0, 114.8, 120.3, 123.9, 124.3, 127.8, 129.0, 132.3, 132.6, 138.2, 154.1, 161.6; HRMS (FAB) calcd for $[M+H]^+$ ($C_{17}H_{15}NO_2Cl$) *m*/*z* 300.0791, found 300.0792.

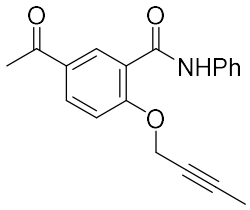
benzamide 3h



Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3h** as a colorless solid: mp 112–113 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.92 (t, 3 H, J = 2.0 Hz, CH_3), 4.92 (q, 2 H, J = 2.0 Hz, CH_2), 7.15 (t, 1 H, J = 7.5 Hz, Ar*H*), 7.30 (s, 1 H, Ar*H*), 7.38 (t, 2 H, J = 7.5 Hz, Ar*H*), 7.42 (d, 1 H, J = 8.0 Hz, Ar*H*), 7.70 (d, 2 H, J = 8.5 Hz,

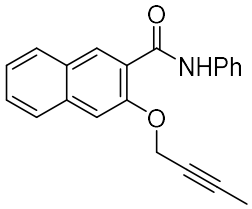
Ar*H*), 8.41 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 9.82 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 58.6, 72.0, 86,4, 110.3 (q, J_{C-F} = 3.8 Hz), 118.9 (q, J_{C-F} = 3.8 Hz), 120.3, 123.3 (q, J_{C-F} = 273.0 Hz), 124.5, 125.6, 129.0, 133.4, 134.5 (q, J_{C-F} = 32.7 Hz), 138.1, 155.6, 161.6; ^{19}F NMR ($CDCl_3$, 470 MHz) δ −63.1 (s); HRMS (EI) calcd for $[M]^+$ ($C_{18}H_{14}NO_2F_3$) *m*/*z* 333.0977, found 333.0970.

benzamide 3i



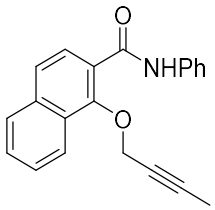
Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3i** as a colorless solid: mp 188–189 °C (dec); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.93 (s, 3 H, C*H*$_3$), 2.65 (s, 3 H, C*H*$_3$), 4.95 (s, 2 H, C*H*$_2$), 7.16 (d, 2 H, *J* = 8.0 Hz, Ar*H*), 7.38 (t, 2 H, *J* = 8.0 Hz, Ar*H*), 7.71 (d, 2 H, *J* = 8.0 Hz, Ar*H*), 8.16 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 8.89 (s, 1 H, Ar*H*), 9.79 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 26.6, 58.3, 72.1, 86.3, 113.2, 120.3, 121.9, 124.4, 129.0, 131.4, 132.9, 133.8, 138.2, 158.9, 162.1, 196.6; HRMS (FAB) calcd for $[M+H]^+$ ($C_{19}H_{18}NO_3$) *m*/*z* 308.1287, found 308.1293.

benzamide 3j



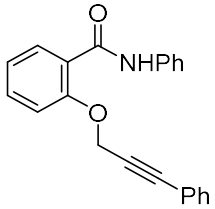
Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3j** as a colorless solid: mp 144–145 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.94 (t, 3 H, *J* = 2.5 Hz, C*H*$_3$), 4.95 (q, 2 H, *J* = 2.5 Hz, C*H*$_2$), 7.14 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.29 (s, 1 H, Ar*H*), 7.38 (t, 2 H, *J* = 7.5 Hz, Ar*H*), 7.41–7.44 (m, 1 H, Ar*H*), 7.52–7.56 (m, 1 H, Ar*H*), 7.77 (d, 3 H, *J* = 8.5 Hz, Ar*H*), 7.93 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 8.87 (s, 1 H, Ar*H*), 10.1 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 58.1, 72.8, 85.4, 108.3, 120.3, 122.7, 124.1, 125.0, 126.4, 128.5, 128.7, 129.0, 129.3, 134.4, 135.6, 138.6, 152.8, 162.8; HRMS (FAB) calcd for $[M+H]^+$ ($C_{21}H_{18}NO_2$) *m*/*z* 316.1338, found 316.1338.

benzamide 3k



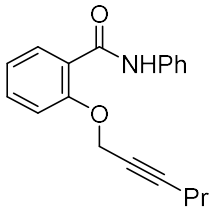
Procedure A was followed. Column chromatography (10/1 hexane/EtOAc) afforded **3k** as a pale yellow oil; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.76 (s, 3 H, C*H*$_3$), 4.79 (s, 2 H, C*H*$_2$), 7.15 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.40 (t, 2 H, *J* = 7.5 Hz, Ar*H*), 7.58–7.60 (m, 2 H, Ar*H*), 7.75 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 7.81 (d, 2 H, *J* = 8.0 Hz, Ar*H*), 7.87 (m, 1 H, Ar*H*), 8.20 (m, 2 H, Ar*H*), 9.94 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 64.5, 73.0, 86.5, 120.2, 122.8, 123.3, 124.1, 125.3, 126.7, 126.8, 127.5, 128.1, 128.2, 128.9, 136.6, 138.5, 152.7, 163.5; HRMS (FAB) calcd for $[M+H]^+$ ($C_{21}H_{18}NO_2$) *m*/*z* 316.1338, found 316.1336.

benzamide 3l



Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3l** as a colorless solid: mp 111–112 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.11 (s, 2 H, C*H*$_2$), 7.07–7.13 (m, 2 H, Ar*H*), 7.19 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.25–7.30 (m, 2 H, Ar*H*), 7.33–7.38 (m, 3 H, Ar*H*), 7.47 (d, 2 H, *J* = 8.0 Hz, Ar*H*), 7.51 (t, 1 H, *J* = 8.0 Hz, Ar*H*), 7.73 (d, 2 H, *J* = 7.5 Hz, Ar*H*), 8.35 (d, 1 H, *J* = 7.5 Hz, Ar*H*), 10.0 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 58.3, 82.3, 88.7, 113.0, 120.1, 121.6, 122.4, 122.5, 124.0, 128.5, 128.9, 129.2, 131.8, 132.7, 133.1, 138.5, 155.6, 162.8; HRMS (FAB) calcd for $[M+H]^+$ ($C_{22}H_{18}NO_2$) *m*/*z* 328.1338, found 328.1335.

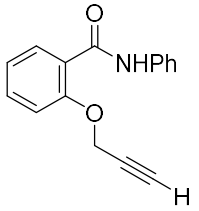
benzamide 3m



Procedure A was followed. Column chromatography (20/1 to 5/1 hexane/EtOAc), followed by recrystallization, afforded **3m** as a colorless solid: mp 61–62 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.98 (t, 3 H, *J* = 7.5 Hz, C*H*$_3$), 1.56 (qt, 2 H, *J* = 7.5, 7.5 Hz, C*H*$_2$), 2.25 (t, 2 H, *J* = 7.5 Hz, C*H*$_2$), 4.88 (s, 2 H, C*H*$_2$), 7.06 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 7.10–7.17 (m, 2 H, Ar*H*), 7.35 (t, 2 H, *J* = 7.5 Hz, Ar*H*), 7.48 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.73 (d, 2 H, *J* = 7.5 Hz, Ar*H*), 8.31 (d, 1 H, *J* = 7.5 Hz, Ar*H*), 9.99 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.4, 20.7, 21.8, 58.2, 73.7, 89.8, 113.1, 120.2, 122.3,

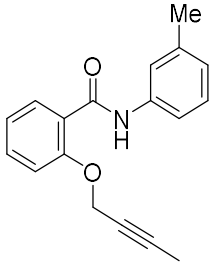
122.4, 124.0, 128.9, 132.6, 133.0, 138.6, 155.7, 162.9; HRMS (FAB) calcd for $[M+H]^+$ ($C_{19}H_{20}NO_2$) *m*/*z* 294.1494, found 294.1492.

benzamide 3n



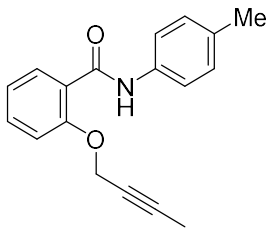
Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3n** as a colorless solid: mp 120–122 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.69 (t, 1 H, *J* = 2.5 Hz, C≡C*H*), 4.90 (d, 2 H, *J* = 2.5 Hz, CH_2), 7.06 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 7.13 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.18 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.36 (t, 2 H, *J* = 8.0 Hz, Ar*H*), 7.48–7.51 (m, 1 H, Ar*H*), 7.71 (d, 2 H, *J* = 8.0 Hz, Ar*H*), 8.31 (dd, 1 H, *J* = 7.5, 1.5 Hz, Ar*H*), 9.76 (brs, 1 H, N*H*); HRMS (FAB) calcd for $[M]^+$ ($C_{16}H_{13}NO_2$) *m*/*z* 251.0946, found 251.0943. ^{1}H NMR spectroscopic data of **1o** are in good agreement with those reported in literature.[2]

benzamide 3o



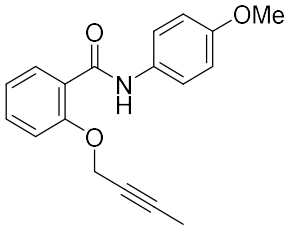
Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3o** as a colorless solid: mp 78–79 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.92 (t, 3 H, *J* = 2.5 Hz, CH_3), 2.38 (s, 3 H, CH_3), 4.85 (q, 2 H, *J* = 2.5 Hz, CH_2), 6.94 (d, 1 H, *J* = 7.5 Hz, Ar*H*), 7.05 (d, 1 H, *J* = 8.5 Hz, Ar*H*), 7.16 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.24 (t, 1 H, *J* = 8.0 Hz, Ar*H*), 7.46–7.50 (m, 1 H, Ar*H*), 7.52 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.56 (s, 1 H, Ar*H*), 8.30 (dd, 1 H, *J* = 8.0, 2.0 Hz, Ar*H*), 9.93 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 21.6, 58.1, 72.8, 85.3, 113.1, 117.3, 120.8, 122.2, 122.4, 124.8, 128.7, 132.5, 133.0, 138.5, 138.7, 155.7, 162.9; HRMS (FAB) calcd for $[M+H]^+$ ($C_{18}H_{18}NO_2$) *m*/*z* 280.1338, found 280.1333.

benzamide 3p



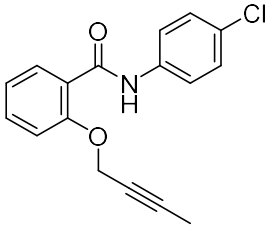
Procedure A was followed. Column chromatography (10/1 to 5/1 hexane/EtOAc), followed by recrystallization, afforded **3p** as a colorless solid: mp 107–108 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.91 (t, 3 H, J = 2.5 Hz, CH_3), 2.34 (s, 3 H, CH_3), 4.85 (q, 2 H, J = 2.5 Hz, CH_2), 7.06 (d, 1 H, J = 8.5 Hz, ArH), 7.15–7.17 (m, 3 H, ArH), 7.46–7.50 (m, 1 H, ArH), 7.60 (d, 2 H, J = 8.5 Hz, ArH), 8.30 (dd, 1 H, J = 8.0, 2.0 Hz, ArH), 9.89 (brs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 20.9, 58.1, 72.8, 85.4, 113.1, 120.2, 122.2, 122.4, 129.4, 132.5, 132.9, 133.5, 136.0, 155.7, 162.8; HRMS (FAB) calcd for $[M]^+$ ($C_{18}H_{17}NO_2$) m/z 279.1259, found 279.1261

benzamide 3q



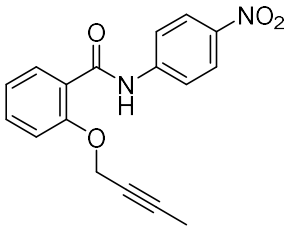
Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3q** as a colorless solid: mp 86–87 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.91 (t, 3 H, J = 2.5 Hz, CH_3), 3.82 (s, 3 H, OCH_3), 4.85 (q, 2 H, J = 2.5 Hz, CH_2), 6.90 (d, 2 H, J = 9.0 Hz, ArH), 7.06 (d, 1 H, J = 8.0 Hz, ArH), 7.16 (t, 1 H, J = 7.5 Hz, ArH), 7.46–7.49 (m, 1 H, ArH), 7.63 (d, 2 H, J = 8.5 Hz, ArH), 8.30 (dd, 1 H, J = 8.0, 1.5 Hz, ArH), 9.83 (brs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 55.5, 58.1, 72.9, 85.4, 113.2, 114.1, 121.8, 122.3, 122.5, 131.8, 132.5, 132.9, 155.7, 156.2, 162.7; HRMS (EI) calcd for $[M]^+$ ($C_{18}H_{17}NO_3$) m/z 295.1208, found 295.1201.

benzamide 3r



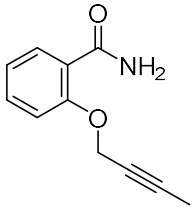
Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **3r** as a colorless solid: mp 136–137 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.92 (t, 3 H, J = 2.5 Hz, CH_3), 4.86 (q, 2 H, J = 2.5 Hz, CH_2), 7.06 (d, 1 H, J = 8.0 Hz, ArH), 7.17 (t, 1 H, J = 7.5 Hz, ArH), 7.31–7.33 (m, 2 H, ArH), 7.48– 7.52 (m, 1 H, ArH), 7.66–7.69 (m, 2 H, ArH), 8.29 (dd, 1 H, J = 8.0, 2.0 Hz, ArH), 10.0 (brs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 58.2, 72.8, 85.5, 113.2, 121.3, 122.0, 122.4, 128.8, 128.9, 132.6, 133.3, 137.2, 155.7, 163.0; HRMS (FAB) calcd for $[M+H]^+$ ($C_{17}H_{15}NO_2Cl$) m/z 300.0791, found 300.0792.

benzamide 3s



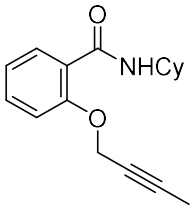
Procedure A was followed. Column chromatography (10/1 to 5/1 hexane/EtOAc), followed by recrystallization, afforded **3s** as a colorless solid: mp 191–192 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.95 (t, 3 H, J = 2.5 Hz, CH_3), 4.90 (q, 2 H, J = 2.5 Hz, CH_2), 7.08 (d, 1 H, J = 8.5 Hz, ArH), 7.20 (t, 1 H, J = 7.5 Hz, ArH), 7.53–7.56 (m, 1 H, ArH), 7.89 (d, 2 H, J = 9.0 Hz, ArH), 8.25 (d, 2 H, J = 9.0 Hz, ArH), 8.30 (dd, 1 H, J = 8.0, 2.0 Hz, ArH), 10.4 (brs, 1 H, NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 58.4, 72.6, 85.8, 113.2, 119.5, 121.4, 122.6, 125.1, 132.7, 134.0, 143.3, 144.5, 155.8, 163.4; HRMS (FAB) calcd for $[M+H]^+$ ($C_{17}H_{15}N_2O_4$) m/z 311.1032, found 311.1039.

benzamide 3t



Procedure B was followed. Column chromatography (10/1 to 2/1 hexane/EtOAc), followed by recrystallization, afforded **3t** as a colorless solid: mp 125–127 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.88 (s, 3 H, CH_3), 2.63 (s, 3 H, CH_3), 4.89 (s, 2 H, CH_2), 6.17 (brs, 1 H, NH), 7.17 (d, 1 H, J = 8.5 Hz, ArH), 7.65 (brs, 1 H, NH), 8.15 (dd, 1 H, J = 9.0, 2.0 Hz, ArH), 8.80 (d, 1 H, J = 2.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.7, 26.6, 57.7, 72.2, 86.0, 113.0, 120.9, 130.9, 133.0, 133.9, 159.4, 165.9, 196.6; HRMS (FAB) calcd for $[M+H]^+$ ($C_{13}H_{14}NO_3$) m/z 232.0974, found 232.0979.

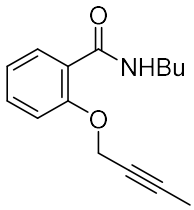
benzamide 3w



Procedure A was followed. Column chromatography (10/1 to 1/1 hexane/EtOAc), followed by recrystallization, afforded **1w** as a colorless solid: mp 96–98 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.28–1.37 (m, 3 H, CH_2), 1.42–1.49 (m, 2 H, CH_2), 1.59–1.63 (m, 1 H, CH_2), 1.71–1.76 (m, 2 H, CH_2), 1.89 (t, 3 H, J = 2.5 Hz, CH_3), 1.97–2.00 (m, 2 H, CH_2), 4.02–4.08 (m, 1 H, CH), 4.75 (q, 2 H, J = 2.5 Hz, CH_2), 7.00 (d, 1 H, J = 8.0 Hz, ArH), 7.10 (t, 1 H, J = 7.5 Hz, ArH), 7.39–7.43 (m, 1 H, ArH), 7.91 (brs, 1 H, NH), 8.21 (dd, 1 H, J = 8.0, 2.0 Hz, ArH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 24.4, 25.8, 32.8, 47.9, 57.8, 73.0, 84.8, 112.9, 121.9, 122.6, 132.2, 155.8, 163.9; HRMS (FAB) calcd for

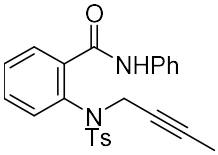
$[M+H]^+$ ($C_{17}H_{22}NO_2$) *m*/*z* 272.1651, found 272.1643.

benzamide 3x



Procedure A was followed. Column chromatography (10/1 to 1/1 hexane/EtOAc), followed by recrystallization, afforded **3x** as a colorless solid: mp 39–40 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.97 (t, 3 H, *J* = 7.5 Hz, C*H*$_3$), 1.45 (qt, 2 H, *J* = 7.5, 7.5 Hz, C*H*$_2$), 1.62 (tt, 2 H, *J* = 7.5, 7.5 Hz, C*H*$_2$), 1.88 (t, 3 H, *J* = 2.5 Hz, C*H*$_3$), 3.46–3.49 (m, 2 H, C*H*$_2$), 4.77 (q, 2 H, *J* = 2.5 Hz, C*H*$_2$), 7.02 (d, 1 H, *J* = 8.0 Hz, Ar*H*), 7.10 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.40–7.44 (m, 1 H, Ar*H*), 7.88 (brs, 1 H, N*H*), 8.22 (dd, 1 H, *J* = 8.0, 2.0 Hz, Ar*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.6, 13.8, 20.2, 31.5, 39.5, 57.6, 73.0, 84.9, 112.8, 121.8, 122.3, 132.26, 132.31, 155.8, 164.9; HRMS (FAB) calcd for $[M+H]^+$ ($C_{15}H_{20}NO_2$) *m*/*z* 246.1494, found 246.1490.

benzamide 3y



Procedure A was followed. Column chromatography (10/1 hexane/EtOAc), followed by recrystallization, afforded **4y** as a colorless solid: mp 141–142 °C (dec); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.63 (s, 3 H, C*H*$_3$), 2.47 (s, 3 H, C*H*$_3$), 4.39 (brs, 2 H, C*H*$_2$), 6.69 (d, 1 H, *J* = 7.5 Hz, Ar*H*), 7.14 (t, 1 H, *J* = 7.0 Hz, Ar*H*), 7.29–7.32 (m, 3 H, Ar*H*), 7.37 (t, 2 H, *J* = 7.5 Hz, Ar*H*), 7.47 (t, 1 H, *J* = 7.5 Hz, Ar*H*), 7.69 (d, 2 H, *J* = 7.5 Hz, Ar*H*), 7.77 (d, 2 H, *J* = 7.5 Hz, Ar*H*), 7.91 (d, 1 H, *J* = 7.5 Hz, Ar*H*), 9.38 (brs, 1 H, N*H*); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 3.4, 21.7, 43.0, 72.3, 83.2, 120.0, 124.3, 128.5, 128.8, 129.0, 129.54, 129.56, 130.7, 131.2, 135.3, 135.5, 138.3, 138.4, 144.5, 164.7; HRMS (FAB) calcd for $[M+H]^+$ ($C_{24}H_{23}N_2O_3S$) *m*/*z* 419.1429, found 419.1430.

X-ray Crystallographic Data of 2m

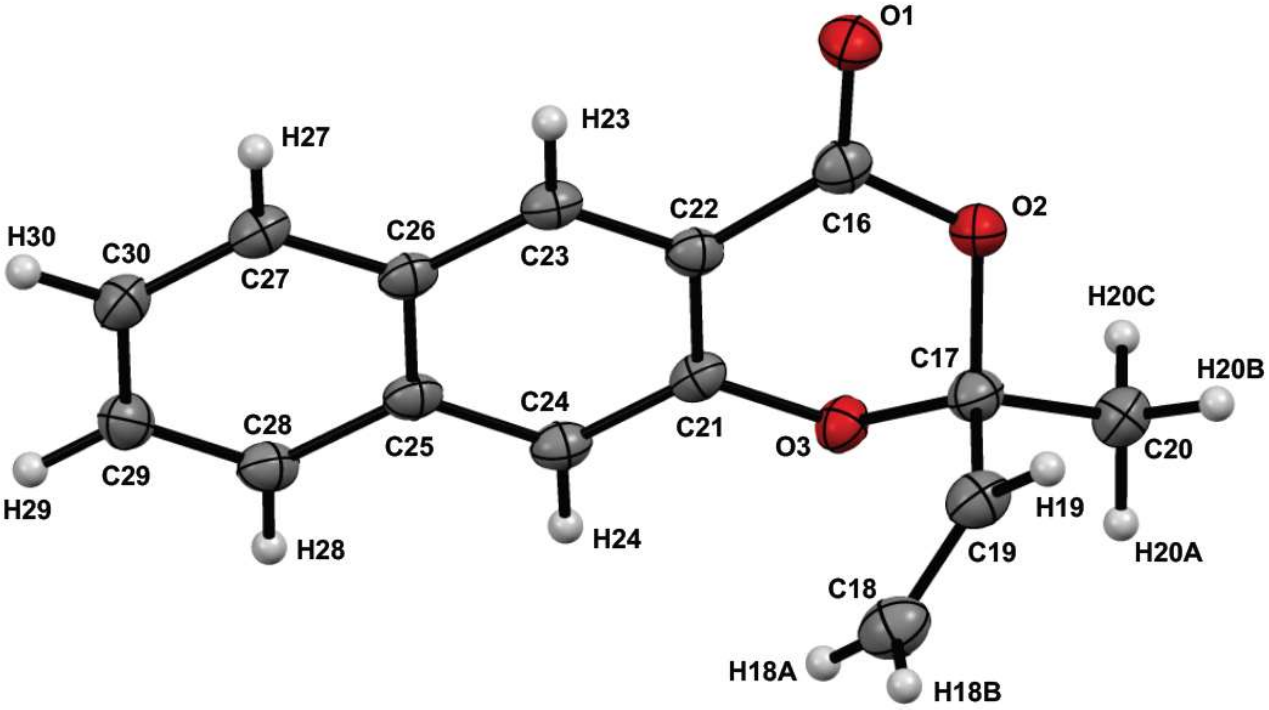


Figure S1. ORTEP drawing of (*S*)-**2m**.

Table S1. Crystal data and structure refinement for **2m**.

Empirical formula	C15 H12 O3	
Formula weight	240.25	
Temperature	103 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 8.0887(6) Å	a = 90°
	b = 6.4489(5) Å	b = 93.7990(10)°
	c = 22.5011(17) Å	g = 90°
V	1171.15(15) Å^3	
Z	4	
Density (calculated)	1.363 mg/mm^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	504	
Crystal size	0.40 × 0.28 × 0.15 mm^3	
Theta range for data collection	1.81 to 25.05°	
Index ranges	−8<=h<=9, −7<=k<=6, −26<=l<=26	
Reflections collected	5764	
Independent reflections	2065 [R(int) = 0.0444]	
Completeness to theta = 25.05°	99.8 %	
Absorption correction	Empirical	
Max. and min. transmission	0.9859 and 0.9631	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2065 / 0 / 164	
Goodness-of-fit on F^2	1.086	
Final R indices [I>2sigma(I)]	R1 = 0.0425, wR2 = 0.1119	
R indices (all data)	R1 = 0.0444, wR2 = 0.1136	
Largest diff. peak and hole	0.318 and −0.259 e. Å^{-3}	

Table S2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **2m**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	6570(1)	2347(2)	41(1)	28(1)
O(2)	8680(1)	889(2)	554(1)	24(1)
O(3)	9572(1)	2020(2)	1522(1)	22(1)
C(16)	7556(2)	2442(2)	466(1)	23(1)
C(17)	10100(2)	1232(2)	974(1)	24(1)
C(18)	12110(2)	4177(3)	945(1)	32(1)
C(19)	11298(2)	2642(3)	688(1)	28(1)
C(20)	10824(2)	−880(2)	1104(1)	28(1)
C(21)	8557(2)	3730(2)	1469(1)	20(1)
C(22)	7581(2)	4049(2)	930(1)	21(1)
C(23)	6572(2)	5761(2)	869(1)	22(1)
C(24)	8453(2)	5037(2)	1943(1)	22(1)
C(25)	7403(2)	6794(2)	1890(1)	21(1)
C(26)	6469(2)	7183(2)	1340(1)	21(1)
C(27)	5463(2)	8987(2)	1283(1)	24(1)
C(28)	7284(2)	8225(2)	2363(1)	24(1)
C(29)	6301(2)	9949(3)	2295(1)	26(1)
C(30)	5383(2)	10336(3)	1749(1)	26(1)

Table S3. Bond lengths [Å] and angles [°] for **2m**.

O(1)−C(16)	1.2051(17)
O(2)−C(16)	1.3588(17)
O(2)−C(17)	1.4554(16)
O(3)−C(21)	1.3752(17)
O(3)−C(17)	1.4258(17)
C(16)−C(22)	1.470(2)
C(17)−C(19)	1.503(2)
C(17)−C(20)	1.504(2)
C(18)−C(19)	1.302(2)
C(18)−H(18A)	0.9500
C(18)−H(18B)	0.9500
C(19)−H(19)	0.9500
C(20)−H(20A)	0.9800
C(20)−H(20B)	0.9800
C(20)−H(20C)	0.9800
C(21)−C(24)	1.366(2)
C(21)−C(22)	1.4178(18)
C(22)−C(23)	1.374(2)
C(23)−C(26)	1.408(2)
C(23)−H(23)	0.9500
C(24)−C(25)	1.416(2)
C(24)−H(24)	0.9500
C(25)−C(28)	1.416(2)
C(25)−C(26)	1.4289(19)
C(26)−C(27)	1.420(2)
C(27)−C(30)	1.367(2)
C(27)−H(27)	0.9500
C(28)−C(29)	1.369(2)
C(28)−H(28)	0.9500
C(29)−C(30)	1.416(2)
C(29)−H(29)	0.9500
C(30)−H(30)	0.9500
C(16)−O(2)−C(17)	118.28(11)
C(21)−O(3)−C(17)	114.98(10)

O(1)−C(16)−O(2)	118.60(13)
O(1)−C(16)−C(22)	125.22(13)
O(2)−C(16)−C(22)	116.04(11)
O(3)−C(17)−O(2)	110.32(10)
O(3)−C(17)−C(19)	113.14(13)
O(2)−C(17)−C(19)	108.53(11)
O(3)−C(17)−C(20)	106.78(11)
O(2)−C(17)−C(20)	105.61(12)
C(19)−C(17)−C(20)	112.20(12)
C(19)−C(18)−H(18A)	120.0
C(19)−C(18)−H(18B)	120.0
H(18A)−C(18)−H(18B)	120.0
C(18)−C(19)−C(17)	126.19(14)
C(18)−C(19)−H(19)	116.9
C(17)−C(19)−H(19)	116.9
C(17)−C(20)−H(20A)	109.5
C(17)−C(20)−H(20B)	109.5
H(20A)−C(20)−H(20B)	109.5
C(17)−C(20)−H(20C)	109.5
H(20A)−C(20)−H(20C)	109.5
H(20B)−C(20)−H(20C)	109.5
C(24)−C(21)−O(3)	119.67(12)
C(24)−C(21)−C(22)	121.21(13)
O(3)−C(21)−C(22)	119.06(12)
C(23)−C(22)−C(21)	119.70(13)
C(23)−C(22)−C(16)	120.99(12)
C(21)−C(22)−C(16)	119.08(13)
C(22)−C(23)−C(26)	120.85(12)
C(22)−C(23)−H(23)	119.6
C(26)−C(23)−H(23)	119.6
C(21)−C(24)−C(25)	119.73(12)
C(21)−C(24)−H(24)	120.1
C(25)−C(24)−H(24)	120.1
C(24)−C(25)−C(28)	121.91(12)
C(24)−C(25)−C(26)	119.57(13)
C(28)−C(25)−C(26)	118.50(13)

C(23)−C(26)−C(27)	121.86(12)
C(23)−C(26)−C(25)	118.84(13)
C(27)−C(26)−C(25)	119.30(13)
C(30)−C(27)−C(26)	120.51(13)
C(30)−C(27)−H(27)	119.7
C(26)−C(27)−H(27)	119.7
C(29)−C(28)−C(25)	120.92(13)
C(29)−C(28)−H(28)	119.5
C(25)−C(28)−H(28)	119.5
C(28)−C(29)−C(30)	120.42(14)
C(28)−C(29)−H(29)	119.8
C(30)−C(29)−H(29)	119.8
C(27)−C(30)−C(29)	120.34(14)
C(27)−C(30)−H(30)	119.8
C(29)−C(30)−H(30)	119.8

Table S4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for **2m**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2a^{*2}U^{11} + ... + 2\ hka^*b^*U^{12}]$.

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	27(1)	34(1)	23(1)	−3(1)	−4(1)	2(1)
O(2)	22(1)	26(1)	25(1)	−3(1)	−1(1)	1(1)
O(3)	22(1)	24(1)	21(1)	2(1)	1(1)	4(1)
C(16)	21(1)	26(1)	22(1)	2(1)	4(1)	−1(1)
C(17)	20(1)	29(1)	22(1)	−2(1)	0(1)	1(1)
C(18)	28(1)	35(1)	34(1)	7(1)	1(1)	0(1)
C(19)	23(1)	33(1)	27(1)	2(1)	2(1)	1(1)
C(20)	24(1)	28(1)	31(1)	−1(1)	2(1)	3(1)
C(21)	16(1)	23(1)	23(1)	3(1)	1(1)	0(1)
C(22)	18(1)	25(1)	20(1)	1(1)	2(1)	−3(1)
C(23)	18(1)	28(1)	19(1)	3(1)	0(1)	−2(1)
C(24)	18(1)	28(1)	19(1)	3(1)	0(1)	−2(1)
C(25)	15(1)	27(1)	21(1)	1(1)	2(1)	−3(1)
C(26)	15(1)	26(1)	22(1)	2(1)	3(1)	−3(1)
C(27)	18(1)	29(1)	24(1)	3(1)	1(1)	1(1)
C(28)	19(1)	32(1)	21(1)	−1(1)	1(1)	−3(1)
C(29)	23(1)	30(1)	25(1)	−5(1)	4(1)	−2(1)
C(30)	20(1)	27(1)	31(1)	−1(1)	3(1)	3(1)

Table S5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **2m**.

	x	y	z	U(eq)
H(18A)	11970	4490	1352	39
H(18B)	12843	4983	727	39
H(19)	11479	2390	282	33
H(20A)	11722	−767	1417	42
H(20B)	11260	−1448	742	42
H(20C)	9961	−1801	1239	42
H(23)	5937	5987	505	26
H(24)	9081	4768	2306	26
H(27)	4842	9259	918	28
H(28)	7895	7986	2731	29
H(29)	6235	10892	2617	31
H(30)	4708	11538	1706	31

X-ray Crystallographic Data of 4s

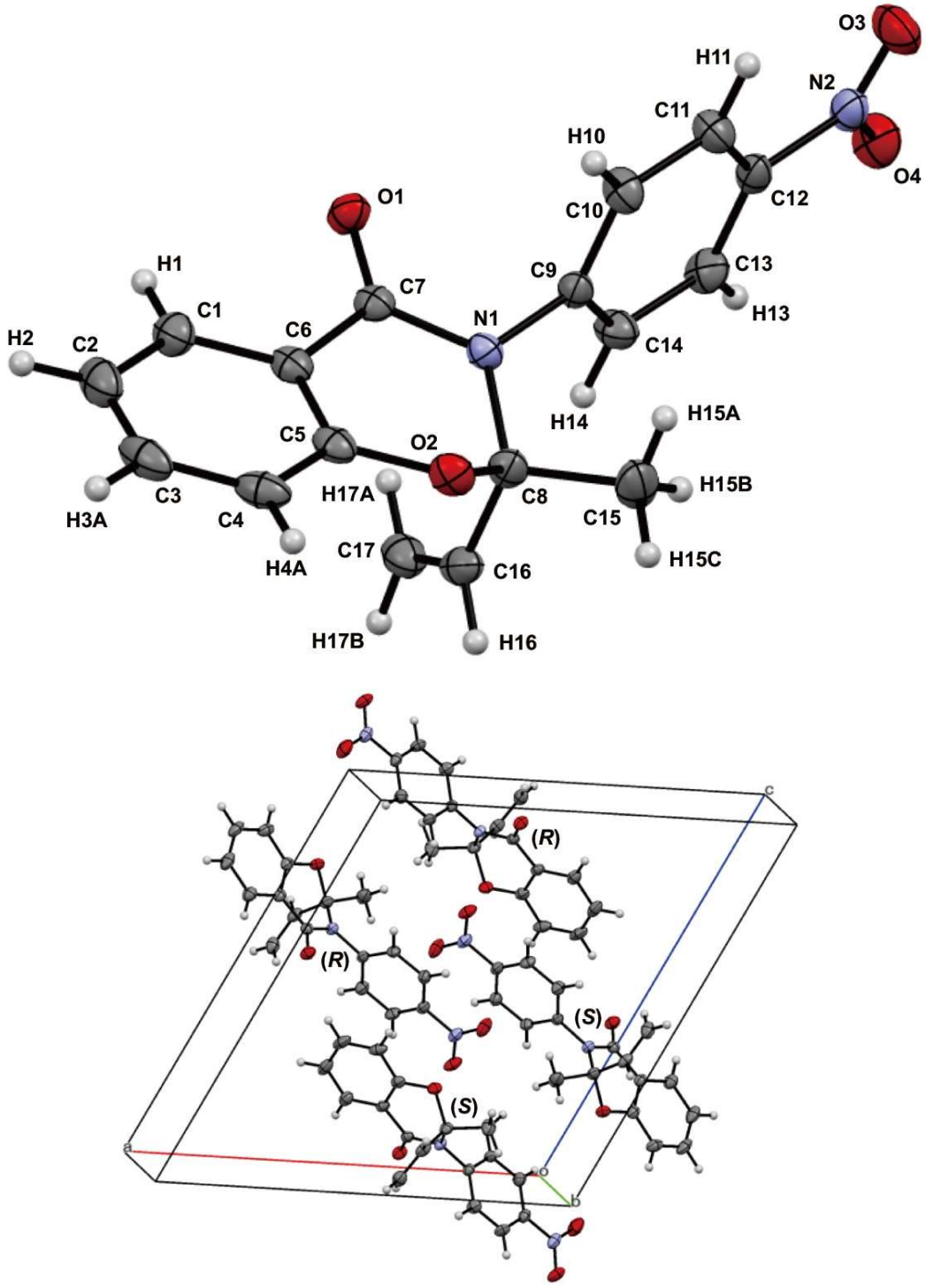


Figure. ORTEP drawing of (a) (*S*)-**4s** and (b) the packing structure.

Table. Crystal data and structure refinement for **4s**

Empirical formula	C17 H14 N2 O4	
Formula weight	310.30	
Temperature	299 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$	
Unit cell dimensions	a = 14.6416(10) Å	α= 90°
	b = 7.2720(5) Å	β= 116.3190(10)°
	c = 15.3586(10) Å	γ= 90°
V	1465.77(17) Å^3	
Z	4	
Density (calculated)	1.406 mg/mm^3	
Absorption coefficient	0.102 mm^{-1}	
F(000)	648	
Crystal size	0.25 × 0.16 × 0.12 mm^3	
Theta range for data collection	1.60 to 25.07°	
Index ranges	−17<=h<=15, −8<=k<=8,	
	−13<=l<=18	
Reflection collected	7363	
Independent reflection	2604 [R(int) = 0.0167]	
Completeness to theta =25.05°	99.8%	
Absorption correction	Empirical	
Max. and min. transmission	0.9879 and 0.9750	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2604 / 0 / 209	
Goodness-of-fit on F^2	1.066	
Final R indices [I > 2sigma(I)]	R1 = 0.0376, wR2 = 0.0897	
R indices (all data)	R1 = 0.0408, wR2 = 0.0918	
Largest diff. peak and hole	0.217 and −0.210 e. Å^{-3}	

Table. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($Å^2 \times 10^3$) for **4s**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4370(1)	6943(1)	874(1)	25(1)
O(2)	4908(1)	10937(1)	2846(1)	24(1)
N(1)	3839(1)	9535(2)	1339(1)	19(1)
O(3)	−740(1)	6936(2)	−743(1)	40(1)
O(4)	−730(1)	8758(2)	−1849(1)	35(1)
N(2)	−310(1)	8007(2)	−1053(1)	27(1)
C(9)	2788(1)	9136(2)	707(1)	19(1)
C(6)	5606(1)	8705(2)	2159(1)	21(1)
C(12)	774(1)	8414(2)	−435(1)	22(1)
C(7)	4569(1)	8304(2)	1391(1)	20(1)
C(5)	5728(1)	9956(2)	2887(1)	23(1)
C(8)	4126(1)	11295(2)	1872(1)	22(1)
C(11)	1280(1)	7422(2)	412(1)	25(1)
C(3)	7485(1)	9139(2)	3748(1)	33(1)
C(14)	2267(1)	10097(2)	−152(1)	25(1)
C(1)	6444(1)	7705(2)	2221(1)	27(1)
C(10)	2301(1)	7789(2)	982(1)	24(1)
C(13)	1245(1)	9738(2)	−732(1)	26(1)
C(4)	6662(1)	10152(2)	3692(1)	29(1)
C(16)	4529(1)	12668(2)	1402(1)	25(1)
C(2)	7385(1)	7939(2)	3011(1)	33(1)
C(15)	3251(1)	12079(2)	2026(1)	33(1)
C(17)	4653(1)	12416(2)	615(1)	30(1)

Table. Bond lengths [Å] and angles [°] for **4s**.

O(1)−C(7)	1.2211(18)
O(2)−C(5)	1.3745(18)
O(2)−C(8)	1.4482(17)
N(1)−C(7)	1.3686(18)
N(1)−C(9)	1.4380(17)
N(1)−C(8)	1.4773(18)
O(3)−N(2)	1.2236(18)
O(4)−N(2)	1.2267(17)
N(2)−C(12)	1.4738(18)
C(9)−C(10)	1.383(2)
C(9)−C(14)	1.386(2)
C(6)−C(5)	1.389(2)
C(6)−C(1)	1.393(2)
C(6)−C(7)	1.4808(19)
C(12)−C(13)	1.374(2)
C(12)−C(11)	1.382(2)
C(5)−C(4)	1.386(2)
C(8)−C(16)	1.499(2)
C(8)−C(15)	1.512(2)
C(11)−C(10)	1.383(2)
C(11)−H(11)	0.9300
C(3)−H(4)	1.383(2)
C(3)−H(2)	1.385(3)
C(3)−H(3A)	0.9300
C(14)−C(13)	1.385(2)
C(14)−H(14)	0.9300
C(1)−C(2)	1.384(2)
C(1)−H(1)	0.9300
C(10)−H(10)	0.9300
C(13)−H(13)	0.9300
C(4)−H(4A)	0.9300
C(16)−C(17)	1.313(2)
C(16)−H(16)	0.9300
C(2)−H(2)	0.9300
C(15)−H(15A)	0.9600
C(15)−H(15B)	0.9600
C(15)−H(15C)	0.9600
C(17)−H(17A)	0.9300

C(17)−H(17B)	0.9300
C(5)−O(2)−C(8)	114.51(11)
C(7)−N(1)−C(9)	118.79(11)
C(7)−N(1)−C(8)	120.77(11)
C(9)−N(1)−C(8)	120.34(11)
O(3)−N(2)−O(4)	123.67(13)
O(3)−N(2)−C(12)	118.10(13)
O(4)−N(2)−C(12)	118.23(13)
C(10)−C(9)−C(14)	120.46(13)
C(10)−C(9)−N(1)	118.63(13)
C(14)−C(9)−N(1)	120.90(13)
C(5)−C(6)−C(1)	119.44(13)
C(5)−C(6)−C(7)	119.37(13)
C(1)−C(6)−C(7)	120.83(14)
C(13)−C(12)−C(11)	122.74(13)
C(13)−C(12)−N(2)	118.86(13)
C(11)−C(12)−N(2)	118.39(13)
O(1)−C(7)−N(1)	122.47(13)
O(1)−C(7)−C(6)	122.86(13)
N(1)−C(7)−C(6)	114.60(12)
O(2)−C(5)−C(4)	118.91(14)
O(2)−C(5)−C(6)	120.34(13)
O(4)−C(5)−C(6)	120.63(14)
O(2)−C(8)−N(1)	108.50(11)
O(2)−C(8)−C(16)	108.52(11)
N(1)−C(8)−C(16)	112.67(12)
O(2)−C(8)−C(15)	104.07(12)
N(1)−C(8)−C(15)	111.17(12)
C(16)−C(8)−C(15)	111.47(13)
C(12)−C(11)−C(10)	118.17(14)
C(12)−C(11)−H(11)	120.9
C(10)−C(11)−H(11)	120.9
C(4)−C(3)−C(2)	120.80(14)
C(4)−C(3)−H(3A)	119.6
C(2)−C(3)−H(3A)	119.6
C(13)−C(14)−C(9)	119.96(14)
C(13)−C(14)−H(14)	120.0
C(9)−C(14)−H(14)	120.0
C(2)−C(1)−C(6)	120.02(15)

C(2)−C(1)−H(1)	120.0
C(6)−C(1)−H(1)	120.0
C(9)−C(10)−C(11)	120.21(14)
C(9)−C(10)−H(10)	119.9
C(11)−C(10)−H(10)	119.9
C(12)−C(13)−C(14)	118.45(14)
C(12)−C(13)−H(13)	120.8
C(14)−C(13)−H(13)	120.8
C(3)−C(4)−C(5)	119.24(15)
C(3)−C(4)−H(4A)	120.4
C(5)−C(4)−H(4A)	120.4
C(17)−C(16)−C(8)	126.57(15)
C(17)−C(16)−H(16)	116.7
C(8)−C(16)−H(16)	116.7
C(1)−C(2)−C(3)	119.79(15)
C(1)−C(2)−H(2)	120.1
C(3)−C(2)−H(2)	120.1
C(8)−C(15)−H(15A)	109.5
C(8)−C(15)−H(15B)	109.5
H(15A)−C(15)−H(15B)	109.5
C(8)−C(15)−H(15C)	109.5
H(15A)−C(15)−H(15C)	109.5
H(15B)−C(15)−H(15C)	109.5
C(16)−C(17)−H(17A)	120.0
C(16)−C(17)−H(17B)	120.0
H(17A)−C(17)−H(17B)	120.0

1-6. References

(1) Selected examples: (a) Krafft G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459–5466. (b) Chan, D. M. T.; Marder, T. B.; Milstein, D.; Taylor, N. J. *J. Am. Chem. Soc.* **1987**, *109*, 6385–6388. (c) Chaudhuri, G.; Kundu, N. G. *J. Chem. Soc., Perkin Trans.* **2000**, *1*, 775. (d) Alemán, J.; del Solar, V.; Navarro-Ranninger, C. *Chem. Commun.* **2010**, *46*, 454–456. (e) Alemán, J.; del Solar, V.; Cubo, L.; Quiroga, A. G.; Ranninger, C. N. *Dalton Trans.* **2010**, *39*, 10601–10607. (f) Nebra, N.; Monot, J.; Shaw, R.; Martin-Vaca, B.; Bourissou, D. *ACS Catal.* **2013**, *3*, 2930. (g) Nolla-Saltiel, R.; Robles- Marín, E.; Porcel, S. *Tetrahedron Lett.* **2014**, *55*, 4484. (h) Huang, Y.; Zhang, X.; Dong, X.-Q.; Zhang, X. *Adv. Synth. Catal.* **2020**, *362*, 782–788.

(2) Huo, Z.; Patil, N. T.; Jin, T.; Pahadi, N. K.; Yamamotoa, Y. *Adv. Synth. Catal.* **2007**, *349*, 680–684

(3) Lumbroso, A.; Abermil, N.; Breit, B. *Chem. Sci.* **2012**, *3*, 789–793.

(4) Lin, F.; Song, Q.; Gao Y.; Cui, X. *RSC Adv.* **2014**, 4, 19856–19860.

(5) (a) Carrillo-Arcos, U. A.; Rojas-Ocampoa, J.; Porcel, S. *Dalton Trans.* **2016**, *45*, 479–483. (b) Manna, K.; Begam, H. M.; Samanta, K.; Jana R. *Org. Lett.* **2020**, *22*, 7443–7449.

(6) The structure of **2a** was determined by ^{1}H and ^{13}C NMR, ^{1}H-^{1}H COSY, HMQC, and HMBC analyses. The ^{1}H and ^{13}C NMR spectroscopic data of **2a** are also in good agreement with those reported.

(7) CCDC No. 1569284 (2m). The crystallographic data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

(8) See the Supporting Information for details.

(9) Scherrer, V.; Jackson-Mülly, M.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta* **1978**, *61*, 716–.

(10) CCDC No. 1571311 (**2s**). The crystallographic data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

(11) The nitrogen linker connecting the aryl and propargyl fragments in substrate **3y** was also tolerated, although the yield of the cyclization product **4y** was relatively low (28%).

(12) Selected examples: (a) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301. (b) Kadota, I.; Shibuya, A.; Gyoung, Y. S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 10262. (c) Kadota, I.; Lutete, L. M.; Shibuya, A.; Yamamoto, Y. *Tetrahedron Lett.* **2001**, *42*, 6207. (d) Patil, N. T.; Huo, Z.; Bajracharya, G. B.; Yamamoto, Y. *J. Org. Chem.* **2006**, *71*, 3612. (e) Chen, Q.-A.; Chen, Z.; Dong, V. M. *J. Am. Chem. Soc.* **2015**, *137*, 8392.

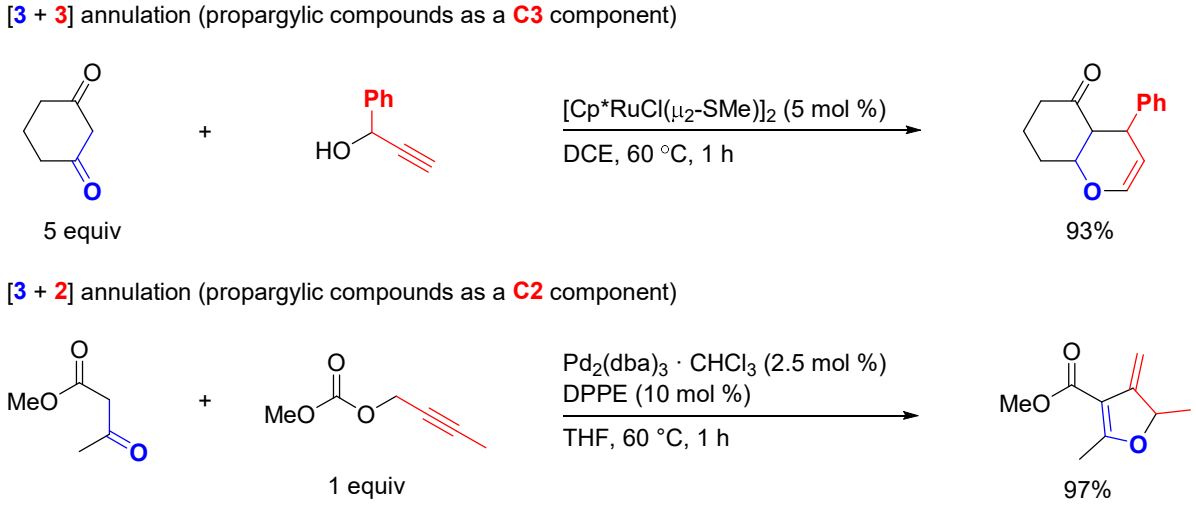
(13) Selected examples of oxidative addition of propargylic C−OAr bond to palladium (0): (a) Pal, M.; Parasuraman, K.; Yeleswarapu, K. R. *Org. Lett.* **2003**, *5*, 349. (b) Rambabu, D.; Bhavani, S.; Swamy, N. K.; Basaveswara Rao, M. V.; Pal, M. *Tetrahedron Lett.* **2013**, *54*, 1169.

Chapter 3.

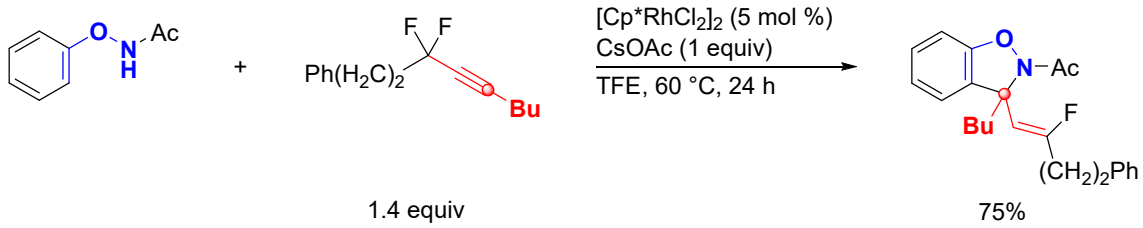
Palladium-Catalyzed [5 + 1] Annulation of Salicylic acid derivatives and propargylic carbonates

Introduction

Propargylic compounds including propargyl alcohols and their derivatives, have been widely utilized as versatile building blocks in transition-metal-catalyzed annulations that give a variety of complicated cyclic molecules.[1] Among these reactions, the propargylic compounds usually contribute a two- or three-carbon component, via [n + 2][2–5] or [n + 3][6–8] annulations, to the heterocycles (**Scheme 1**). However, synthetic examples using these propargylic compounds as a one-carbon (C1) component via a [n + 1]-type cyclization are less explored (**Scheme 2**).[9–11]



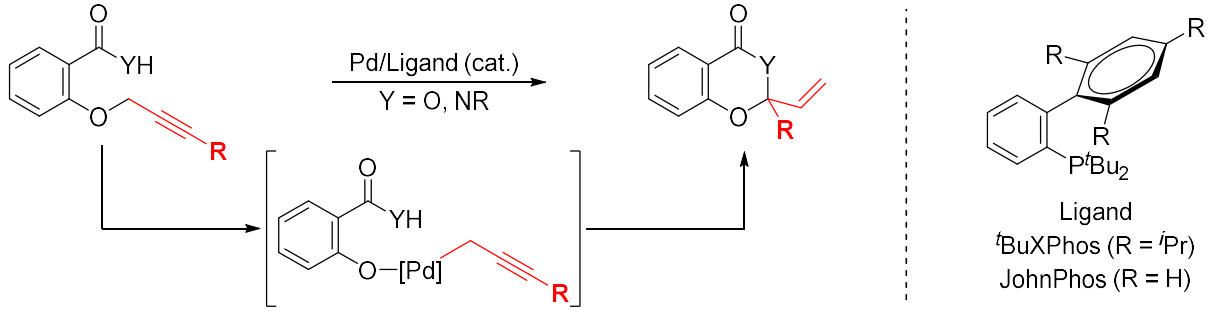
Scheme 1. Transition-metal-catalyzed [**m** + **n**] annulations using **propargylic compounds**



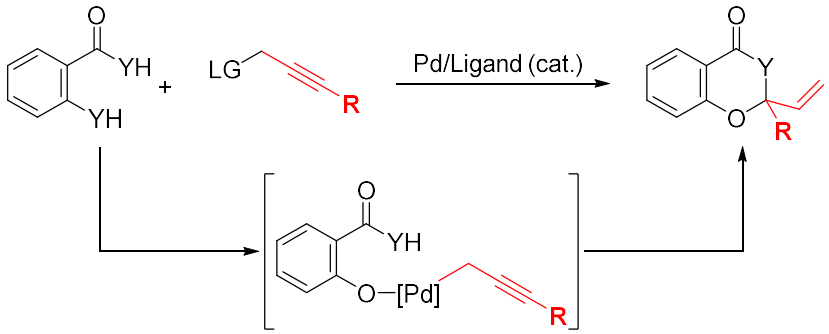
Scheme 2. Rhodium-catalyzed [**4** + **1**] annulation using propargylic compound as **C1** component

In chapter 1, palladium-catalyzed intramolecular cyclization of salicylic acid or salicylamide derivatives bearing a propargyl group at the phenol oxygen, which provides vinyl dioxanone derivatives with a fully substituted allylic carbon are described (**Scheme 3**).[12] Previous mechanistic studies suggest that the intramolecular cyclization reaction starts with the cleavage of the propargylic C–O bond by the palladium catalytic system, and that the resulting propargyl fragment behaves a C1 component for the heterocyclic structure. Based on the most plausible mechanism for this reaction, it is envisioned that an intermolecular manner would also proceed for the construction of the same

architectures via a similar intermediate as well as those assumed in the intramolecular reaction (**Scheme 4**).

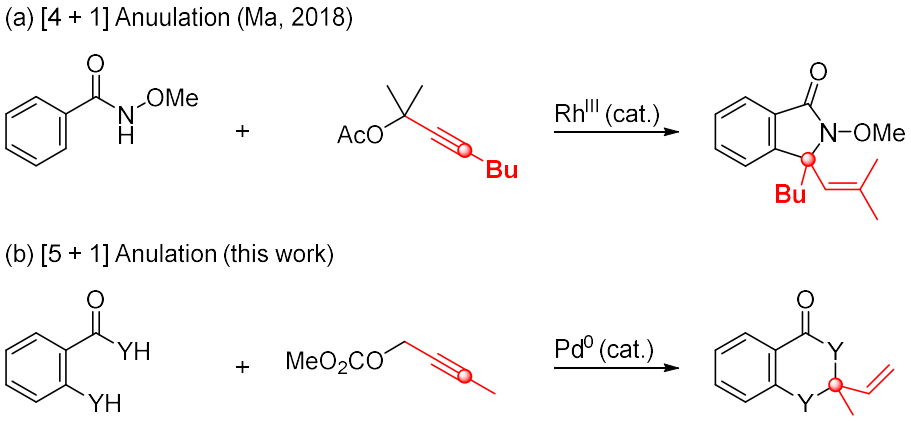


Scheme 3. Palladium-catalyzed intramolecular cyclization of alkynoic acid (**Chapter 2**)



Scheme 4. Palladium-catalyzed synthesis of vinyl-substituted heterocycles bearing a fully substituted allylic carbon (**Chapter 3**)

In 2018, Ma and co-workers reported a rhodium-catalyzed annulation between *N*-methoxybenzamide derivatives and propargylic acetates for the formation of isoindolin-1-one derivatives.[10g] Here, the alkyne carbon in the propargylic starting material furthest from the propargylic C–O bond performs as the C1 component of the [4 + 1] annulation, and the carbon atom forms part of the resulting 5-membered heterocycles (**Scheme 5a**). In contrast to this work, a novel palladium-catalyzed [5 + 1] annulation between salicylic acid derivatives and propargylic carbonates to furnish vinyl-substituted heterocycles has been demonstrated, and the detailed results are described in chapter 3 (**Scheme 5b**).



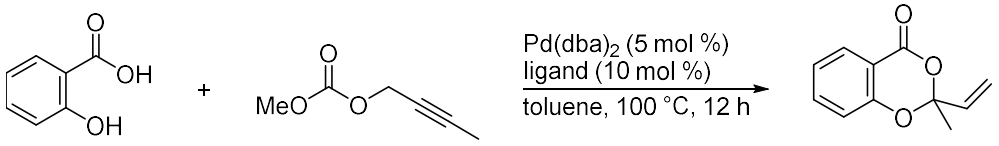
Scheme 5. Transition-metal-catalyzed [n + 1] annulation that employ propargylic compounds as C1 component

Results and discussion

3-1. Optimization of the annulation between salicylic acid 1 and propargylic carbonate 2

Using salicylic acid (**1**) and propargylic carbonate **2** as the substrates, we began by investigating the optimization of the reaction conditions required to produce 4*H*-1,3-benzodioxin-4-one derivative **3** (Table 1). The screening of several monodentate and bidentate ligands in combination with $Pd(dba)_2$ (entries 1–10) revealed that the JohnPhos ligand produced heterocycle **3** in the highest yield (48%; entry 5). Increasing the amount of propargylic carbonate **2** used further improved the yield (entries 5, 11, 12). An optimal result of 94% yield (83% isolated yield) of **3** was obtained using the following conditions: **1** (1 equiv), **2** (1.5 equiv), $Pd(dba)_2$ (5 mol%), JohnPhos (10 mol%), toluene 100 °C, 12 h (entry 12).

Table 1. Optimization of the reaction conditions for the [5 + 1] annulation between **1** and **2**[a]



1 **2** (X equiv) **3**

entry	ligand	X / equiv	GC yield / %
1	PPh_3	1.0	5
2	PCy_3	1.0	2
3	P^tBu_3	1.0	0
4	DPPE	1.0	1
5	DPPP	1.0	2
6	DPPB	1.0	1
7	Xantphos	1.0	36
8	^{t}BuXPhos	1.0	39
9	CyJohnPhos	1.0	2
10	JohnPhos	1.0	48
11	JohnPhos	1.2	60
12	JohnPhos	1.5	94 (83)[b]

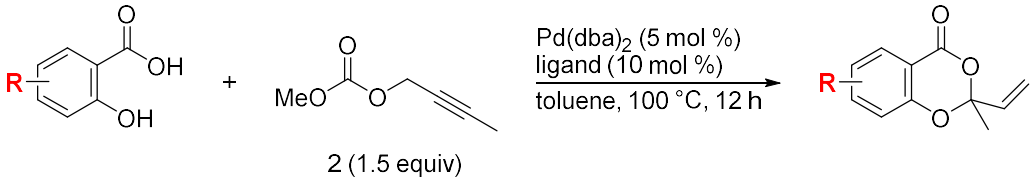
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5–0.75 mmol), $Pd(dba)_2$ (0.025 mmol), ligand (0.025 or 0.05 mmol), toluene (0.5 mL), 100 °C, 12 h. [b]Isolated yield (scale: 1 mmol).

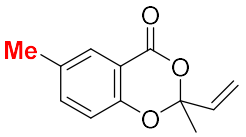
3-2. Substrate scope with respect to salicylic acids and non-salicylic acids

With the optimal reaction conditions in hand, we explored the effect of varying the substituents on the salicylic acid component (**Table 2**). Electron-donating groups, such as a methyl, amino, or methoxy group were tolerated to furnish the corresponding products **4**–**6**. Salicylic acids with halogens at the 5-position, including fluorine and chlorine, were transformed into the corresponding products **7** and **8** in high yields. However, an obvious decrease in the yield of **9** was observed for the

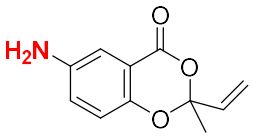
corresponding salicylic acid with a bromide substituent. Although substrates with a phenyl or nitro substituent at the 3-position furnished the corresponding products in moderate yields, 3,5-di-*tert*-butylsalicylic acid provided heterocycle **12** in an excellent yield.

Table 2. Substrate scope with respect to salicylic acids[a]

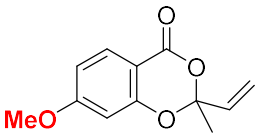




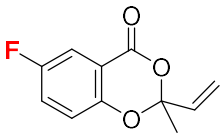
4: 92%



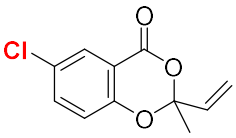
5: 56%[b]



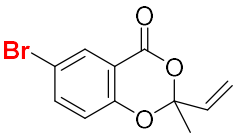
6: 96%



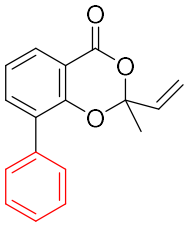
7: 68%



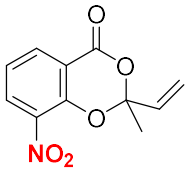
8: 81%



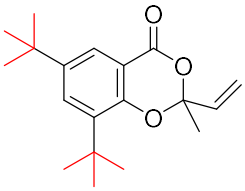
9: 24%[c]



10: 62%



11: 50%

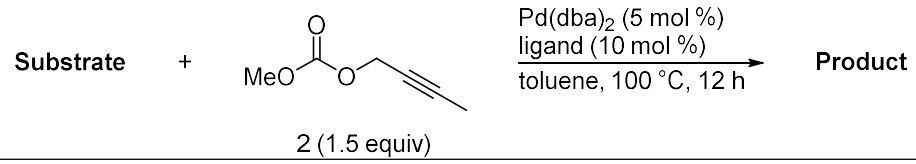


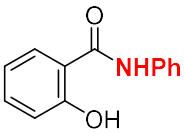
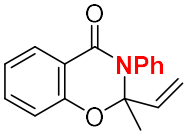
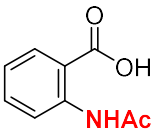
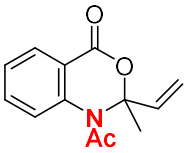
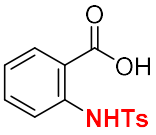
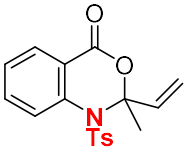
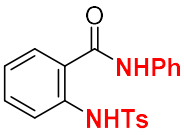
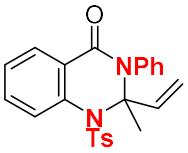
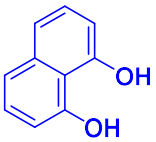
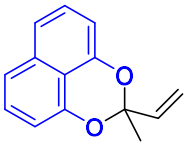
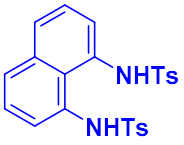
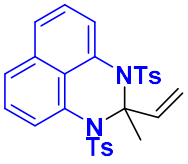
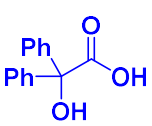
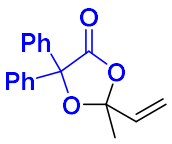
12: 89%

[a]Reaction conditions: Salicylic acid (1.0 mmol), **2** (1.5 mmol), $Pd(dba)_2$ (0.05 mmol), JohnPhos (0.1 mmol), toluene (1 mL), 100 °C, 12 h. Isolated yields are shown. [b]1,4-Dioxane (3 mL) was used instead of toluene (scale: 0.5 mmol). [c]Scale: 0.5 mmol.

We then examined the reactivity of nucleophilic compounds other than salicylic acids with the propargylic carbonate **2** (**Table 3**). In a manner similar to the reaction of salicylic acid (**1**), salicylanilide also engaged in the annulation reaction with **2** to afford the expected product **13** in 86% isolated yield (entry 1). Although *N*-acyl-anthranilic acid did not give cyclic product **14** (entry 2), *N*-tosyl-anthranilic acid and an *N*-tosyl-anthranilamide derivatives provided **15** and **16**, respectively (entries 3 and 4). Annulations that employ other starting materials with different carbon skeletons,

Table 3. Substrate scope with respect to non-salicylic acid nucleophiles[a]



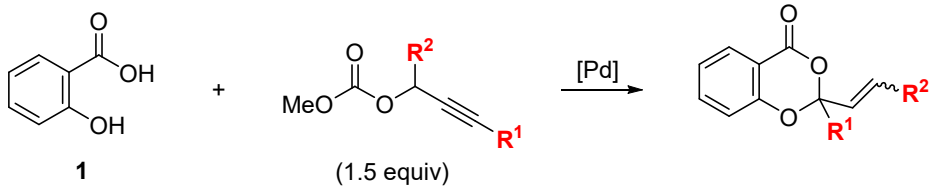
entry	substrate	product	yield / %
1		 **13**	86
2		 **14**	0
3		 **15**	49
4[b,c]		 **16**	42
5		 **17**	24
6[b,d]		 **18**	43
7[c]		 **19**	83

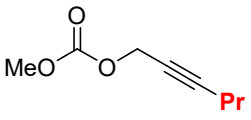
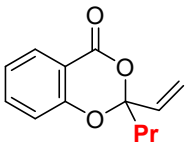
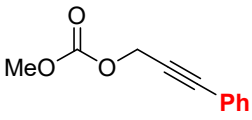
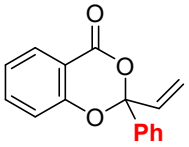
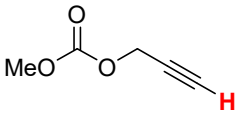
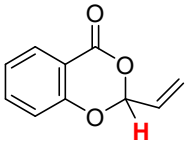
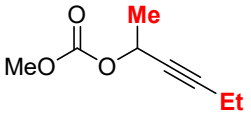
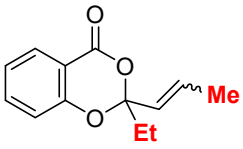
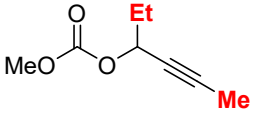
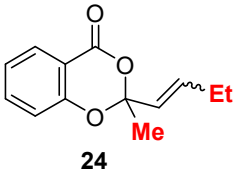
[a]Reaction conditions: Substrate (1.0 mmol), **2** (1.5 mmol), $Pd(dba)_2$ (0.05 mmol), JohnPhos (0.1 mmol), toluene (1 mL), 100 °C, 12 h. [b]1,4-Dioxane (3 mL) was used instead of toluene. [c]Scale: 0.5 mmol. [d]Pd/P = 15/30 mol%.

such as 1,8-dihydroxynaphthalene and 1,8-diaminonaphthalene, also proceeded to form six-membered heterocycles (entries 5 and 6). In addition to six-membered products it is notable that five-membered heterocycle **19** could also be synthesized in high yield from benzylic acid via this method (entry 7).

3-3. Substrate scope of propargylic carbonates

Table 4. Substrate scope with respect to propargylic carbonates[a]



entry	substrate	product	yield / %
1		 **20**	77%
2		 **21**	43%
3		 **22**	0%
4[b,c]		 **23**	82% (E/Z = 91/9)
5[c]		 **24**	78% (E/Z = 96/4)

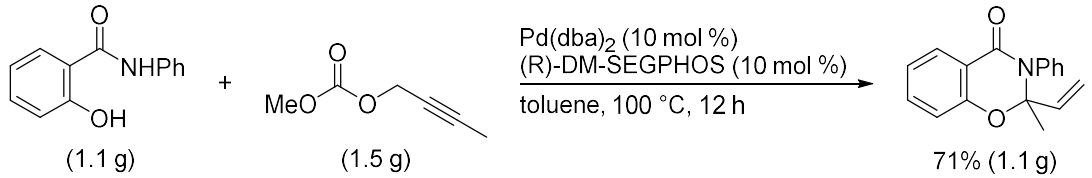
[a]Reaction conditions: **1** (1.0 mmol), propargylic carbonate (1.5 mmol), $Pd(dba)_2$ (0.05 mmol), JohnPhos (0.1 mmol), toluene (1 mL), 100 °C, 12 h. [b]Scale: 0.5 mmol. [c]Xantphos (5 mol%) was used instead of JohnPhos (10 mol%).

Subsequently, we investigated the substrate scope with respect to the propargylic compounds (**Table 3**). The reaction between salicylic acid (**1**) and propargylic carbonates bearing substituents other than a methyl group on the alkyne produced heterocycles **20** and **21** in 77% and 43% yield, respectively. These products contain either an *n*-propyl or a phenyl group attached to a fully substituted allylic carbon (entries 1 and 2). In contrast, annulation product **22** was not detected and the starting substrate **1** was recovered when a terminal alkyne was used (entry 3). In the cases where branched propargylic carbonates were used as substrates, Xantphos was found to be a more effective ligand for the annulation than JohnPhos.[13] Heterocycles **23** and **24**, which bear 1,2-di-substituted olefins, were isolated with a *trans* stereochemistry (entries 4 and 5).[14]

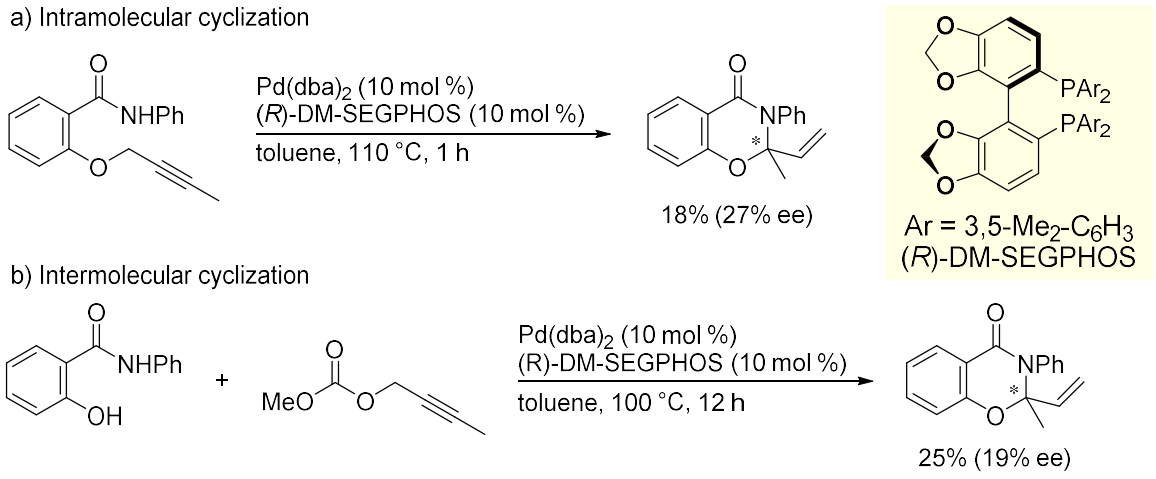
3-4. Application of the synthetic method for vinyl-substituted heterocycles

Synthetic applications of the developed method were described. First, a gram-scale reaction between salicylic acid (1.1 g) and propargylic carbonate (1.5 g) has been performed. As the result, the desired vinyl-dioxanone product was isolated in 71% yield (**Scheme 4**).

Furthermore, enantioselective synthesis of a vinyl-substituted heterocycle was also attempted using a chiral ligand. After several examination of chiral ligands, intramolecular cyclization of a salicylamide derivative using (*R*)-DM-SEGPHOS produce the corresponding heterocycle in 18% yield with 27% ee (enantiomeric excess of the product was determined by using chiral HPLC) (**Scheme 5a**). Similarly, intermolecular cyclization between salicylanilide and propargylic carbonate gave the product in 25% yield with 19% ee (**Scheme 5b**).

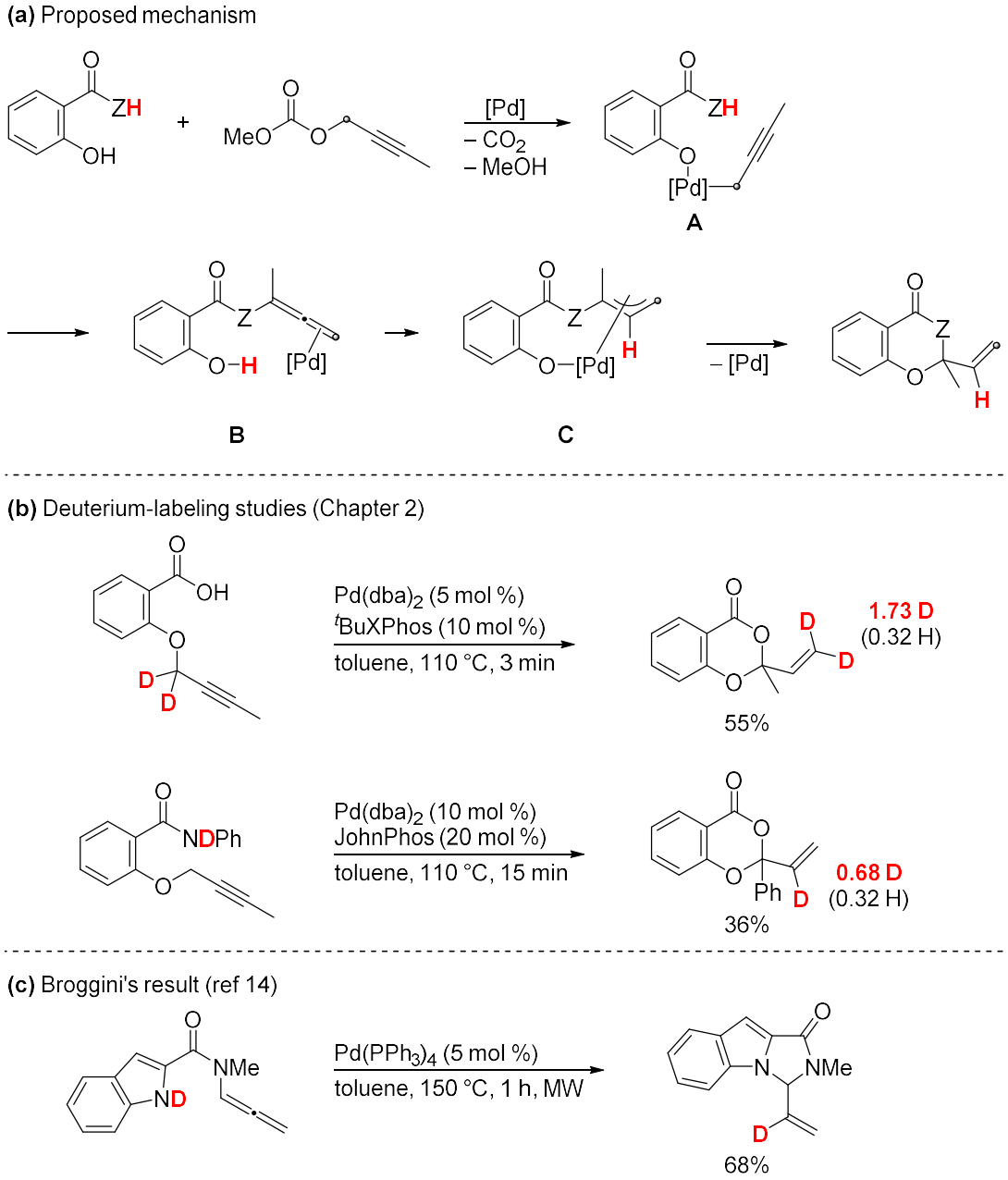


Scheme 4. Gram scale synthesis



Scheme 5. Enantioselective synthesis of the vinyl-substituted heterocycle

3-5. Proposed mechanism



Scheme 6. Proposed reaction mechanism for the annulation and previous deuterium-labeling studies

A plausible mechanism for the reaction is proposed in Scheme 4a. Based on our initial working hypothesis, we propose that the reaction proceeds via palladium aryloxy propargyl intermediate **A**, which is formed from the starting substrates and the palladium catalyst. Subsequently, an intramolecular S_N2'-type attack of a carboxylic acid could occur at the methyl-substituted alkyne carbon to generate allene intermediate **B**. The formation of π-allylpalladium species **C** from **B** and the subsequent C–O reductive elimination of the cyclization product would then proceed under regeneration of the palladium catalyst.[15] This pathway is supported by previous deuterium-labeling studies by both our group (**Scheme 6b**)[12] and that of Broggini (**Scheme 6c**).[16]

3-6. Conclusion

Based on our previous intramolecular cyclization of alkynoic acids, we have developed an efficient method to construct vinyl-dioxanone derivatives bearing a fully substituted allylic carbon from readily accessible salicylic acids and propargylic carbonates. In this annulation, propargylic carbonates function as a synthetic equivalent of the carbon components bearing a vinyl group. Various types of nucleophilic compounds, not only salicylic acids but also anthranilic acid, anthranilamide, 1,8-dihydroxy or 1,8-diamino-naphthalenes engage in this reaction and furnish the corresponding six-membered vinyl-substituted heterocycles. Benzylic acid could also be used for this annulation, and this result indicates the potential for the synthesis of a wide range of five-membered heterocycles from glycolic acid derivatives.

3-7. Experimental section

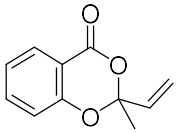
General Information

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts in the ^{1}H and ^{13}C NMR spectra are reported in ppm relative to residual solvent peaks, such as those of chloroform (^{1}H: δ 7.26; ^{13}C: δ 77.0), or the internal reference tetramethylsilane (^{1}H and ^{13}C: δ 0.00). Chemical shifts in the ^{19}F NMR spectra are reported in ppm relative to the external reference α,α,α-trifluorotoluene ($CF_3C_6H_5$, ^{19}F: δ −62.6). GC analyses were performed using a DB-5 capillary column (30 m × 0.25 mm; film thickness: 0.25 μm). High-resolution mass spectra (HRMS) were measured using NBA (3-nitrobenzylalcohol) as a matrix. Toluene was distilled from Na/benzophenone ketyl prior to use. $Pd(dba)_2$, the phosphine ligands, salicylic acid (**1**) and its derivatives were purchased from common commercial suppliers and used without further purification. *N*-Tosylation substrates[17] and propargylic carbonates[18] were prepared via modified literature procedures. Unless otherwise noted, all reactions were performed under a nitrogen atmosphere.

General procedure for the Pd-catalyzed annulation of salicylic acids and propargylic carbonates

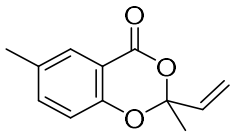
A screw-capped vial in a glovebox was charged with salicylic acid (1 mmol), propargylic carbonate **2** (1.5 mmol), $Pd(dba)_2$ (28.8 mg, 0.05 mmol), phosphine ligand (0.10 mmol), and toluene (1 mL) (added in this order). The vial was then sealed and removed from the glovebox, and the mixture was stirred at 100 °C for 12 h. After the reaction, the volatile materials were removed under reduced pressure, and the crude material was purified by column chromatography on silica gel, followed by gel permeation chromatography if necessary, to give the corresponding product.

Annulation product 3[12a]



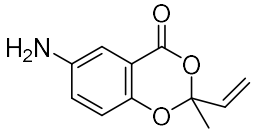
The general procedure was followed with salicylic acid (138.1 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.1 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 50/1 to 30/1, v/v) afforded **3** (168.7 mg, 83%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92 (dd, J = 8.0, 1.5 Hz, 1 H, Ar*H*), 7.56–7.52 (m, 1 H, Ar*H*), 7.10 (t, J = 7.5 Hz, 1 H, Ar*H*), 6.99 (d, J = 8.0 Hz, 1 H, Ar*H*), 5.90 (dd, J = 17.0, 11.0 Hz, 1 H, C=C*H*), 5.52 (d, J = 17.0 Hz, 1 H, C=C*H*), 5.32 (d, J = 11.0 Hz, 1 H, C=C*H*), 1.82 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.4, 156.2, 136.4, 136.3, 129.6, 122.7, 119.6, 116.9, 114.5, 105.2, 26.7; LRMS (EI) *m*/*z* (% relative intensity) 190 (M^+, 14), 120 (100), 92 (56).

Annulation product 4[12a]



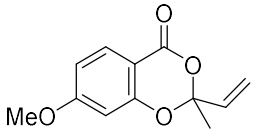
The general procedure was followed with 5-methyl salicylic acid (152.2 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.2 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 30/1, v/v) afforded **4** (188.1 mg, 92%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (t, J = 6.5 Hz, 1 H, Ar*H*), 7.34 (t, J = 6.5 Hz, 1 H, Ar*H*), 6.95 (t, J = 6.5 Hz, 1 H, Ar*H*), 5.85 (dd, J = 17.0, 11.0 Hz, 1 H, C=C*H*), 5.43 (d, J = 17.0 Hz, 1 H, C=C*H*), 5.25 (d, J = 11.0 Hz, 1 H, C=C*H*), 2.23 (s, 3 H, CH_3), 1.80 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.6, 154.4, 137.1, 136.6, 127.0, 126.3, 122.1, 119.0, 114.0, 104.9, 26.7, 14.9; LRMS (EI) *m*/*z* (% relative intensity) 204 (M^+, 12), 134 (100), 106 (74).

Annulation product 5



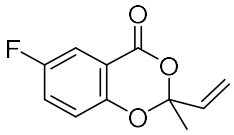
The general procedure was followed with 5-amino salicylic acid (76.3 mg, 0.5 mmol) and 2-butyn-1-yl methyl carbonate (96.1 mg, 0.75 mmol), except that the reaction was performed in 1,4-dioxane (3 mL) instead of toluene. Column chromatography (hexane/EtOAc: 3/1, v/v) afforded **5** (57.4 mg, 56%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.18 (d, J = 3.0 Hz, 1 H, Ar*H*), 6.88 (dd, J = 8.5, 3.0 Hz, 1 H, Ar*H*), 6.80 (d, J = 8.5 Hz, 1 H, Ar*H*), 5.88 (dd, J = 17.0, 11.0 Hz, 1 H, C=C*H*), 5.49 (d, J = 17.0 Hz, 1 H, C=C*H*), 5.30 (d, J = 11.0 Hz, 1 H, C=C*H*), 3.63 (s, 2 H, NH_2), 1.78 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.7, 148.9, 141.7, 136.8, 123.6, 119.3, 117.6, 114.9, 113.9, 105.0, 26.6; HRMS (EI) calcd for $[M]^+$ ($C_{11}H_{11}NO_3$) *m*/*z* 205.0733, found 205.0728.

Annulation product 6[12a]



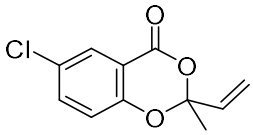
The general procedure was followed with 4-methoxy salicylic acid (168.2 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.2 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 30/1, v/v) afforded **6** (213.4 mg, 96%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 (d, J = 8.5 Hz, 1 H, Ar*H*), 6.59–6.56 (m, 1 H, Ar*H*), 6.40 (d, J = 2.0 Hz, 1 H, Ar*H*), 5.86 (dd, J = 17.5, 11.0 Hz, 1 H, C=C*H*), 5.47 (d, J = 17.5 Hz, 1 H, C=C*H*), 5.25 (d, J = 11.0 Hz, 1 H, C=C*H*), 3.79 (s, 3 H, CH_3), 1.74 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.1, 161.0, 158.0, 136.4, 131.0, 119.1, 110.2, 107.0, 105.0, 100.8, 55.6, 26.5; LRMS (EI) *m*/*z* (% relative intensity) 220 (M^+, 7), 150 (100), 122 (36), 107 (15).

Annulation product 7



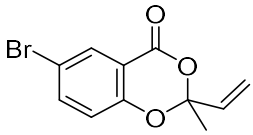
The general procedure was followed with 5-fluoro salicylic acid (157.0 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.2 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 50/1, v/v) afforded **7** (142.5 mg, 68%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.49 (dd, J = 8.0, 3.0 Hz, 1 H, Ar*H*), 7.19–7.16 (m, 1 H, Ar*H*), 6.90 (dd, J = 8.5, 4.0 Hz, 1 H, Ar*H*), 5.79 (dd, J = 17.0, 11.0 Hz, 1 H, C=C*H*), 5.42 (d, J = 17.0 Hz, 1 H, C=C*H*), 5.25 (d, J = 11.0 Hz, 1 H, C=C*H*), 1.73 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 160.4, 157.5 (d, $J_{C\text{-}F}$ = 242.7 Hz), 152.3 (d, $J_{C–F}$ = 2.5 Hz), 136.1, 123.6 (d, $J_{C–F}$ = 23.9 Hz), 119.9, 118.5 (d, $J_{C–F}$ = 7.5 Hz), 115.1, 115.0 (d, $J_{C–F}$ = 25.2 Hz), 105.5, 26.5; ^{19}F NMR ($CDCl_3$, 471 MHz) δ –118.8; HRMS (EI) calcd for $[M]^+$ ($C_{11}H_9O_3F$) *m*/*z* 208.0530, found 208.0536.

Annulation product 8[12a]



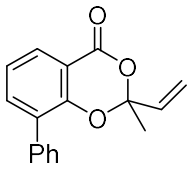
The general procedure was followed with 5-chloro salicylic acid (172.6 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (191.2 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 50/1, v/v) afforded **8** (163.6 mg, 81%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88 (d, J = 2.5 Hz, 1 H, Ar*H*), 7.49 (dd, J = 7.5, 2.5 Hz, 1 H, Ar*H*), 6.96 (d, J = 7.5 Hz, 1 H, Ar*H*), 5.87 (dd, J = 17.5, 11.0 Hz, 1 H, C=C*H*), 5.51 (d, J = 17.5 Hz, 1 H, C=C*H*), 5.35 (d, J = 11.0 Hz, 1 H, C=C*H*), 1.82 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 160.2, 154.6, 136.2, 136.0, 129.0, 128.0, 120.0, 118.6, 115.5, 105.6, 26.6; HRMS (EI) calcd for $[M]^+$ ($C_{11}H_9O_3Cl$) *m*/*z* 224.0235, found 224.0232.

Annulation product 9[12a]



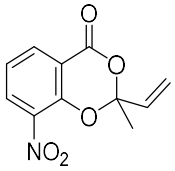
The general procedure was followed with 5-bromo salicylic acid (108.5 mg, 0.5 mmol) and 2-butyn-1-yl methyl carbonate (128.1 mg, 1.0 mmol). Column chromatography (hexane/EtOAc: 30/1, v/v) afforded **9** (33.1 mg, 24%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.04 (d, J = 2.5 Hz, 1 H, Ar*H*), 7.63 (dd, J = 8.5, 2.5 Hz, 1 H, Ar*H*), 6.90 (d, J = 8.5 Hz, 1 H, Ar*H*), 5.87 (dd, J = 17.0, 11.0 Hz, 1 H, C=C*H*), 5.51 (d, J = 17.0 Hz, 1 H, C=C*H*), 5.35 (d, J = 11.0 Hz, 1 H, C=C*H*), 1.82 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 160.1, 155.1, 139.0, 136.0, 132.0, 120.1, 118.9, 115.9, 115.0, 105.6, 26.6; LRMS (EI) *m*/*z* (% relative intensity) 270 (13), 268 (M^+, 13), 200 (100).

Annulation product 10



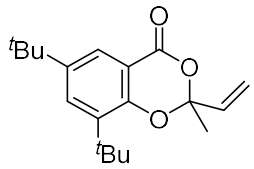
The general procedure was followed with 3-phenyl salicylic acid (214.2 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.2 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 10/1, v/v) afforded **10** (164.8 mg, 62%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.93 (dd, J = 7.5, 2.0 Hz, 1 H, Ar*H*), 7.60 (dd, J = 7.5, 1.5 Hz, 1 H, Ar*H*), 7.54–7.52 (m, 2 H, Ar*H*), 7.47–7.44 (m, 2 H, Ar*H*), 7.41–7.37 (m, 1 H, Ar*H*), 7.17 (t, J = 8.0 Hz, 1 H, Ar*H*), 5.87 (dd, J =17.5, 11.0 Hz, 1 H, C=C*H*), 5.45 (d, J = 17.5 Hz, 1 H, C=C*H*), 5.29 (d, J = 11.0 Hz, 1 H, C=C*H*), 1.79 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.5, 153.0, 136.9, 136.3, 135.6, 130.4, 129.0, 128.8, 128.3, 127.8, 122.7, 119.6, 115.0, 105.1, 26.6; HRMS (EI) calcd for $[M]^+$ ($C_{17}H_{14}O_3$) *m*/*z* 266.0937, found 266.0942.

Annulation product 11[12a]



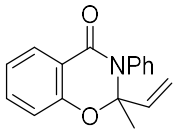
The general procedure was followed with 3-nitro salicylic acid (183.1 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.2 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 10/1, v/v) afforded **11** (118.2 mg, 50%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.24–8.20 (m, 2 H, Ar*H*), 7.27–7.23 (m, 1 H, Ar*H*), 5.94 (dd, J = 17.0, 10.5 Hz, 1 H, C=C*H*), 5.62 (d, J = 17.0 Hz, 1 H, C=C*H*), 5.40 (d, J = 10.5 Hz, 1 H, C=C*H*), 1.93 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 164.8, 148.8, 143.5, 142.9, 136.4, 129.2, 124.9, 123.4, 120.5, 74.8, 10.5; LRMS (EI) *m*/*z* (% relative intensity) 235 (M^+, 9), 220 (5), 193 (6), 165 (100), 135 (12).

Annulation product 12



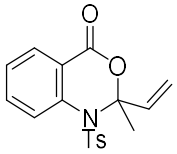
The general procedure was followed with 3,5-di-*tert*-butyl salicylic acid (250.6 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.1 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 70/1 to 10/1, v/v) afforded **12** (270.6 mg, 89%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.80 (d, J = 2.5 Hz, 1 H, Ar*H*), 7.56 (d, J = 2.5 Hz, 1 H, Ar*H*), 5.92 (d, J = 17.5, 10.5 Hz, 1 H, C=C*H*), 5.60 (d, J = 17.5 Hz, 1 H, C=C*H*), 5.34 (d, J = 10.5 Hz, 1 H, C=C*H*), 1,84 (s, 3 H, CH_3), 1.40 (s, 9 H, CH_3), 1.31 (s, 9 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 162.5, 152.4, 144.9, 137.5, 136.7, 130.8, 123.8, 119.5, 114.4, 104.2, 34.8, 34.6, 31.3, 29.7, 26.5; HRMS (EI) calcd for $[M]^+$ ($C_{19}H_{26}O_3$) *m*/*z* 302.1876, found 302.1887.

Annulation product 13[12b]



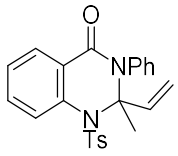
The general procedure was followed with salicylanilide (213.2 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.2 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 10/1, v/v) afforded **13** (213.2 mg, 86%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.97 (d, J = 7.5 Hz, 1 H, Ar*H*), 7.45–7.39 (m, 3 H, Ar*H*), 7.36–7.33 (m, 1 H, Ar*H*), 7.25 (d, J = 7.5 Hz, 2 H, Ar*H*), 7.07 (t, J = 7.5 Hz, 1 H, Ar*H*), 6.95 (d, J = 8.5 Hz, 1 H, Ar*H*), 6.00 (dd, J = 16.5, 11.0 Hz, 1 H, C=C*H*), 5.47 (d, J = 16.5 Hz, 1 H, C=C*H*), 5.29 (d, J = 11.0 Hz, 1 H, C=C*H*), 1.47 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 162.1, 155.1, 137.7, 137.4, 134.2, 129.1, 128.03, 128.00, 126.0, 122.0, 118.4, 118.0, 116.6, 92.2, 26.0; HRMS (EI) calcd for $[M]^+$ ($C_{17}H_{15}NO_2$) m/z 265.1097, found 265.1087.

Annulation product 15[12a]



The general procedure was followed with *N*-tosyl-anthranilic acid (291.3 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.1 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 10/1, v/v) afforded **15** (169.4 mg, 49%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.87 (d, J = 7.5 Hz, 1 H, Ar*H*), 7.79 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.69 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.43 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.28 (d, J = 8.5 Hz, 2 H, Ar*H*), 7.18 (d, J = 8.5 Hz, 2 H, Ar*H*), 5.92 (d, J = 17.0, 11.0 Hz, 1 H, C=C*H*), 5.28 (d, J = 17.0 Hz, 1 H, C=C*H*), 5.09 (d, J = 11.0 Hz, 1 H, C=C*H*), 1.95 (s, 3 H, CH_3), 2.38 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.8, 145.0, 140.0, 139.3, 135.1, 134.3, 129.8, 129.0, 128.9, 128.0, 127.7, 123.3, 116.7, 94.0, 27.8, 21.6; HRMS (FAB) calcd for $[M+H]^+$ ($C_{18}H_{18}NO_4S$) m/z 344.0951, found 344.0956.

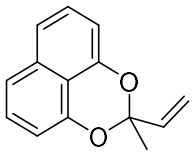
Annulation product 16[12b]



The general procedure was followed with *N*-tosyl-anthranilanilide (133.0 mg, 0.5 mmol) and 2-butyn-1-yl methyl carbonate (96.2 mg, 0.75 mmol), except that the reaction was performed in dioxane (3 mL) instead of toluene. Column chromatography (hexane/EtOAc: 3/1, v/v) and gel permeation chromatography afforded **16** (70.0 mg, 46%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.00 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.70 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.59 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.48 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.42 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.33 (d, J = 8.5 Hz, 2 H, Ar*H*), 7.30 (t, J = 7.0 Hz,

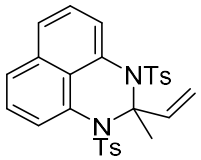
1 H, Ar*H*), 7.24 (t, *J* = 8.0 Hz, 1 H, Ar*H*), 7.12 (t, *J* = 7.5 Hz, 1 H, Ar*H*), 7.01 (d, *J* = 7.5 Hz, 1 H, Ar*H*), 5.87 (dd, *J* = 17.0, 11.0 Hz, 1 H, C=C*H*), 5.60 (d, *J* = 7.0 Hz, 1 H, C*H*), 5.22 (d, *J* = 17.0 Hz, 1 H, C=C*H*), 5.06 (d, *J* = 11.0 Hz, 1 H, C=C*H*), 2.46 (s, 3 H, CH_3), 1.66 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 163.0, 144.4, 140.7, 139.1, 138.1, 137.8, 132.3, 130.1, 129.7, 128.9, 128.8, 128.6, 128.1, 127.9, 127.6, 127.3, 126.7, 116.1, 79.3, 25.7, 21.5; HRMS (FAB) calcd for $[M+H]^+$ ($C_{24}H_{23}N_2O_3S$) *m*/*z* 419.1424, found 419.1423.

Annulation product 17



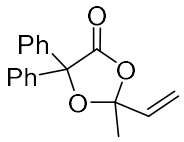
The general procedure was followed with 1,8-dihydroxynaphthalene (160.1 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.2 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 70/1, v/v) afforded **17** (49.9 mg, 24%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.43–7.36 (m, 4 H, Ar*H*), 6.89 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 5.88 (dd, *J* = 17.0, 10.5 Hz, 1 H, C=C*H*), 5.44 (d, *J* = 17.0 Hz, 1 H, C=C*H*), 5.12 (d, *J* = 10.5 Hz, 1 H, C=C*H*), 1.83 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.3, 137.1, 134.2, 127.2, 120.2, 118.8, 114.1, 108.7, 101.1, 26.6; HRMS (EI) calcd for $[M]^+$ ($C_{14}H_{12}O_2$) *m*/*z* 212.0832, found 212.0832.

Annulation product 18



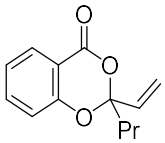
The general procedure was followed with *N*-tosyl-1,8-diaminonaphthalene (233.2 mg, 1.0 mmol) and 2-butyn-1-yl methyl carbonate (192.1 mg, 1.5 mmol), except that the reaction was performed in 1,4-dioxane (3 mL) instead of toluene, $Pd(dba)_2$ (45.1 mg, 0.15 mmol), JohnPhos (44.5 mg, 0.30 mmol). Column chromatography (hexane/EtOAc: 10/1, v/v) and gel permeation chromatography afforded **18** (111.1 mg, 43%) as a pale red oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, *J* = 7.0 Hz, 4 H, Ar*H*), 7.71 (d, *J* = 7.5 Hz, 2 H, Ar*H*), 7.57 (d, *J* = 8.5 Hz, 2 H, Ar*H*), 7.38–7.34 (m, 2 H, Ar*H*), 7.22 (d, *J* = 8.0 Hz, 4 H, Ar*H*), 5.62 (dd, *J* = 17.0, 10.5 Hz, 1 H, C=C*H*), 4.97 (d, *J* = 17.0 Hz, 1 H, C=C*H*), 4.57 (d, *J* = 10.5 Hz, 1 H, C=C*H*), 2.45 (s, 3 H, CH_3), 2.37 (s, 6 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.8, 145.0, 140.0, 139.3, 135.1, 134.3, 129.8, 128.9, 128.0, 127.7, 123.3, 116.7, 94.0, 27.8, 21.6; HRMS (FAB) calcd for $[M+H]^+$ ($C_{28}H_{27}N_2O_4S_2$) *m*/*z* 519.1407, found 519.1409.

Annulation product 19



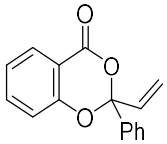
The general procedure was followed with benzilic acid (91.3 mg, 0.5 mmol) and 2-butyn-1-yl methyl carbonate (76.9 mg, 0.75 mmol). Column chromatography (hexane/EtOAc: 30/1 to 10/1, v/v) afforded **19** (92.8 mg, 83%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.55–7.54 (m, 2 H, Ar*H*), 7.48–7.46 (m, 2 H, Ar*H*), 7.38–7.29 (m, 6 H, Ar*H*), 5.92 (dd, J = 17.0, 11.0 Hz, 1 H, C=C*H*), 5.42 (d, J = 17.0 Hz, 1 H, C=C*H*), 5.16 (d, J = 11.0 Hz, 1 H, C=C*H*), 1.70 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 171.3, 140.1, 139.7, 136.8, 128.3, 128.3, 128.24, 128.20, 126.4, 126.1, 117.0, 108.5, 84.1, 26.0; HRMS (FAB) calcd for $[M]^+$ ($C_{18}H_{16}O_3$) m/z 280.1094, found 280.1099.

Annulation product 20



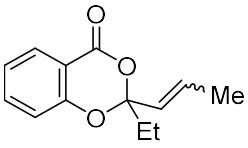
The general procedure was followed with salicylic acid (152.1 mg, 1.0 mmol) and 2-hexyn-1-yl methyl carbonate (192.2 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 4/1, v/v) afforded **20** (218.3 mg, 70%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, J = 7.5 Hz, 1 H, Ar*H*), 7.54–7.51 (m, 1 H, Ar*H*), 7.10–7.06 (m, 1 H, Ar*H*), 6.98 (d, J = 8.0 Hz, 1 H, Ar*H*), 5.82 (dd, J = 17.0, 11.0 Hz, 1 H, C=C*H*), 5.48 (d, J = 17.0 Hz, 1 H, C=C*H*), 5.33 (d, J = 11.0 Hz, 1 H, C=C*H*), 2.03–1.98 (m, 2 H, CH_2), 1.63–1.58 (m, 2 H, CH_2), 0.99 (m, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.5, 156.3, 136.1, 135.8, 129.5, 122.5, 120.2, 116.9, 114.6, 106.7, 41.4, 16.0, 13.8; HRMS (EI) calcd for $[M]^+$ ($C_{13}H_{14}O_3$) m/z 218.0937, found 218.0930.

Annulation product 21[12a]



The general procedure was followed with salicylic acid (138.1 mg, 1.0 mmol) and 3-phenyl-2-propyn-1-yl methyl carbonate (285.3 mg, 1.5 mmol). Column chromatography (hexane/EtOAc: 10/1, v/v) afforded **21** (108.6 mg, 43%) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.88 (dd, J = 7.5, 1.5 Hz, 1 H, Ar*H*), 7.58 (dd, J = 8.0, 1.5 Hz, 2 H, Ar*H*), 7.53 (td, J = 7.5, 1.5 Hz, 1 H, Ar*H*), 7.38–7.31 (m, 3 H, Ar*H*), 7.10 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.07–7.04 (m, 1 H, Ar*H*), 6.16 (dd, J = 17.0, 11.0 Hz, 1 H, C=C*H*), 5.56 (d, J = 17.0 Hz, 1 H, C=C*H*), 5.42 (d, J = 10.0 Hz, 1 H, C=C*H*); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.0, 156.1, 138.1, 136.44, 136.35, 129.7, 129.3, 128.6, 126.4, 122.9, 119.2, 117.2, 114.9, 105.5; HRMS (EI) calcd for $[M]^+$ ($C_{16}H_{12}O_3$) m/z 252.0781, found 252.0790.

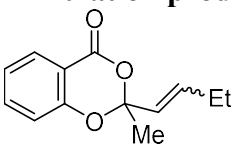
Annulation product 23



(*E*/*Z* = 91/9)

The general procedure was followed with salicylic acid (69.8 mg, 0.5 mmol) and 1-methyl-2-pentyn-1-yl methyl carbonate (96.2 mg, 0.75 mmol), except that reaction was performed with Xantphos (14.5 mg, 0.025 mmol) instead of JohnPhos (0.05 mmol). Column chromatography (hexane/EtOAc: 70/1, v/v) afforded **23** (218.3 mg, 82%, *E*/*Z* = 91/9) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.92–7.90 (m, 1.1 H, Ar*H*), 7.52 (td, *J* = 8.0, 1.5 Hz, 1.1 H, Ar*H*), 7.12–7.06 (m, 1.1 H, Ar*H*), 7.00–6.96 (m, 1.1 H, Ar*H*), 5.93 (dq, *J* = 15.5, 6.5 Hz, 1 H, C=C*H*, (*E*)), 5.68 (dq, *J* = 12.0, 7.5 Hz, 0.1 H, C=C*H*, (*Z*)), 5.50–5.44 (m, 1.1 H, C=C*H*), 2.13 (q, *J* = 7.5 Hz, 1 H, CH_2), 2.08–1.93 (m, 0.2 H, CH_2), 1.82 (dd, *J* = 7.5, 1.5 Hz, 0.3 H, CH_3), 1.64 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.14 (t, *J* = 7.5 Hz, 0.3 H, CH_3), 1.08 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.9, 156.5, 136.1, 132.0, 129.5, 128.7, 122.4, 116.9, 114.6, 107.1, 33.0, 17.5, 7.1; HRMS (EI) calcd for $[M]^+$ ($C_{13}H_{14}O_3$) *m*/*z* 218.0937, found 218.0941.

Annulation product 24



(*E*/*Z* = 96/4)

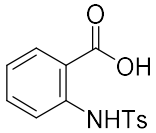
The general procedure was followed with salicylic acid (138.1 mg, 1.0 mmol) and 1-ethyl-2-butyn-1-yl methyl carbonate (234.2 mg, 1.5 mmol), except that the reaction was performed with Xantphos (29.1 mg, 0.05 mmol) instead of JohnPhos (0.1 mmol). Column chromatography (hexane/EtOAc: 30/1, v/v) afforded **24** (90.4 mg, 78%, *E*/*Z* = 96/4) as a pale yellow oil: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 (d, *J* = 8.0 Hz, 1 H, Ar*H*), 7.84 (d, *J* = 8.0 Hz, 0.04 H, Ar*H*), 7.53 (t, *J* = 7.5 Hz, 1 H, Ar*H*), 7.48–7.46 (m, 0.04 H, Ar*H*), 7.09 (t, *J* = 7.5 Hz, 1 H, Ar*H*), 6.99–6.96 (m, *J* = 8.5 Hz, 1 H, Ar*H*), 6.89 (t, *J* = 7.5 Hz, 0.04 H, Ar*H*), 6.00 (dt, *J* = 16.0, 7.5 Hz, 1 H, C=C*H*, (*E*)), 5.95–5.90 (m, 0.04 H, C=C*H*, (*Z*)), 5.51 (d, *J* = 16.0 Hz, 1 H, C=C*H*, (*E*)), 5.45 (d, *J* = 13.0 Hz, 0.04 H, C=C*H*, (*Z*)), 1.98 (quin, *J* = 7.5 Hz, 2 H, CH_2), 1.81 (s, 3 H, CH_3), 0.96 (t, *J* = 7.5 Hz, 0.12 H, CH_3), 0.89 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.6, 156.2, 137.6, 136.1, 129.4, 127.2, 122.5, 116.9, 114.5, 105.3, 27.0, 24.8, 12.7; HRMS (EI) calcd for $[M]^+$ ($C_{13}H_{14}O_3$) *m*/*z* 218.0937, found 218.0938.

Procedure for the *N*-tosylation

To a solution of corresponding amino benzene compound in DCM (10 mL), pyridine (20 mmol) was added. The reaction mixture was stirred at 0 °C for 10 min before *p*-tosyl chloride (15 mmol) was slowly added. After stirring the reaction mixture for overnight, saturated aqueous solution of NH_4Cl was added. The organic phase was extracted with DCM (3 x 10 mL) and dried over Na_2SO_4. Next, the combined organic phase was evaporated. The residue was recrystallization from hexane and ethyl acetate, affording the corresponding product.

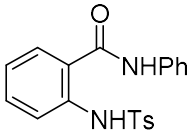
Spectral data of *N*-tosylation substrates

***N*-tosyl-anthranilic acid[19]**



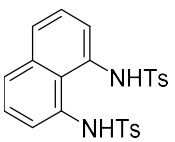
According to procedure for the *N*-tosylation, the product was obtained as a white solid after recrystallization (hexane/EtOAc): mp 231–233 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.93 (d, J = 8.0 Hz, 1 H, Ar*H*), 7.66–7.64 (m, 3 H, Ar*H*), 7.46 (t, J = 7.5 Hz, 1 H, Ar*H*), 7.26 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.06 (t, J = 7.5 Hz, 1 H, Ar*H*), 3.34 (s, 1 H, N*H*), 2.33 (s, 3 H, CH_3); ^{13}C NMR (CD_3OD, 126 MHz) δ 170.0, 144.3, 140.5, 136.1, 134.0, 131.5, 129.4, 127.1, 123.0, 119.1, 116.7, 20.1; LRMS (FAB) *m*/*z* 292 ([M+H]$^+$, 95).

***N*-tosyl-anthranilanilide**



According to procedure for the *N*-tosylation, the product was obtained as a white solid after recrystallization (hexane/EtOAc/MeOH): mp 142–144 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.21 (s, 1 H, N*H*), 7.70 (d, J = 8.5 Hz, 1 H, Ar*H*), 7.62 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.59 (s, 1 H, N*H*), 7.49 (d, J = 7.5 Hz, 3 H, Ar*H*), 7.46–7.42 (m, 1 H, Ar*H*), 7.38 (t, J = 8.0 Hz, 2 H, Ar*H*), 7.22–7.18 (m, 1 H, Ar*H*), 7.15–7.12 (m, 1 H, Ar*H*), 7.08 (d, J = 8.0 Hz, 2 H, Ar*H*), 2.26 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.5, 143.6, 138.5, 137.0, 136.3, 132.8, 129.5, 129.1, 127.2, 126.6, 125.2, 124.1, 123.2, 122.7, 120.5, 21.4; HRMS (FAB) calcd for [M+H]$^+$ ($C_{20}H_{19}N_2O_3S$) *m*/*z* 367.1111, found 367.1115.

***N*-tosyl-1,8-diaminonaphthalene[20]**



According to procedure for the *N*-tosylation, the product was obtained as a white solid. after recrystallization (hexane/EtOAc/MeOH): mp 204–206 °C; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.64 (d, J = 8.0 Hz, 2 H, Ar*H*), 7.54 (d, J = 8.0 Hz, 4 H, Ar*H*), 7.23–7.21 (m, 6 H), 6.97 (d, J = 7.0 Hz, 2 H,

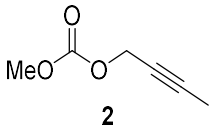
Ar*H*), 2.33 (s, 6 H, CH_3); ^{13}C NMR (CD_3OD, 126 MHz) δ 145.6, 137.6, 136.5, 133.3, 130.5, 129.1, 128.5, 126.5, 124.7, 124.3, 21.4; LRMS (FAB) *m*/*z* 467.1 ([M+H]$^+$, 97).

Procedure for the synthesis of propargylic carbonates

To a solution of propargyl alcohol (10 mmol) and pyridine (20 mmol) in chloroform (20 mL), methyl chloroformate (15 mmol) was added with stirring at 0 °C for 2 h. After the reaction was complete, the reaction mixture was added by water and the organic layer was separated. The aqueous layer was extracted with chloroform (3 x 20 mL). The combined organic layer was dried over sodium sulfate. After removal of the solvent with a rotary evaporator, the residue was purified by column chromatography.

Spectral data of propargylic carbonates

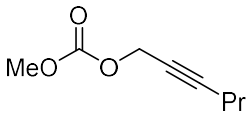
2-butyn-1-yl methyl carbonate[21]



2

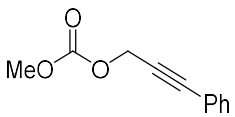
According to procedure for the synthesis of propargylic carbonates, the product was obtained as a clear liquid after column chromatography (hexane/EtOAc: 30/1, v/v): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.70 (q, *J* = 2.5 Hz, 2 H, CH_2), 3.81 (s, 3 H, CH_3), 1.86 (t, *J* = 2.5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.3, 84.0, 72.6, 56.2, 55.0, 3.6; LRMS (EI) *m*/*z* (% relative intensity) 128 (M$^+$, 4), 113 (58), 69 (77), 53 (100).

2-hexyn-1-yl methyl carbonate[22]



According to procedure for the synthesis of propargylic carbonates, the product was obtained as a clear liquid after column chromatography (hexane/EtOAc: 30/1, v/v): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.73 (t, *J* = 2.0 Hz, 2 H, CH_2), 3.80 (s, 3 H, CH_3), 2.16–2.12 (m, 2 H, CH_2), 1.54 (sext, *J* = 7.5 Hz, 2 H, CH_2), 0.98 (t, *J* = 7.5 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.2, 88.2, 73.4, 56.1, 54.8, 21.7, 20.6, 13.3; LRMS (EI) *m*/*z* (% relative intensity) 156 (M$^+$, 1), 127 (22), 79 (100).

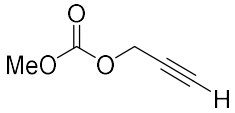
3-phenyl-2-propyn-1-yl methyl carbonate[23]



According to procedure for the synthesis of propargylic carbonates, the product was obtained as a clear liquid after column chromatography (hexane/EtOAc: 30/1, v/v): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.46 (dd, *J* = 7.5, 2.0 Hz, 2 H, Ar*H*), 7.36–7.29 (m, 3 H, Ar*H*), 4.97 (s, 2 H, CH_2), 3.84 (s, 3 H,

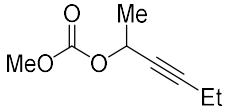
C*H*$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.3, 131.9, 128.9, 128.3, 122.0, 87.2, 82.2, 56.2, 55.2; LRMS (EI) *m*/*z* (% relative intensity) 190 (M^+, 17), 114 (100), 77 (27).

2-propyn-1-yl methyl carbonate[24]



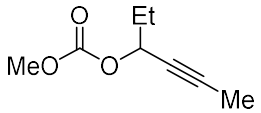
According to procedure for the synthesis of propargylic carbonates, the product was obtained as a clear liquid after column chromatography (hexane/EtOAc: 30/1, v/v): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.74 (d, *J* = 2.5 Hz, 2 H, C*H*$_2$), 3.83 (s, 3 H, C*H*$_3$), 2.53 (t, *J* = 2.5 Hz, 1 H, C≡C*H*); LRMS (EI) *m*/*z* (% relative intensity) 114 (M^+, 1), 99 (10), 68 (100). ^{1}H NMR spectroscopic data are in good agreement with those reported in literature[6].

1-methyl-2-pentyn-1-yl methyl carbonate[21]



According to procedure for the synthesis of propargylic carbonates, the product was obtained as a clear liquid after column chromatography (hexane/EtOAc: 30/1, v/v): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.31 (q, *J* = 7.0 Hz, 1 H, C*H*), 3.80 (s, 3 H, C*H*$_3$), 2.22 (q, *J* = 7.5 Hz, 2 H, C*H*$_2$), 1.51 (d, *J* = 7.0 Hz, 3 H, C*H*$_3$), 1.13 (t, *J* = 7.5 Hz, 3 H, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.9, 87.7, 77.3, 64.9, 54.7, 21.7, 13.5, 12.3; LRMS (EI) *m*/*z* (% relative intensity) 156 (M^+, 2), 141 (20), 97 (22) 79 (100).

1-ethyl-2-butyn-1-yl methyl carbonate[25]



According to procedure for the synthesis of propargylic carbonates, the product was obtained as a clear liquid after column chromatography (hexane/EtOAc: 30/1, v/v): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.15–5.12 (m, 1 H, C*H*), 3.80 (d, *J* = 3.0 Hz, 3 H, C*H*$_3$), 1.86–1.83 (m, 3 H, C*H*$_3$), 1.83–1.78 (m, 2 H, C*H*$_2$), 1.02 (td, *J* = 7.5, 3.0 Hz, 3 H, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 155.0, 82.6, 75.8, 69.7, 54.6, 28.2, 9.1, 3.4; LRMS (EI) *m*/*z* (% relative intensity) 156 (M^+, 7), 127 (59), 97 (94), 77 (80), 68 (100).

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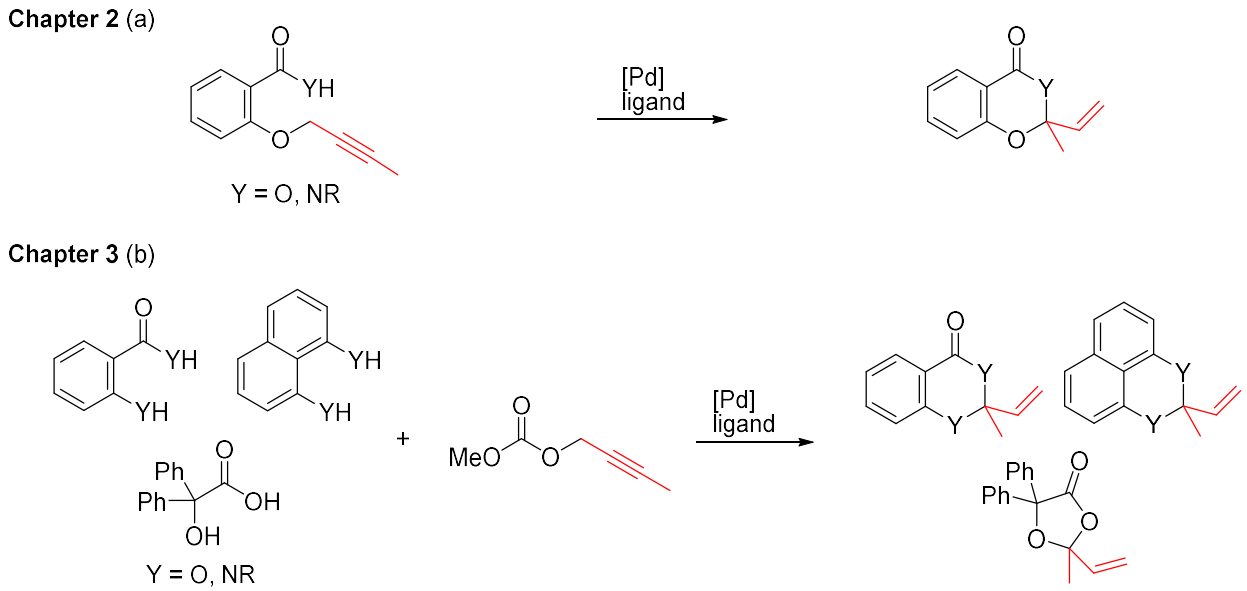
4. Conclusion

In this thesis, the author developed palladium-catalyzed cyclizations to synthesize novel vinyl-substituted heterocycles using propargylic compounds.

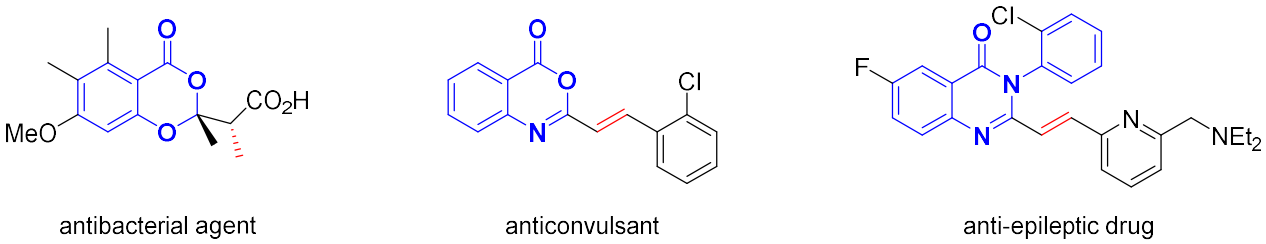
In Chapter 2, the author found a novel cyclization pattern with alkynoic acids. Then, the intramolecular cyclization was applied for salicylic acid or salicylamide derivatives to produce vinyl-dioxanone derivatives bearing a fully substituted allylic carbon, which has not been synthesized before. The mechanistic studies indicate the cleavage of propargylic C-O bond by palladium catalyst proceed as initial step in this cyclization (**Scheme 1a**).

In Chapter 3, the author developed an intermolecular cyclization of readily accessible starting materials, salicylic acid and propargylic carbonate derivatives, based on chapter 2. This annulation can be applied for not only salicylic acids, but also various bis-nucleophiles, such as 1,8-dihydroxy or 1,8-diamino-naphthalenes derivatives and benzylic acid (**Scheme 1b**).

In conclusion, the author established palladium-catalyzed synthetic methodology for vinyl-substituted heterocycles using propargylic compounds. These cyclizations could be applied for conversion of molecules with salicylic acid skeleton[1] or protection of salicylic acid moiety in total synthesis[2]. The author hope that these studies will contribute to organic synthetic, transition-metal or heterocyclic chemistries. In addition to that, novel 48 vinyl-substituted heterocycles were synthesized from these synthetic methods in this research. These similar structures have been found in various heterocycles with biological or physiological activities[3] (**figure 1**), novel vinyl-substituted heterocycles are expected to be promising compounds for medicinal and agricultural chemistries. Moreover, vinyl group can be transformed into various functional groups, hence the heterocycles would be also used as synthetic intermediates for total synthesis and monomers for functional polymers[4] (**figure 2**).

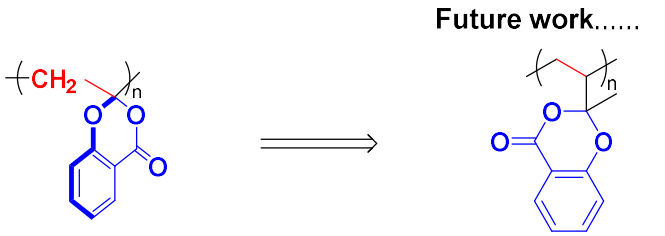


Scheme 1. Summary of these studies



antibacterial agent anticonvulsant anti-epileptic drug

Figure 1. Vinyl dioxanone analogues with biological and biological activities



polymer material[1] expected polymer

Figure 2. Applications as a monomer of polymeric material (Future work)

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5. List of Publications

1. Palladium-Catalyzed Cyclization of Alkynoic Acids To Form Vinyl Dioxanones Bearing a Quaternary Allylic Carbon
(パラジウム触媒を用いたアルキン酸の分子内環化反応による第四級アリル炭素を有するビニルジオキサノン誘導体の合成)
Yohei Ogiwara, Kazuya Sato, and Norio Sakai
Organic Letters, Vol.19, Issue19, pp.5296-5299 (2017 年 9 月)
DOI: 10.1021/acs.orglett.7b02572

2. Construction of *N*-Heterocyclic Systems Containing a Fully Substituted Allylic Carbon by Palladium/Phosphine Catalysis
(パラジウム/ホスフィン触媒系による全置換アリル炭素を有する含窒素複素環骨格の構築)
Yohei Ogiwara, Yui Suzuki, Kazuya Sato, and Norio Sakai
Organic Letters, Vol.20, Issue21, pp.6965-6969 (2018 年 10 月)
DOI: 10.1021/acs.orglett.8b03127

3. Palladium-Catalyzed [5 + 1] Annulation of Salicylic Acid Derivatives and Propargylic Carbonates
(パラジウム触媒を用いたサリチル酸誘導体と炭酸プロパルギルエステルの[5 + 1]環化反応)
Kazuya Sato, Yohei Ogiwara, and Norio Sakai
Bulletin of the Chemical Society of Japan, Vol.93, pp.1595-1602 (2020 年 8 月)
DOI: 10.1246/bcsj.20200199

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