Regular Article

Palladium-Catalyzed Double C–H Functionalization of Arenes at the Positions *ortho* and *meta* to Their Directing Group: Concise Synthesis of Benzocyclobutenes

Takeshi Nanjo, Chihiro Tsukano, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University; 46–29 Yoshida-Shimo-Adachi, Sakyo-ku, Kyoto 606–8501, Japan.

Received May 31, 2016; accepted June 29, 2016

The synthesis of benzocyclobutenes from simple arenes bearing a directing group was investigated *via* the palladium-catalyzed cyclization of norbornene derivatives. This approach allowed for the facile construction of benzocyclobutenes along with the double functionalization of the C–H bonds at the positions *ortho* and *meta* to the directing group. This result shows that the key palladacyclopentene intermediate in the Catellani reaction can be prepared by the directed double *ortho* C–H activation of the substrate. The results of this study also revealed that the combination of an *N*-protected amino acid with benzoquinone (BQ) was effective for this transformation.

Key words C–H functionalization; benzocyclobutene; palladium; directing group; double functionalization

The functionalization of aromatic rings has been widely investigated as a fundamental transformation for over a century. In particular, the simultaneous functionalization of two C–H bonds at adjacent positions on an aromatic ring is a direct and effective approach for the synthesis of multi-substituted arenes. Two major routes have been developed for the multiple functionalization of arenes in this way, including (i) the reaction of benzyne intermediates[1–4] and (ii) the norbornene-mediated *ortho* C–H functionalization of arenes.[5–7] Benzyne is a highly reactive species because of its strained structure, making it a useful intermediate for the transformation of aromatic rings through cycloaddition and multicomponent reactions.[1–4] Regarding the *ortho* C–H functionalization of arenes, various norbornene-mediated strategies have been developed for the *ipso* and *ortho* functionalization of aryl halides using palladium catalysts, including those reported by Catellani *et al.*,[8,9] Lautens and colleagues,[10–12] Malacria and colleagues,[13] Dong Z. and Dong G.,[14] Liang and colleagues,[15] Ritter and colleagues[16] and Zhou and colleagues.[17] Although these strategies can be applied to various transformations involving aromatic rings by simply changing the reagents, they need at least one reactive substituent such as a halogen at the appropriate position of the aromatic ring to achieve the desired transformation. The norbornene-mediated C–H functionalization of arenes has been extended to the direct functionalization of indoles[18,19] and the *meta*-selective C–H functionalization of arenes and heteroarenes.[20–24] However, only one functional group can be introduced at the *meta* position using these reactions, thus the development of a more efficient approach is still highly desired.

The metal-catalyzed double C–H functionalization of arenes has recently attracted considerable interest from numerous researchers. For example, the research groups of Miura and colleagues and Jiao and colleagues reported the rhodium-catalyzed double C–H functionalization of arenes bearing a directing group at the positions *ortho* and *meta* to the directing group.[25–29] These methods can also be applied to the construction of benzene and indole rings fused to another arene ring system. Furthermore, Hiyama and colleagues developed a dehydrogenative carbon–carbon bond forming reaction involving *ortho* and *meta* C–H functionalization steps using an alkynyloxy moiety as a directing group. It is noteworthy that the alkynyloxy moiety works as a hydrogen acceptor in this case, thereby avoiding the need to add an oxidant and base to the reaction.[30]

During the course of our recent studies,[31] we became interested in the way in which norbornene facilitates the *ortho* functionalization of aryl halides (Chart 1). According to the mechanism reported by Catellani, this reaction proceeds by the oxidative addition of an aryl halide to palladium(0) (Pd(0)) to give an arylpalladium intermediate (Chart 1a). This intermediate would then react with norbornene to form a palladacycle intermediate *via* the activation of the *ortho* C–H bond. Given that the directed *ortho* C–H activation step in this mechanism occurs in the presence of a Pd(II) catalyst, we envisaged that the norbornene-mediated *meta* C–H activation of a benzene ring bearing a directing group would provide the same palladacycle (Chart 1b). Yu and colleagues recently reported the formation of benzocyclobutene during the course of their work towards the development of a new *meta* C–H functionalization strategy based on the ideas discussed above.[21,22] However, they only investigated this reaction using a specific substrate for their double functionalization, leaving the scope of this reaction unexplored. Herein, we report the palladium-catalyzed, norbornene-mediated double C–H functionalization of arenes bearing a directing group at the positions *ortho* and *meta* to the directing group. Notably, this strategy provides a direct and concise approach for a synthesis of benzocyclobutene,[32] which is a useful intermediate for the preparation of complicated aromatic compounds. We have also investigated the scope and limitations of this reaction in detail.

The initial reaction of the *O*-methyloxime of tetralone **1a**[33] with norbornene (**2a**) in the presence of $Pd(OAc)_2$ (10 mol%) in *N*,*N*-dimethylformamide (DMF) at 100°C gave a trace amount of the desired benzocyclobutene **3aa** (Table 1, entry 1). We subsequently screened a variety of different

* To whom correspondence should be addressed. e-mail: takemoto@pharm.kyoto-u.ac.jp

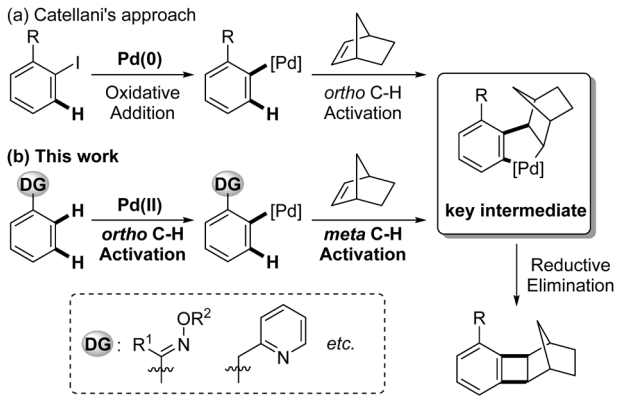
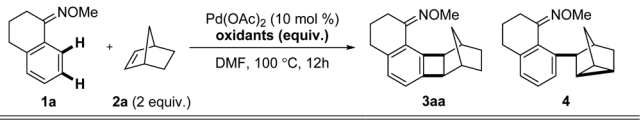


Chart 1. (a) Catellani Reaction and (b) Our Strategy for the Double Functionalization of the *ortho* and *meta* C–H Bonds of a Benzene Ring Bearing a Directing Group

Table 1. Screening of Various Oxidants



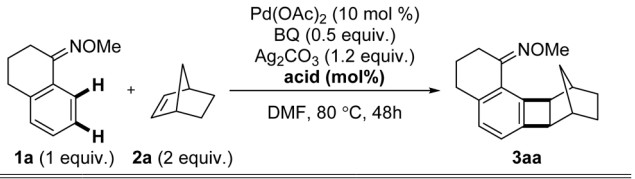
Entry	Oxidant (eq)	Conversion (**3aa**:**1a**)[a]
1	None	Trace
2	$PhI(OAc)_2$ (2)	Complex mixture[b]
3	NFSI (2)	Complex mixture
4	$Cu(OAc)_2$ (1), O_2	5:95
5	$K_2S_2O_8$ (2)	N.D.[c]
6	AgOAc (8)	Trace
7	Ag_2O (4)	Trace
8	Ag_2CO_3 (4)	7:93
9	Ag_2CO_3 (4), BQ (0.5)	10:90

a) The ratio was determined by ^{1}H-NMR analysis of the crude reaction mixture. *b*) The starting material was also recovered in approximately 70% yield. *c*) Compound **4** was obtained (**4**:**1a**=33:67). NFSI=*N*-fluorobis(phenylsulfonyl)amine, BQ=1,4-benzoquinone, N.D.=Not detected.

oxidants against the reaction to affect the oxidation of the palladium catalyst. Although the addition of $PhI(OAc)_2$ or *N*-fluorobis(phenylsulfonyl)amine (NFSI) resulted in a complex mixture (Table 1, entries 2, 3), a combination of $Cu(OAc)_2$ and oxygen gave a small amount of the desired product **3aa** (Table 1, entry 4). Interestingly, the use of $K_2S_2O_8$ as an oxidant resulted in the formation of compound **4** (Table 1, entry 5). Pleasingly, we found that the addition of a silver salt was effective for this conversion, with Ag_2CO_3 affording the best conversion of all of the silver salts tested in the current study (Table 1, entries 6–9). It is noteworthy that the addition of benzoquinone (BQ) led to an increase in the conversion of **1a**, although the yield of **3aa** was still low (**3aa**:**1a**=10:90) (Table 1, entry 9).

We subsequently investigated the addition of various acids to this reaction at 80°C to improve the yield of the desired product **3aa** (Table 2). The addition of a carboxylic acid such as AcOH or trifluoroacetic acid (TFA) led to an increase in the production-ratio of **3aa**, whereas the addition of pivalic acid had no discernible impact on the conversion (Table 2, entries 1–4). Further screening revealed that the addition of a catalytic amount of *N*-9-fluorenylmethoxycarbonyl (Fmoc)-protected amino acid (20 mol%) led to a dramatic increase in the conversion of **1a** to the desired product **3aa**. This result was consistent with the results reported by Yu for a related reaction,[34] with valine providing the best result of all of the amino acids tested in the current study (Table 2, entries 5–9). The nature of the protecting group on the nitrogen atom of the amino acid was also found to be very important. Although the use of a formyl or acetyl (Ac) group did not lead to an improvement in the conversion of **1a** (Table 2, entries 10, 11), the use of a carbamate protecting group such as a *t*-butyloxycarbonyl (Boc), methoxycarbonyl or (−)-menthyloxycarbonyl (Men) group led to an increase in the conversion (Table 2, entries 12–14). In contrast to previous reports from the literature,[34] the use of a smaller charge of (−)-Men-Val-OH (5 mol%) led to an increase in the conversion of **1a** (Table 2, entry 15). After fine tuning the conditions for this reaction, we established that the use of 2.0 eq of Ag_2CO_3 with 1.5 eq of BQ led to the complete conversion of **1a**, with benzocyclobutene **3aa** being isolated in 84% yield after silica gel column chromatography (Table 2, entry 16).

Table 2. Screening of Several Acid-Additives



Entry	Acid (mol%)	Conversion (**3aa**:**1a**)[a]
1	None	8:92
2	PivOH (100)	7:93
3	TFA (100)	11:89
4	AcOH (100)	16:84
5	Fmoc-Ile-OH (20)	49:51
6	Fmoc-Leu-OH (20)	42:58
7	Fmoc-Ala-OH (20)	34:66
8	Fmoc-Phe-OH (20)	42:58
9	Fmoc-Val-OH (20)	50:50
10	Formyl-Val-OH (20)	17:83
11	Ac-Val-OH (20)	6:94
12	Boc-Val-OH (20)	43:57
13	MeO_2C-Val-OH (20)	51:49
14	(−)-Men-Val-OH (20)	58:42
15	(−)-Men-Val-OH (5)	75:25
16[b]	(−)-Men-Val-OH (5)	>98:2 (84%)[c]

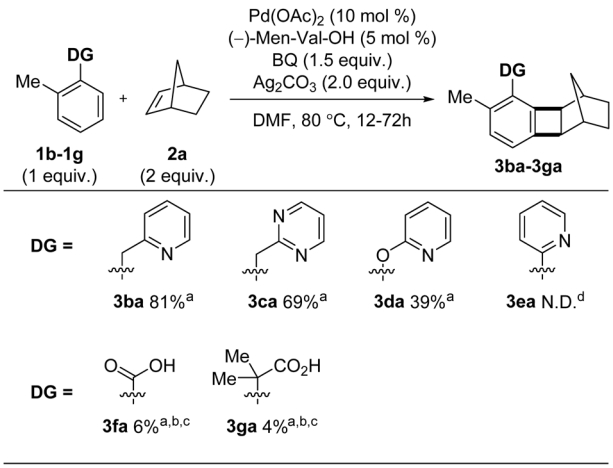
a) The ratio was determined by ^{1}H-NMR analysis of the crude reaction mixture. *b*) 1.5 eq of BQ and 2 eq of Ag_2CO_3 were used in this reaction over a reaction time of 96 h. *c*) Isolated yield. (−)-Men-=(−)-menthyl-OC(O)-.

With the optimal conditions in hand, we screened several other directing groups against this transformation (Chart 2). The reaction of 2-(pyridylmethyl)toluene (**1b**)[35,36] under the optimal conditions gave benzocyclobutene **3ba** in 81% yield. The 2-pyrimidylmethyl and pyridyl-2-oxy bearing substrates **1c** and **d** also performed well in this transformation, affording the corresponding cyclobutene products **3ca** and **da** in lower yields. In these reactions, the nitrogen atoms in the aromatic rings behaved as directing groups for the C–H activation. In contrast, the reaction of 2-(2-pyridyl)toluene (**1e**) did not afford any of the corresponding benzocyclobutene **3ea**, with **1e** being recovered unchanged. These results therefore indicate that the location of the directing groups is critical to the stability and reactivity of the palladium complex generated by

the *ortho* C–H activation step. We also investigated the use of a carboxylic acid as a directing group. Notably, *o*-toluic acid (**1f**) and *o*-tolylacetic acid (**1g**) afforded the corresponding benzocyclobutenes **3fa** and **ga**, respectively, albeit in very low yields with the starting materials being recovered largely unchanged. These results can be rationalized in terms of the differences in the coordinative affinities of the different directing groups to the palladium catalyst (*i.e.*, oxime and pyridine *vs.* carboxylic acid).

Having identified the most applicable directing groups for this reaction, we subsequently investigated the scope of the arene substrate under the optimal conditions (Table 3). The reactions of *O*-methyloximes **1h**[33] and **i**,[37] which were derived from acetophenone and propiophenone, gave the desired products **3ha** and **ia** in moderate yields, respectively (Table 3, entries 1, 2). These reactions also afforded the corresponding symmetrical products **4ha** and **ia**, which were generated by the reactions of **3ha** and **ia**. The yield of **3ja** was low because of the unreactive nature of the (*Z*)-isomer of the oxime substrate **1j** (*ca.* 50%), which did not isomerize under the reaction conditions to give the more reactive (*E*)-isomer (Table 3, entry 3). When *O*-benzyloxime was used instead of *O*-methyloxime, the desired product **3ka** was obtained in 63% yield (Table 3, entry 4). The reaction of the 3-methylacetophenone oxime **1l** gave the desired product **3la** in 35% yield (Table 3, entry 5). We subsequently investigated the electronic effects of the arene substrate using various 2-substituted 1-(2-pyridylmethyl)benzenes (**1m**–**p**). The reaction of substrate **1m** bearing a methoxy group on its benzene ring proceeded smoothly to give benzocyclobutene **3ma** in 72% yield (Table 3, entry 6). Compared with **1b** and **m**, the reactions of **1n** and **o** bearing electron-withdrawing groups on their benzene ring resulted in relatively lower yields (Table 3, entries 7, 8). Notably, the reaction of the simple (2-pyridylmethyl)benzene substrate **1p** gave a mixture of **3pa** and **4pa** in a combined yield of 68% (Table 3, entry 9). The reaction of substrate **1q** bearing a methyl group at its 3-position under the optimized conditions led to a decrease in the yield to 49%, presumably because the product can react with norbornene (**2a**) (Table 3, entry 10). The introduction of a methyl group at the 4-position of the benzene ring of the substrate also had an adverse impact of the reaction, most likely because of steric hindrance in the key palladacycle (**3ra**) (Table 3, entry 11).

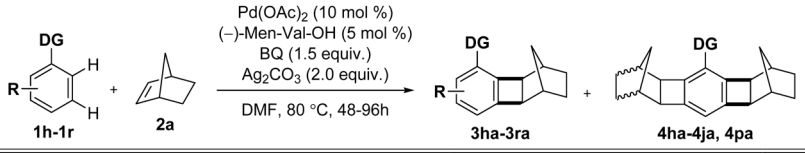
We then proceeded to investigate the scope of the norbornene (Chart 3). Norbornenes **2b** and **c** bearing a cyano and an acetal group gave the corresponding benzocyclobutenes **3ab** and **ac** in 60 and 77% yields, respectively. Although the inclu-

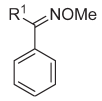
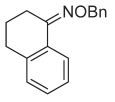
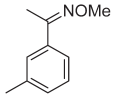
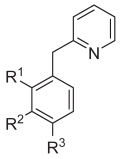


[a]Isolated yield. [b]NMR yield. [c]The reaction was performed in the absence of (−)-Men-Val-OH and BQ. [d]Starting material **1e** was recovered. N.D.=Not detected.

Chart 2. Screening of Different Directing Groups

Table 3. Scope of Arenes

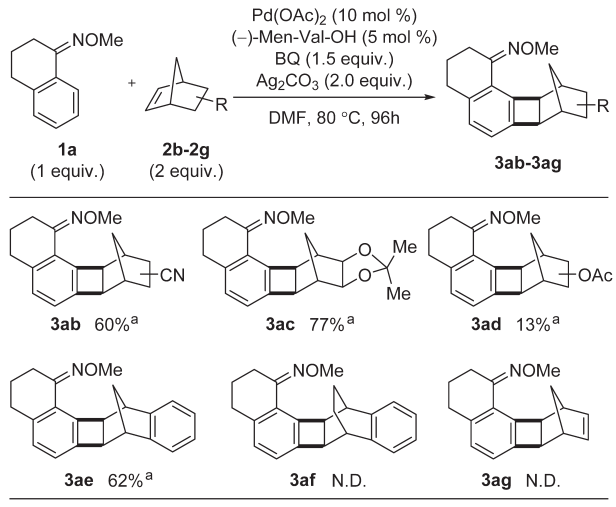


Entry	Arene		Total yield (%)[a)]	Ratio (**3xa**:**4xa**)
1		**1h** (R^1=Me)	38	20:18
2		**1i** (R^1=Et)	39	22:17
3		**1j** (R^1=^{i}Pr)	22	11:11
4		**1k**	63	NA[b)]
5		**1l**	35	NA[b)]
6		**1m** (R^1=OMe, R^2=R^3=H)	72	NA[b)]
7		**1n** (R^1=F, R^2=R^3=H)	62	NA[b)]
8		**1o** (R^1=CO_2Me, R^2=R^3=H)	43	NA[b)]
9		**1p** (R^1=H, R^2=R^3=H)	68	13:55
10		**1q** (R^1=H, R^2=Me, R^3=H)	49	NA[b)]
11		**1r** (R^1=Me, R^2=H, R^3=Me)	15	NA[b)]

a) Isolated yield. *b*) Compound **3xa** was only produced. NA=Not applicable.

sion of a cyano group had no discernible impact on the yield of the product **3ab**, the presence of an acetyl group accelerated the formation of palladium black, leading to a decrease in the yield of **3ad**. The reaction of norbornene analogue **2e** fused with a benzene ring provided benzocyclobutene **3ae** in 62% yield. The use of bicyclo[2.2.2]octadiene **2f** failed to afford any of the desired product **3af**, indicating that the bicyclo[2.2.1]nonene skeleton would be essential for this transformation. Additionally, norbornadiene **2g** did not afford benzocyclobutene **3ag**, probably because of the inhibition of the catalytic cycle by the coordination to the palladium catalyst.

To gain an insight into the mechanism of this reaction, we conducted two kinetic isotope effect (KIE) experiments (Chart 4). The reaction of the *ortho*-deuterated substrate **1e**-d_3[38] under the optimized conditions gave a KIE value 1.4, which was estimated from a ratio of the products (a). In contrast, the *meta*-deuterated substrate **1e**-d_6 showed a KIE value of 2.3 (b). These results indicated that the cleavage of the C–H bond at the *meta* position required a larger activation energy rather than that of the *ortho* position.



[a]Isolated yield. N.D.=Not detected.

Chart 3. Scope of the Norbornene

Based on the results of the KIE experiments, we have proposed a plausible mechanism for this reaction, which is shown in Chart 5. The directing group of substrate **1** and (−)-Men-Val-OH would initially coordinate to the divalent Pd center, resulting in the cleavage of the *ortho* C–H bond along with the formation of a C–Pd bond. The results of our screening experiments showed that the protected amino acid ligand was essential for this step.[34] The subsequent insertion of norbornene (**2**) into the resulting intermediate, followed by the *meta* C–H activation of the benzene ring would afford the key palladacycle from Catellani's *ortho* C–H functionalization mechanism. Reductive elimination from the palladacycle, which is assumed to be a rate-determining step in this transformation, would give the desired benzocyclobutene product **3** along with a Pd(0) species, which would be re-oxidized to Pd(II) by the oxidant. BQ improved the yield of the product, but was not essential for the catalytic reaction.[39] In contrast, the presence of Ag_2CO_3 was critical to the success of this reaction. Taken together, these results indicate that BQ simply enhanced the rate of the reductive elimination, with Ag_2CO_3 acting as an oxidant.

In summary, we have conducted an extensive investigation of the palladium-catalyzed double C–H functionalization of arenes bearing a directing group, with the functionalization taking place at the positions *ortho* and *meta* to the directing groups. Notably, this transformation allows for the facile construction of benzocyclobutenes from simple arenes. This reaction presumably proceeds *via* the key palladacycle intermediate formed in Catellani's reaction, and we are currently investigating the development of this reaction as a general method for the double C–H functionalization of arenes.

Experimental

General Experimental Details Unless otherwise noted, all the reagents were purchased from chemical companies and used without further purification. Analytical TLC was performed with Merck Silica gel 60. Silica gel column chromatography was performed with Kanto silica gel 60 (particle size, 63–210 μm) and Fuji silysia Chromatorex BW-300. All melting points (mp) were determined on YANAGIMOTO

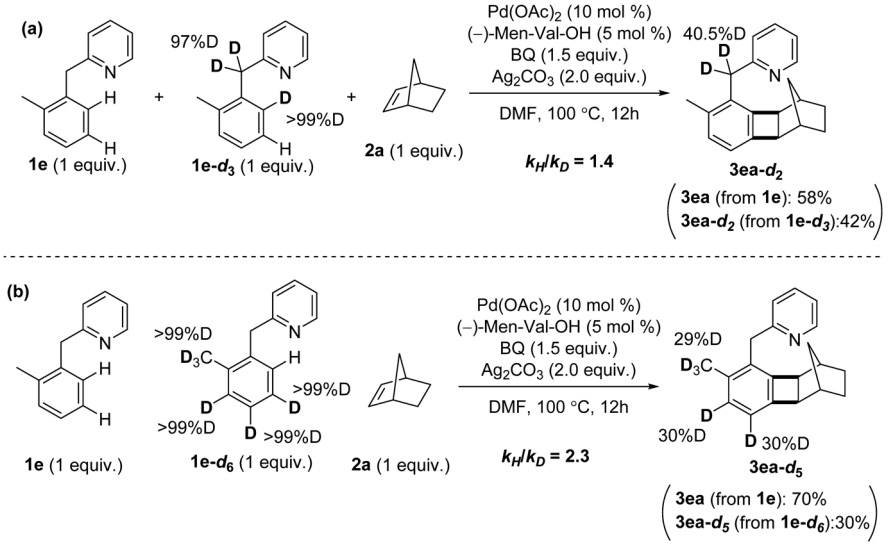


Chart 4. KIE Study

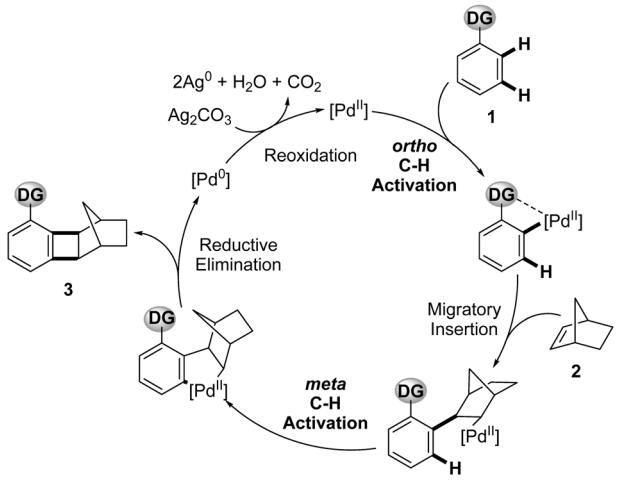


Chart 5. Plausible Mechanism

micro melting point apparatus. ^{1}H-NMR spectra were recorded on a JEOL JNM-LA 500 at 500 MHz. Chemical shifts are reported relative to Me_4Si (δ 0.00) in $CDCl_3$. Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); sep (septet); m (multiplet); br (broad). ^{13}C-NMR spectra were recorded on a JEOL JNM-LA 500 at 126 MHz. Chemical shifts are reported relative to $CDCl_3$ (δ 77.0). Infrared spectra were recorded on a FT/IR-4100 (JASCO). Low and high resolution mass spectra were recorded on JEOL MS700 mass spectrometer for FAB-MS, and Shimadzu LCMS-IT-TOF for ESI-MS.

Procedure for the Synthesis of Benzocyclobutenes

General Procedure

In a sealed tube, to a mixture of substrate (0.200 mmol, 1.0 equiv.), norbornene derivative (0.400 mmol, 2.0 eq) in DMF (2 mL) were added benzoquinone (32.4 mg, 0.300 mmol, 1.5 eq), Ag_2CO_3 (110 mg, 0.4 mmol, 2.0 eq), (−)-Men-Val-OH (3.0 mg, 0.0100 mmol, 0.05 eq) and $Pd(OAc)_2$ (4.5 mg, 0.0200 mmol, 0.1 eq). The tube was filled with argon and the mixture was heated to 80°C. After stirring for 48–96 h, the mixture was cooled to room temperature, diluted with EtOAc and filtrated. The solution was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane–EtOAc or hexane–CH_2Cl_2) to give the corresponding benzocyclobutene.

3,4,6b,7,8,9,10,10a-Octahydro-7,10-methanobenzo[*a*]-biphenylen-1(2*H*)-one *O*-Methyl Oxime (**3aa**)

According to the general procedure, the reaction gave the product in 84% yield as a white solid: mp 89.9–91.4°C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.96 (d, 1H, J=7.5 Hz), 6.84 (d, 1H, J=7.5 Hz), 3.98 (s, 3H), 3.26 (d, 1H, J=3.0 Hz), 3.07 (d, 1H, J=3.0 Hz), 2.72–2.67 (m, 4H), 2.55 (s, 1H), 2.24 (s, 1H), 1.88–1.74 (m, 2H), 1.63–1.54 (m, 2H), 1.22–1.15 (m, 2H), 0.92 (d, 1H, J=10.0 Hz), 0.85 (d, 1H, J=10.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 153.9, 144.5, 143.9, 138.1, 127.6, 125.6, 122.0, 62.0, 52.3, 49.8, 36.6, 35.1, 32.0, 30.3, 27.9, 27.8, 24.0, 21.8; IR (attenuated total reflectance (ATR)) 2937, 1617, 1417, 1050 cm^{-1}; high resolution (HR)-MS (FAB$^+$) Calcd for $C_{18}H_{22}NO$: ([M+H]$^+$) 268.1701: Found 268.1694.

2-((6-Methyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylen-5-yl)methyl)pyridine (**3ba**)

According to the general procedure, the reaction gave the product in 81% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.54 (d, 1H, J=4.9 Hz), 7.51 (ddd, 1H, J_1=J_2=7.8 Hz, J_3=1.7 Hz), 7.11 (dd, 1H, J_1=J_2=7.5 Hz), 7.03 (d, 1H, J=7.8 Hz), 6.88 (d, 1H, J=7.8 Hz), 6.81 (d, 1H, J=7.5 Hz), 4.11 (d, 1H, J=16.1 Hz), 4.07 (d, 1H, J=16.1 Hz), 3.07 (d, 1H, J=3.8 Hz), 3.00 (d, 1H, J=3.8 Hz), 2.23 (d, 1H, J=3.2 Hz), 2.19 (s, 3H), 1.95 (d, 1H, J=3.2 Hz), 1.58–1.46 (m, 2H), 1.16–1.04 (m, 2H), 0.90 (d, 1H, J=10.1 Hz), 0.88 (d, 1H, J=10.1 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 160.6, 149.1, 145.9, 143.7, 136.3, 135.4, 131.7, 129.5, 122.3, 121.0, 120.3, 49.4, 48.9, 37.6, 36.5, 36.1, 31.9, 27.8, 27.8, 19.8; IR (ATR) 2946, 1588, 1472, 1434 cm^{-1}; HR-MS (electrospray ionization (ESI)$^+$) Calcd for $C_{20}H_{22}N$: ([M+H]$^+$) 276.1752: Found 267.1754.

2-((6-Methyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylen-5-yl)methyl)pyrimidine (**3ca**)

According to the general procedure, the reaction gave the product in 69% yield as a colorless: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.65 (d, 2H, J=4.9 Hz), 7.09 (t, 1H, J=4.9 Hz), 7.03 (d, 1H, J=7.2 Hz), 6.79 (d, 1H, J=7.2 Hz), 4.24 (d, 1H, J=15.4 Hz), 4.20 (d, 1H, J=15.4 Hz), 3.04 (d, 1H, J=4.0 Hz), 2.95 (d, 1H, J=4.0 Hz), 2.31 (s, 3H), 2.20 (d, 1H, J=2.9 Hz), 2.00 (d, 1H, J=2.9 Hz), 1.56–1.45 (m, 2H), 1.14–1.03 (m, 2H), 0.88–0.84 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 170.0, 157.1, 145.7, 143.5, 135.2, 131.2, 129.3, 120.3, 118.4, 49.4, 48.9, 39.2, 36.4, 36.0, 31.9, 27.8, 27.7, 20.1; IR (ATR) 2946, 1559, 1417 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{19}H_{21}N_2$: ([M+H]$^+$) 277.1705: Found 277.1700.

2-((6-Methyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylen-5-yl)oxy)pyridine (**3da**)

According to the general procedure, the reaction gave the product in 39% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.22–8.21 (m, 1H), 7.68–7.65 (m, 1H), 7.12 (d, 1H, J=7.5 Hz), 6.99–6.97 (m, 1H), 6.86–6.85 (m, 1H), 6.76 (d, 1H, J=7.5 Hz), 3.09 (d, 1H, J=3.8 Hz), 2.88 (d, 1H, J=3.8 Hz), 2.23–2.21 (m, 4H), 1.78–1.77 (m, 1H), 1.54–1.41 (m, 2H), 1.12–1.07 (m, 1H), 0.98–0.90 (m, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 163.3, 147.9, 146.2, 145.6, 139.2, 135.6, 130.7, 128.3, 118.8, 118.2, 110.9, 49.8, 48.9, 36.4, 35.7, 32.0, 27.7, 27.5, 16.6; IR (ATR) 2948, 1586, 1464, 1426, 1243 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{19}H_{20}NO$: ([M+H]$^+$) 278.1545: Found 278.1537.

1-(1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylen-5-yl)ethan-1-one *O*-Methyl Oxime (**3ha**)

According to the general procedure, the reaction gave the product in 20% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.49 (d, 1H, J=8.0 Hz), 7.20 (dd, 1H, J_1=8.0 Hz, J_2=7.3 Hz), 6.96 (d, 1H, J=7.3 Hz), 3.99 (s, 3H), 3.31 (d, 1H, J=4.0 Hz), 3.16 (d, 1H, J=4.0 Hz), 2.41 (d, 1H, J=2.8 Hz), 2.28 (d, 1H, J=2.8 Hz), 2.20 (s, 3H), 1.64–1.56 (m, 2H), 1.25–1.18 (m, 2H), 0.96 (d, 1H, J=10.3 Hz), 0.88 (d, 1H, J=10.3 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 153.5, 146.9, 144.2, 130.8, 127.7, 124.1, 122.2, 61.9, 52.0, 50.1, 36.7, 36.4, 32.0, 27.84, 27.81, 12.7; IR (ATR) 2951, 1472, 1057 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{16}H_{20}NO$: ([M+H]$^+$) 242.1545: Found 242.1544.

1,2,3,4,4a,5b,6,7,8,9,9a,10b-Dodecahydro-1,4:6,9-dimethanobenzo[3,4]cyclobuta[1,2-*b*]biphenylen-5-yl)ethan-1-one *O*-Methyl Oxime (**4ha**)

According to the general procedure, the reaction gave the mixture of the products in 18% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.62–6.60 (m, 1H), 3.99–3.98 (m, 3H), 3.24–3.19 (m, 2H), 3.05 (m, 2H), 2.41 (s, 0.8H), 2.35 (s, 1.2H), 2.23–2.19 (m, 5H), 1.59–1.56, (m, 4H), 1.19–1.14 (m,

4H), 0.94–0.85 (m, 2.8H), 0.81 (d, 1.2H, J=10.3 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 153.0, 152.9, 145.8, 142.4, 142.3, 125.7, 125.5, 116.2, 116.1, 61.9, 51.8, 51.6, 49.7, 49.5, 36.9, 36.8, 36.6, 36.3, 31.9, 27.9, 27.8, 12.9, 12.8 (some peaks were missing due to overlapping); IR (ATR) 2945, 1453, 1052 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{23}H_{28}NO$: ([M+H]$^+$) 334.2171: Found 334.2166.

1-(1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylen-5-yl)propan-1-one *O*-Methyl Oxime (**3ia**)

According to the general procedure, the reaction gave the product in 22% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.41 (d, 1H, J=8.0 Hz), 7.17 (dd, 1H, J_1=8.0 Hz, J_2=7.2 Hz), 6.93 (d, 1H, J=7.2 Hz), 3.94 (s, 3H), 3.25 (d, 1H, J=3.7 Hz), 3.11 (d, 1H, J=3.7 Hz), 2.74 (dq, 1H, J_1=12.9 Hz, J_2=7.8 Hz), 2.61 (dq, 1H, J_1=12.9 Hz, J_2=7.8 Hz), 2.37 (d, 1H, J=2.8 Hz), 2.24 (d, 1H, J=2.8 Hz), 1.59–1.53 (m, 2H), 1.18–1.14 (m, 2H), 1.08 (t, 3H, J=7.8 Hz), 0.93 (d, 1H, J=10.0 Hz), 0.85 (d, 1H, J=10.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 158.8, 147.0, 144.3, 129.9, 127.7, 124.7, 122.1, 61.9, 51.9, 50.0, 36.7, 36.4, 32.0, 27.8, 19.9, 11.1 (one peak was missing due to overlapping.); IR (ATR) 2951, 1463, 1053 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{17}H_{22}NO$: ([M+H]$^+$) 256.1701: Found 256.1699.

1,2,3,4,4a,5b,6,7,8,9,9a,10b-Dodecahydro-1,4:6,9-dimethanobenzo[3,4]cyclobuta[1,2-*b*]biphenylen-5-yl)propan-1-one *O*-Methyl Oxime (**4ia**)

According to the general procedure, the reaction gave the mixture of the products in 17% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.63–6.60 (m, 1H), 3.97–3.96 (m, 3H), 3.22–3.17 (m, 2H), 3.04 (m, 2H), 2.83–2.76 (m, 0.6H), 2.71–2.66 (m, 0.8H), 2.60–2.53 (m, 0.6H), 2.40 (s, 0.8H), 2.34 (s, 1.2H), 2.23–2.21 (m, 2H), 1.62–1.51 (m, 4H), 1.18–1.14 (m, 4H), 1.10 (t, 3H, J=7.6 Hz), 0.94–0.87 (m, 2.8H), 0.84 (d, 1.2H, J=10.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 158.3, 158.1, 145.9, 145.8, 142.6, 142.5, 124.89, 124.85, 116.1, 116.0, 61.9, 51.6, 51.5, 49.6, 49.5, 36.84, 36.79, 36.7, 36.4, 31.9, 27.9, 20.2, 20.0, 11.21, 11.19 (some peaks were missing due to overlapping); IR (ATR) 2951, 1453, 1051 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{24}H_{30}NO$: ([M+H]$^+$) 348.2327: Found 348.2321.

1-(1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylen-5-yl)-2-methylpropan-1-one *O*-Methyl Oxime (**3ja**)

According to the general procedure, the reaction gave the product in 11% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.24 (d, 1H, J=7.8 Hz), 7.18 (dd, 1H, J_1=7.8 Hz, J_2=7.2 Hz), 6.96 (d, 1H, J=7.2 Hz), 3.93 (s, 3H), 3.38 (sep, 1H, J=7.2 Hz), 3.25 (d, 1H, J=3.8 Hz), 3.14 (d, 1H, J=3.8 Hz), 2.37 (s, 1H), 2.27 (s, 1H), 1.61–1.56 (m, 2H), 1.24 (d, 3H, J=7.2 Hz), 1.19 (d, 3H, J=7.2 Hz), 1.19–1.17 (m, 2H), 0.97 (d, 1H, J=10.3 Hz), 0.89 (d, 1H, J=10.3 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 162.4, 146.8, 144.7, 130.5, 127.3, 126.3, 121.9, 61.7, 51.3, 49.9, 36.6, 31.9, 28.9, 27.9, 27.8, 19.3, 19.2; IR (ATR) 2952, 1465, 1059 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{18}H_{24}NO$: ([M+H]$^+$) 270.1858: Found 270.1859.

1,2,3,4,4a,5b,6,7,8,9,9a,10b-Dodecahydro-1,4:6,9-dimethanobenzo[3,4]cyclobuta[1,2-*b*]biphenylen-5-yl)-2-methylpropan-1-one *O*-Methyl Oxime (**4ja**$_{meso}$)

According to the general procedure, the reaction gave the product in 4% yield as a white solid: mp 136.5–138.0°C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.62 (s, 1H), 3.93 (s, 3H), 3.23 (sep, 1H, 7.2 Hz), 3.13 (d, 2H, J=3.7 Hz), 3.02 (d, 2H, J=3.7 Hz), 2.37 (s, 2H), 2.22 (s, 2H), 1.58–1.57 (m, 4H), 1.25 (d, 6H, J=7.2 Hz), 1.16–1.15 (m, 4H), 0.94–0.89 (m, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 160.7, 145.6, 142.9, 126.0, 116.0, 61.8, 51.2, 49.3, 37.0, 36.7, 31.9, 30.0, 28.0, 27.9, 18.8; IR (ATR) 2947, 1454, 1326, 1043 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{25}H_{32}NO$: ([M+H]$^+$) 362.2484: Found 362.2480.

1,2,3,4,4a,5b,6,7,8,9,9a,10b-Dodecahydro-1,4:6,9-dimethanobenzo[3,4]cyclobuta[1,2-*b*]biphenylen-5-yl)-2-methylpropan-1-one *O*-Methyl Oxime (**4ja**$_{racemic}$)

According to the general procedure, the reaction gave the product in 7% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.60 (s, 1H), 3.92 (s, 3H), 3.26 (sep, 1H, 7.3 Hz), 3.20 (d, 2H, J=3.8 Hz), 3.04 (d, 2H, J=3.8 Hz), 2.26 (s, 2H), 2.20 (s, 2H), 1.61–1.50 (m, 4H), 1.28 (d, 3H, J=7.3 Hz), 1.19 (d, 3H, J=7.3 Hz), 1.17–1.13 (m, 4H), 0.89 (d, 2H, J=10.0 Hz), 0.81 (d, 2H, J=10.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 161.1, 145.7, 142.7, 125.6, 115.9, 61.8, 51.1, 49.4, 36.9, 36.4, 31.9, 29.7, 27.9, 19.0, 18.9; IR (ATR) 2948, 1454, 1327, 1040 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{25}H_{32}NO$: ([M+H]$^+$) 362.2484: Found 362.2483.

3,4,6b,7,8,9,10,10a-Octahydro-7,10-methanobenzo[*a*]-biphenylen-1(2*H*)-one *O*-Benzyl Oxime (**3ka**)

According to the general procedure, the reaction gave the product in 63% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$, 50°C) δ: 7.43 (d, 2H, J=8.0 Hz), 7.35 (dd, 2H, J_1=J_2=8.0 Hz), 7.29 (t, 1H, J=8.0 Hz), 6.95 (d, 1H, J=7.4 Hz), 6.83 (d, 1H, J=7.4 Hz), 5.20 (d, 1H, J=12.3 Hz), 5.16 (d, 1H, J=12.3 Hz), 3.16 (s, 1H), 3.05 (s, 1H), 2.74 (t, 2H, J=6.6 Hz), 2.69 (t, 2H, J=6.0 Hz), 2.32 (s, 1H), 2.22 (s, 1H), 1.87–1.74 (m, 2H), 1.56–1.54 (m, 2H), 1.17–1.13 (m, 2H), 0.87 (d, 1H, J=10.0 Hz), 0.79 (d, 1H, J=10.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$, 50°C) δ: 154.3, 144.4, 143.9, 138.6, 138.1, 128.5, 128.2, 127.6, 127.5, 125.6, 122.0, 76.2, 52.2, 49.8, 36.6, 35.0, 32.0, 30.3, 27.9, 27.8, 24.3, 21.8; IR (ATR) 2946, 1455, 910 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{24}H_{26}NO$: ([M+H]$^+$) 344.2014: Found 344.2009.

1-(7-Methyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylen-5-yl)ethan-1-one *O*-Methyl Oxime (**3la**)

According to the general procedure, the reaction gave the product in 35% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.33 (s, 1H), 6.80 (s, 1H), 3.99 (s, 3H), 3.25 (d, 1H, J=3.8 Hz), 3.12 (d, 1H, J=3.8 Hz), 2.36 (d, 1H, J=2.8 Hz), 2.33 (s, 3H), 2.25 (d, 1H, J=2.8 Hz), 2.19 (s, 3H), 1.61–1.56 (m, 2H), 1.20–1.16 (m, 2H), 0.94 (d, 1H, J=10.3 Hz), 0.88 (d, 1H, J=10.3 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 153.8, 146.9, 141.2, 137.4, 130.5, 124.6, 123.1, 61.9, 51.4, 49.8, 36.7, 36.5, 31.9, 27.83, 27.82, 22.0, 12.8; IR (ATR) 2869, 1602, 1053 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{17}H_{22}NO$: ([M+H]$^+$) 256.1701: Found 256.1702.

2-((6-Methoxy-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylen-5-yl)methyl)pyridine (**3ma**)

According to the general procedure, the reaction gave the product in 72% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.52 (d, 1H, J=4.9 Hz), 7.51 (dd, 1H, J_1=J_2=7.8 Hz), 7.08–7.06 (m, 1H), 7.02 (d, 1H, J=8.0 Hz), 6.84 (d, 1H, J=7.8 Hz), 6.74 (d, 1H, J=8.0 Hz), 4.09 (s, 2H), 3.75 (s, 3H), 3.02 (d, 1H, J=3.8 Hz), 2.92 (d, 1H, J=3.8 Hz), 2.19 (d, 1H, J=3.2 Hz), 1.90 (d, 1H, J=3.2 Hz), 1.55–1.43 (m, 2H), 1.13–1.01 (m, 2H), 0.86 (d, 1H, J=10.0 Hz), 0.82 (d, 1H, J=10.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 161.0, 157.0, 148.9, 146.6, 138.3, 136.1, 122.6, 122.5, 120.9, 120.8, 110.3, 55.7, 49.0, 48.7, 36.7, 36.0, 34.7, 31.9, 27.73, 27.66; IR (ATR) 2948, 1590, 1542, 1473, 1250 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{20}H_{22}NO$:

([M+H]$^+$) 292.1701: Found 292.1701.

2-((6-Fluoro-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylen-5-yl)methyl)pyridine (**3na**)

According to the general procedure, the reaction gave the product in 62% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.54 (d, 1H, J=4.9 Hz), 7.56 (ddd, 1H, J_1=J_2=7.8 Hz, J_3=1.7 Hz), 7.12–7.08 (m, 2H), 6.90 (dd, 1H, J_1=12.1, J_2=8.1 Hz), 6.82 (dd, 1H, J_1=7.7 J_2=4.0 Hz), 4.10 (s, 2H), 3.02 (d, 1H, J=4.0 Hz), 2.92 (d, 1H, J=4.0 Hz), 2.20 (d, 1H, J=3.0 Hz), 2.00 (d, 1H, J=3.0 Hz), 1.56–1.44 (m, 2H), 1.13–1.02 (m, 2H), 0.87 (d, 1H, J=10.0 Hz), 0.77 (d, 1H, J=10.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 160.6 (d, J=244.0 Hz), 159.8, 149.1, 146.7 (d, J=3.6 Hz), 141.4 (d, J=3.6 Hz), 136.4, 122.8, 121.7 (d, J=8.4 Hz), 121.4, 121.2, 114.7 (d, J=24.2 Hz), 48.9 (d, J=2.4 Hz), 48.8, 36.5, 36.0, 34.1 (d, J=2.4 Hz), 31.8, 27.62, 27.58; IR (ATR) 2949, 1590, 1471, 1434, 1231 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{19}H_{19}FN$: ([M+H]$^+$) 280.1502: Found 280.1501.

Methyl 5-(Pyridin-2-ylmethyl)-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylene-6-carboxylate (**3oa**)

According to the general procedure, the reaction gave the product in 43% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.54–8.52 (m, 1H), 7.88 (d, 1H, J=7.8 Hz), 7.50 (ddd, 1H, J_1=J_2=7.8 Hz, J_3=1.7 Hz), 7.09–7.06 (m, 1H), 6.97 (d, 1H, J=7.8 Hz), 6.91 (d, 1H, J=7.8 Hz), 4.47 (d, 1H, J=16.0 Hz), 4.44 (d, 1H, J=16.0 Hz), 3.75 (s, 3H), 3.11 (d, 1H, J=3.7 Hz), 3.02 (d, 1H, J=3.7 Hz), 2.27 (d, 1H, J=3.0 Hz), 1.97 (d, 1H, J=3.0 Hz), 1.58–1.47 (m, 2H), 1.17–1.05 (m, 2H), 0.90 (d, 1H, J=10.3 Hz), 0.80 (d, 1H, J=10.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 168.4, 160.9, 151.1, 148.9, 147.3, 136.2, 134.5, 131.0, 128.6, 122.3, 120.8, 120.4, 51.7, 49.5, 49.2, 38.2, 36.3, 35.9, 31.9, 27.7, 27.6; IR (ATR) 2950, 1716, 1590, 1433, 1271 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{21}H_{22}NO_2$: ([M+H]$^+$) 320.1651: Found 320.1649.

2-((1,2,3,4,4a,8b-Hexahydro-1,4-methanobiphenylen-5-yl)-methyl)pyridine (**3pa**)

According to the general procedure, the reaction gave the product in 13% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.55–8.54 (m, 1H), 7.56 (ddd, 1H, J_1=7.8 Hz, J_2=7.4 Hz, J_3=1.7 Hz), 7.16 (dd, 1H, J_1=J_2=7.5 Hz), 7.12–7.09 (m, 1H), 7.07–7.05 (m, 2H), 6.87 (d, 1H, J=7.2 Hz), 4.06 (s, 2H), 3.11 (d, 1H, J=3.8 Hz), 3.02 (d, 1H, J=3.8 Hz), 2.23 (d, 1H, J=2.8 Hz), 1.92 (d, 1H, J=2.8 Hz), 1.58–1.46 (m, 2H), 1.15–1.05 (m, 2H), 0.89 (d, 1H, J=10.0 Hz), 0.81 (d, 1H, J=10.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 160.8, 149.1, 146.6, 145.2, 136.3, 133.6, 127.84, 127.83, 123.1, 121.1, 120.0, 49.9, 49.8, 40.7, 36.5, 35.9, 31.9, 27.8, 27.7; IR (ATR) 2949, 1590, 1472, 1434 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{19}H_{20}N$: ([M+H]$^+$) 262.1596: Found 262.1589.

1,2,3,4,4a,5b,6,7,8,9,9a,10b-Dodecahydro-1,4 : 6,9-dimethanobenzo[3,4]cyclobuta[1,2-*b*]biphenylen-5-yl)-methyl)pyridine (**4pa**)

According to the general procedure, the reaction gave the mixture of the product in 55% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.54 (d, 1H, J=4.3 Hz), 7.54 (ddd, 1H, J_1=J_2=8.0 Hz, J_3=1.5 Hz), 7.10 (dd, 1H, J_1=J_2=6.2 Hz), 7.00 (m, 1H), 6.55–6.54 (m, 1H), 3.98 (m, 2H), 3.03–3.01 (m, 2H), 2.96–2.94 (m, 2H), 2.20–2.17 (m, 2H), 1.91–1.89 (m, 2H), 1.56–1.43 (m, 4H), 1.13 (m, 4H), 0.88–0.76, (m, 4H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 160.8, 148.9, 145.5, 145.4, 143.4, 143.4, 136.2, 128.1, 128.0, 123.0, 121.1, 121.0, 114.3, 114.2, 49.4, 49.3, 49.1, 36.84, 36.83, 36.6, 36.08, 36.05, 31.8, 27.8, 27.74, 27.73 (Some peaks were missing due to overlapping); IR (ATR) 2944, 1590, 1452, 1434, 1328 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{26}H_{28}N$: ([M+H]$^+$) 354.2222: Found 354.2213.

2-((7-Methyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylen-5-yl)methyl)pyridine (**3qa**)

According to the general procedure, the reaction gave the product in 49% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.55–8.53 (m, 1H), 7.55 (ddd, 1H, J_1=J_2=7.6 Hz, J_3=1.7 Hz), 7.11–7.08 (m, 1H), 7.02 (d, 1H, J=7.8 Hz), 6.90 (s, 1H), 6.70 (s, 1H), 4.02 (s, 2H), 3.06 (d, 1H, J=3.8 Hz), 2.95 (d, 1H, J=3.8 Hz), 2.29 (s, 3H), 2.20 (d, 1H, J=3.0 Hz), 1.90 (d, 1H, J=3.0 Hz), 1.56–1.44 (m, 2H), 1.14–1.03 (m, 2H), 0.88–0.80 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 160.9, 149.1, 146.5, 141.9, 137.5, 136.3, 133.3, 128.6, 123.1, 121.1, 120.7, 49.6, 49.2, 40.7, 36.4, 35.9, 31.9, 27.8, 27.7, 22.0; IR (ATR) 2948, 1591, 1472, 1434 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{20}H_{22}N$: ([M+H]$^+$) 276.1752: Found 276.1752.

2-((6,8-Dimethyl-1,2,3,4,4a,8b-hexahydro-1,4-methanobiphenylen-5-yl)methyl)pyridine (**3ra**)

According to the general procedure, the reaction gave the product in 15% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.54–8.53 (m, 1H), 7.51 (ddd, 1H, J_1=J_2=7.5 Hz, J_3=1.7 Hz), 7.09 (dd, 1H, J_1=7.5 Hz, J_2=4.9 Hz), 6.89 (d, 1H, J_1=7.5 Hz), 6.84 (s, 1H), 4.07 (d, 1H, J=16.1 Hz), 4.03 (d, 1H, J=16.1 Hz), 3.04 (d, 1H, J=3.7 Hz), 2.96 (d, 1H, J=3.7 Hz), 2.26 (d, 1H, J=3.2 Hz), 2.16 (s, 3H), 2.14 (s, 3H), 1.94 (d, 1H, J=3.2 Hz), 1.60–1.44 (m, 2H), 1.22–1.04 (m, 2H), 0.92–0.87 (m, 2H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 161.0, 149.1, 145.4, 142.0, 136.3, 135.7, 130.4, 130.3, 128.9, 122.3, 120.9, 48.7, 48.0, 37.4, 35.9, 35.7, 32.0, 27.9, 27.8, 19.8, 16.3.; IR (ATR) 2946, 1589, 1472, 1434 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{21}H_{24}N$: ([M+H]$^+$) 290.1909: Found 290.1906.

1-(Methoxyimino)-1,2,3,4,6b,7,8,9,10,10a-decahydro-7,10-methanobenzo[*a*]biphenylenecarbonitrile (**3ab**)

According to the general procedure, the reaction gave the mixture of the products in 60% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.02–7.00 (m, 1H), 6.89–6.85 (m, 1H), 4.00–3.97 (m, 3H), 3.89 (d, 0.15H, J=3.8 Hz), 3.71 (d, 0.4H, J=3.4 Hz), 3.43 (d, 0.4H, J=3.4 Hz), 3.30–3.29 (m, 0.6H), 3.12 (s, 0.45H), 2.95 (s, 0.15H), 2.90–2.89 (m, 0.15H), 2.84–2.80 (m, 0.6H), 2.73–2.65 (m, 5H), 2.58 (m, 0.45H), 2.43 (d, 0.15H, J=3.7 Hz), 2.40–2.34 (m, 0.6H), 2.13–2.10 (m, 0.45H), 1.96–1.94 (m, 0.45H), 1.87–1.67 (m, 2.5H), 1.53–1.45 (m, 0.45H), 1.37–1.34 (m, 0.45H), 1.08–1.07 (m, 1H), 1.02–1.00 (m, 0.6H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 153.7, 153.7, 153.4, 143.3, 143.1, 142.7, 142.54, 142.51, 142.3, 142.0, 141.6, 138.9, 138.7, 138.6, 128.5, 128.3, 128.2, 126.0, 125.89, 125.86, 123.6, 123.5, 122.2, 122.14, 122.08, 122.05, 122.0, 62.15, 62.13, 62.0, 51.3, 51.0, 50.5, 49.0, 48.6, 48.1, 47.5, 45.1, 42.0, 40.6, 39.8, 38.5, 36.7, 36.4, 35.2, 34.9, 34.5, 34.4, 33.5, 32.53, 32.49, 31.0, 30.21, 30.16, 29.40, 29.37, 28.9, 28.8, 23.91, 23.89, 23.8, 21.68, 21.66, 21.6 (Some peaks were missing due to overlapping); IR (ATR) 2939, 2235, 1465, 1432, 1043 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{19}H_{21}N_2O$: ([M+H]$^+$) 293.1654: Found 293.1659.

9,9-Dimethyl-3,4,6b,7,7a,10a,11,11a-octahydro-7,11-methanobenzo[5,6]biphenyleno[2,3-*d*][1,3]dioxol-1(2*H*)-one *O*-Methyl Oxime (**3ac**)

According to the general procedure, the reaction gave the product in 77% yield as a white solid: mp 117.6–119.8°C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.00 (d, 1H, J=7.5 Hz), 6.88 (d,

1H, J=7.5 Hz), 4.11 (d, 1H, J=5.0 Hz), 4.06 (d, 1H, J=5.0 Hz), 3.96 (s, 3H), 3.18 (d, 1H, J=3.5 Hz), 3.00 (d, 1H, J=3.5 Hz), 2.73–2.66 (m, 5H), 2.36 (s, 1H), 1.90–1.73 (m, 2H), 1.51 (d, 1H, J=10.9 Hz), 1.47 (s, 3H), 1.34 (s, 3H), 0.76 (d, 1H, J=10.9 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 153.6, 142.2, 141.7, 138.6, 128.1, 126.0, 122.2, 109.3, 81.6, 81.4, 62.1, 46.7, 44.3, 41.0, 39.5, 30.2, 25.7, 25.5, 24.0, 23.9, 21.7; IR (ATR) 2934, 1618, 1205, 1045 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{21}H_{26}NO_3$: ([M+H]$^+$) 340.1913: Found 340.1913.

1-(Methoxyimino)-1,2,3,4,6b,7,8,9,10,10a-decahydro-7,10-methanobenzo[*a*]biphenylenyl Acetate (**3ad**)

According to the general procedure, the reaction gave the mixture of the products in 13% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.00–6.98 (m, 1H), 6.90–6.83 (m, 1H), 4.00–3.97 (m, 3H), 3.39–3.35 (m, 1H), 3.19 (s, 1H), 2.85 (s, 0.4H), 2.73–2.67 (m, 4H), 2.61 (d, 0.6H, J=4.0 Hz), 2.51 (s, 0.4H), 2.48–2.43 (m, 1H), 2.32–2.31 (m, 0.6H), 2.23–2.22 (m, 3H), 2.11–2.00 (m, 1H), 1.89–1.75 (m, 2H), 1.39–1.34 (m, 0.4H), 1.29–1.24 (m, 0.6H), 1.01–0.95 (m, 1H), 0.81–0.75 (m, 1H); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 209.8, 209.6, 153.9, 153.8, 144.0, 143.4, 143.0, 142.5, 138.5, 138.4, 128.0, 127.9, 125.8, 122.2, 122.14, 122.11, 62.04, 61.96, 53.6, 53.5, 52.2, 52.0, 49.75, 49.67, 40.2, 39.3, 36.6, 35.08, 35.05, 30.5, 30.3, 30.2, 29.8, 29.6, 29.4, 29.13, 29.05, 24.0, 23.9, 21.7 (some peaks were missing due to overlapping); IR (ATR) 2935, 1705, 1431, 1357, 1044 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{20}H_{24}NO_2$: ([M+H]$^+$) 310.1807: Found 310.1797.

3,4,6b,7,12,12a-Hexahydro-7,12-methanodibenzo[*a*,*h*]-biphenylen-1(2*H*)-one *O*-Methyl Oxime (**3ae**)

According to the general procedure, the reaction gave the product in 62% yield as a colorless oil: ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.29–7.25 (m, 2H), 7.11 (m, 2H), 7.03 (d, 1H, J=7.5 Hz), 6.97 (d, 1H, J=7.5 Hz), 4.09 (s, 3H), 3.58 (s, 1H), 3.39 (d, 1H, J=3.5 Hz), 3.29 (s, 1H), 3.21 (d, 1H, J=7.5 Hz), 2.75–2.73 (m, 4H), 1.91–1.79 (m, 2H), 1.66 (d, 1H, J=10.0 Hz), 1.29 (d, 1H, J=10.0 Hz); ^{13}C-NMR (126 MHz, $CDCl_3$) δ: 153.8, 148.2, 147.9, 143.1, 142.7, 138.5, 128.0, 125.8, 125.6, 125.5, 122.1, 121.4, 121.3, 62.1, 51.1, 48.8, 43.7, 42.5, 42.4, 30.2, 24.0, 21.8; IR (ATR) 2938, 1463, 1430, 1458, 1052 cm^{-1}; HR-MS (ESI$^+$) Calcd for $C_{22}H_{22}NO$: ([M+H]$^+$) 316.1701: Found 316.1693.

KIE Studies In a sealed tube, to a mixture of **1e** (1.0 eq), **1e**-d_3/**1e**-d_6 (1.0 eq), norbornene **2a** (1.0 eq) in DMF were added benzoquinone (1.5 eq), Ag_2CO_3 (2.0 eq), (−)-Men-Val-OH (0.05 eq), and $Pd(OAc)_2$ (0.1 eq). The tube was filled with argon and the mixture was heated to 100°C. After stirring for 12 h, the mixture was cooled to room temperature, diluted with EtOAc and filtrated. The solution was washed with water and brine, dried over Na_2SO_4, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (hexane–EtOAc or hexane–CH_2Cl_2) to give the corresponding benzocyclobutene. The ratio of **3ea** and **3ea**-d_2/**3ea**-d_5 were estimated by ^{1}H-NMR spectra.

Acknowledgments This work was supported by a Grant-in-Aid for Scientific Research on Platform for Drug Discovery, Informatics and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan (Y.T.) and JSPS Research Fellowships for Young Scientists (T.N.).

Conflict of Interest The authors declare no conflict of interest.

Supplementary Materials The online version of this article contains supplementary materials.

References and Notes

1) Pérez D., Peña D., Guitián E., *Eur. J. Org. Chem.*, **2013**, 5981–6013 (2013).
2) Wu C., Shi F, *Asian J. Org. Chem.*, **2**, 116–125 (2013).
3) Dubrovskiy A. V., Markina N. A., Larock R. C., *Org. Biomol. Chem.*, **11**, 191–218 (2013).
4) Tadross P. M., Stoltz B. M., *Chem. Rev.*, **112**, 3550–3577 (2012).
5) Ferraccioli R., *Synthesis*, **45**, 581–591 (2013).
6) Martins A., Mariampillai B., Lautens M., *Top. Curr. Chem.*, **292**, 1–33 (2010).
7) Catellani M., Motti E., Della Ca' N., *Acc. Chem. Res.*, **41**, 1512–1522 (2008).
8) Catellani M., Frignani F., Rangoni A., *Angew. Chem. Int. Ed. Engl.*, **36**, 119–122 (1997).
9) Faccini F., Motti E., Catellani M., *J. Am. Chem. Soc.*, **126**, 78–79 (2004).
10) Wilhelm T., Lautens M., *Org. Lett.*, **7**, 4053–4056 (2005).
11) Martins A., Lautens M., *Org. Lett.*, **10**, 5095–5097 (2008).
12) Ye J., Lautens M., *Nat. Chem.*, **7**, 863–870 (2015).
13) Larraufie M.-H., Maestri G., Beaume A., Derat Ê., Ollivier C., Fensterbank L., Courillon C., Lacôte E., Catellani M., Malacria M., *Angew. Chem. Int. Ed.*, **50**, 12253–12256 (2011).
14) Dong Z., Dong G., *J. Am. Chem. Soc.*, **135**, 18350–18353 (2013).
15) Zhou P.-X., Ye Y.-Y., Ma J.-W., Zheng L., Tang Q., Qiu Y.-F., Song B., Qiu Z.-H., Xu P.-F., Liang Y.-M., *J. Org. Chem.*, **79**, 6627–6633 (2014).
16) Shi H., Babinski D. J., Ritter T., *J. Am. Chem. Soc.*, **137**, 3775–3778 (2015).
17) Lei C., Jin X., Zhou J., *Angew. Chem. Int. Ed.*, **54**, 13397–13400 (2015).
18) Jiao L., Bach T., *J. Am. Chem. Soc.*, **133**, 12990–12993 (2011).
19) Jiao L., Herdtweck E., Bach T., *J. Am. Chem. Soc.*, **134**, 14563–14572 (2012).
20) Dey A., Agasti S., Maiti D., *Org. Biomol. Chem.*, **14**, 5440–5453 (2016).
21) Dong Z., Wang J., Dong G., *J. Am. Chem. Soc.*, **137**, 5887–5890 (2015).
22) Wang X.-C., Gong W., Fang L.-Z., Zhu R.-Y., Li S., Engle K. M., Yu J.-Q., *Nature* (London), **519**, 334–338 (2015).
23) Shen P.-X., Wang X.-C., Wang P., Zhu R.-Y., Yu J.-Q., *J. Am. Chem. Soc.*, **137**, 11574–11577 (2015).
24) Han J., Zhang L., Zhu Y., Zheng Y., Chen X., Huang Z.-B., Shi D.-Q., Zhao Y., *Chem. Commun.*, **52**, 6903–6906 (2016).
25) Umeda N., Tsurugi H., Satoh T., Miura M., *Angew. Chem. Int. Ed.*, **47**, 4019–4022 (2008).
26) Mochida S., Umeda N., Hirano K., Satoh T., Miura M., *Chem. Lett.*, **39**, 744–746 (2010).
27) Umeda N., Hirano K., Satoh T., Shibata N., Sato H., Miura M., *J. Org. Chem.*, **76**, 13–24 (2011).
28) Shi Z., Tang C., Jiao N., *Adv. Synth. Catal.*, **354**, 2695–2700 (2012).
29) Qi Z., Li X., *Angew. Chem. Int. Ed.*, **52**, 8995–9000 (2013).
30) Minami Y., Kodama T., Hiyama T., *Angew. Chem. Int. Ed.*, **54**, 11813–11816 (2015).
31) Tsukano C., Muto N., Enkhtaivan I., Takemoto Y., *Chem. Asian J.*, **9**, 2628–2634 (2014).
32) Catellani M., Ferioli L., *Synthesis*, **1996**, 769–772 (1996).
33) Tsai A. S., Brasse M., Bergman R. G., Ellman J. A., *Org. Lett.*, **13**, 540–542 (2011).
34) Engle K. M., Wang D.-H., Yu J.-Q., *J. Am. Chem. Soc.*, **132**, 14137–14151 (2010).

35) Niwa T., Yorimitsu H., Oshima K., *Angew. Chem. Int. Ed.*, **46**, 2643–2645 (2007).
36) De Houwer J., Abbaspour Tehrani K., Maes B. U. W., *Angew. Chem. Int. Ed.*, **51**, 2745–2748 (2012).
37) Chu Y., Shan Z., Liu D., Sun N., *J. Org. Chem.*, **71**, 3998–4001 (2006).
38) Ma S., Villa G., Thuy-Boun P. S., Homs A., Yu J.-Q., *Angew. Chem. Int. Ed.*, **53**, 734–737 (2014).
39) Also see Supplementary materials for a detail.