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Metal-Catalyzed Reactions between 2-Azabicyclo[2.2.1]hept-5-en-3-ones and Arylboronic Acids

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Cu- and Rh-catalyzed coupling reactions of 2-azabicyclo[2.2.1]hept-5-en-3-ones (**1**) with arylboronic acids were successful carried out under microwave irradiation conditions and yielded *N*-aryl and *C*-aryl derivatives of **1**, respectively.

Introduction

(–)-Epibatidine (Figure 1) was first obtained in 1992, from the skin of the Ecuadorian poison frog (*Epipedobates tricolor*).[1] This compound and a diverse group of analogues have attracted considerable synthetic and biological interest in recent years, due to their unique 7-azabicyclo[2.2.1]heptane structures and relatively strong analgesic activities, the result of binding with nicotinic acetylcholine (nACh) receptors.[2] A broad range of studies on a number of 2-azabicyclo[2.2.1]heptanes with various aryl substituents have demonstrated significant biological activities, such as antibacterial and mGluR5 antagonist activities.[3]

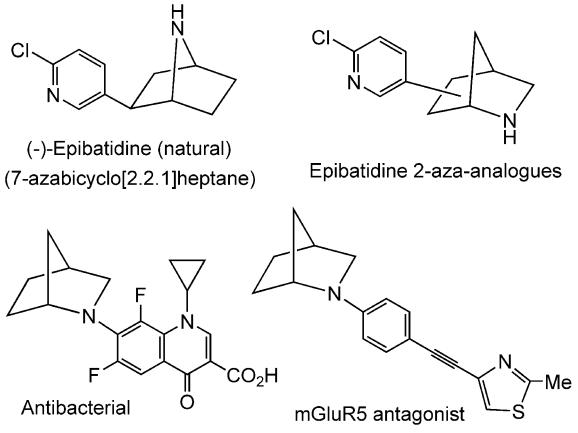

Figure 1. Aryl-substituted azabicyclo[2.2.1]heptanes.

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In connection with our continuing interest in the chemical reactivity and synthetic applications of the 2-azabicyclo[2.2.1]hept-5-en-3-ones **1** (Figure 2),[4] we envisioned that metal-catalyzed arylation of **1** should provide opportunities for straightforward access to aryl-substituted 2-azabicyclo[2.2.1]heptanes. Recent studies have highlighted catalytic coupling reactions of organometallic reagents with unsaturated bonds or heteroatom nucleophiles as potential synthetic methods.[5] Metal-catalyzed addition reactions of arylboronic acids to unsaturated bonds have been successfully developed as potential arylation tools, and so we set out to develop a catalytic system for the arylation of **1** with arylboronic acids in the presence of a metal catalyst.[6]

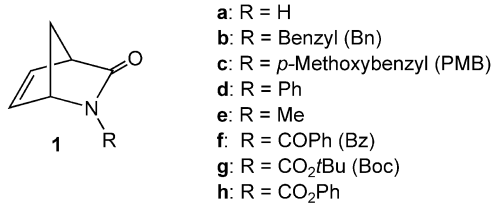
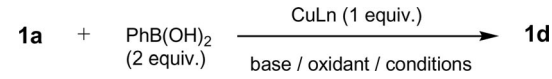


Figure 2. 2-Azabicyclo[2.2.1]hept-5-en-3-ones.

Results and Discussion

Although there are already numerous procedures for *O*- and *N*-arylation in the presence of Cu complexes,[7] there are only two reports on the *N*-phenylation of **1a**, through treatment with $PhB(OH)_2$ or Ph_3Bi in the presence of stoichiometric amounts of $Cu(OAc)_2$.[8] We therefore first reexamined the aerobic oxidative coupling reaction of **1a** with phenylboronic acid in the presence of stoichiometric amounts of $Cu(OAc)_2$, according to the literature. A mixture of **1a**, phenylboronic acid (2 equiv.), $Cu(OAc)_2$ (1 equiv.), and Et_3N (1.1 equiv.) in CH_2Cl_2 was stirred in

Table 1. Cu-Mediated *N*-phenylation of **1a**.



Run	CuL_n	Base (2 equiv.)	Oxidant (1.1 equiv.)	Conditions	Yield [%] of **1d**[d]
1	$Cu(OAc)_2$	Et_3N	none[a]	CH_2Cl_2/60 h/room temp.	19
2	$Cu(OAc)_2$	Et_3N	none[a]	CH_2Cl_2/44 h/reflux	26
3	$Cu(OAc)_2$	Et_3N	none[a]	MeOH/60 h/room temp.	7
4	$Cu(OAc)_2$	Et_3N	none[a]	DMF/60 h/room temp.	18
5	$Cu(OAc)_2$	Et_3N	none[a]	DMSO/60 h/room temp.	10
6	$Cu(OAc)_2$	Et_3N	none[a]	THF/60 h/room temp.	20
7	$Cu(OAc)_2$	Et_3N	none[a]	dioxane/60 h/room temp.	33
8	$Cu(OAc)_2$	Et_3N	none[a]	toluene/60 h/room temp.	32
9	$Cu(OAc)_2$	Et_3N	none[a]	MeCN/60 h/room temp.	70
10	$Cu(OAc)_2$	Et_3N	none[a]	MeCN/20 h/reflux	92
11	$Cu(OAc)_2$	Et_3N	O_2 (1 atm)	MeCN/72 h/room temp.	17
12	$Cu(OAc)_2$	Et_3N	$FeCl_3$	MeCN/96 h/room temp.	2
13	$Cu(OAc)_2$	Et_3N	TEMPO	MeCN/72 h/room temp.	19
14	$Cu(OAc)_2$	Et_3N	pyridine *N*-oxide	MeCN/48 h/room temp.	44
15	$Cu(OAc)_2$	Et_3N	NMO[b]	MeCN/72 h/room temp.	38
16	$Cu(OAc)_2$	Et_3N	$Me_3N(O)$ [c]	MeCN/20 h/room temp.	90
17	$Cu(OAc)_2$	none	$Me_3N(O)$ [c]	MeCN/72 h/room temp.	–[e]
18	$Cu(OTf)_2$	Et_3N	$Me_3N(O)$ [c]	MeCN/72 h/room temp.	8
19	$Cu(acac)_2$	Et_3N	$Me_3N(O)$ [c]	MeCN/72 h/room temp.	–[e]
20	CuCN	Et_3N	$Me_3N(O)$ [c]	MeCN/72 h/room temp.	11
21	CuOAc	Et_3N	$Me_3N(O)$ [c]	MeCN/24 h/room temp.	16
22	CuCl	Et_3N	$Me_3N(O)$ [c]	MeCN/48 h/room temp.	13

[a] In contact with the atmosphere. [b] *N*-Methylmorpholine *N*-oxide. [c] Trimethylamine *N*-oxide. [d] Isolated yield based on **1a**. [e] No reaction.

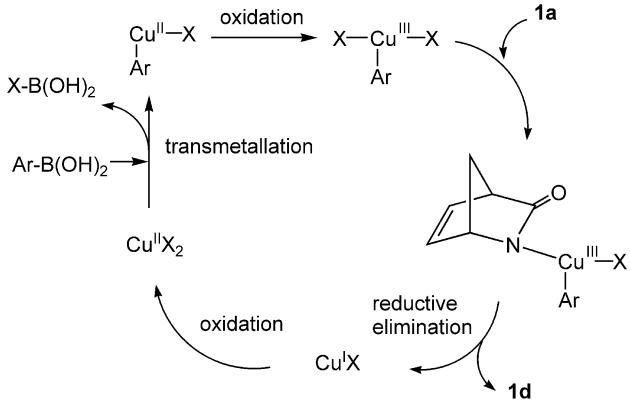
air at room temperature for 60 h. A low yield (19%) of **1d** was invariably reproduced, and running the reaction at reflux for 44 h did not give appreciable improvement (26%; Table 1; Runs 1 and 2).

Hence, in a search for optimized reaction conditions, other solvents were initially screened in order to explore the scope of solvents for the reaction. Table 1 (Runs 3–9) clearly demonstrates that the use of MeCN as a solvent resulted in the best reaction results. A good yield (70%) of **1d** was obtained after treatment at room temperature for 60 h in MeCN. Performing the reaction at reflux for 20 h also considerably increased the yield (92%), although the role of MeCN is not yet fully understood (Table 1; Run 10).

Copper-mediated *N*-arylation is commonly believed to involve the generation of a transient Cu^{III} species through oxidation of a Cu^{II} species, followed by reductive elimination and regeneration of a C^{II} species from a C^{I} species as depicted in Scheme 1.[9]

We therefore examined the reaction to determine whether it would be accelerated by the presence of an oxidant, relative to aerobic oxidation (Table 1; Runs 11–16).[10] It became apparent that the presence of trimethylamine *N*-oxide (1.1 equiv.) was key in obtaining **1d** in satisfactory yield (90%).[11] The reaction did not take place in the absence of Et_3N, whereas the use of $Cu(OAc)_2$ led to the highest levels of conversion of **1a** to **1d** out of the copper complexes screened (Table 1; Runs 18–22).

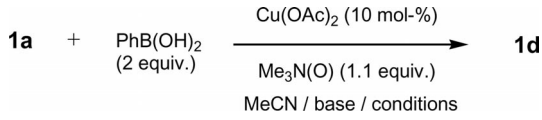
Because the reaction conditions for *N*-arylation in the presence of stoichiometric amounts of $Cu(OAc)_2$ had now been optimized, this led us to investigate the potential for



Scheme 1.

catalytic *N*-arylation. The optimized reaction conditions were first adopted for the reaction through the use of catalytic amounts of $Cu(OAc)_2$ (10 mol-%), but only trace amounts of **1d** were obtained, indicating that reducing the amount of $Cu(OAc)_2$ does not result in the induction of a catalytic cycle. Because the reaction does not take place in the absence of bases, we screened the effects of bases on the reaction in our initial experiments. As shown in Table 2, the use of organic bases resulted either in only trace amounts of **1d** or in no product, and metal carbonates proved to be ineffective (Table 2; Runs 1–5). Pulverized KOH was the only base that produced an acceptable yield (Table 2; Runs 6 and 7).

Table 2. Cu-catalyzed *N*-phenylation of **1a**.



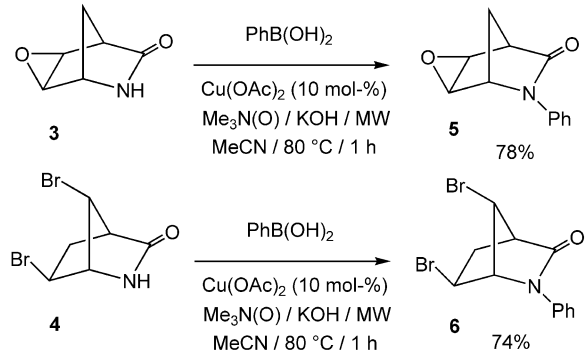
Run	Base	Conditions	Yield [%] of **1d**[a]
1	Et_3N (2 equiv.)	48 h/room temp.	9
2	pyridine (2 equiv.)	20 h/room temp.	3
3	TMEDA (2 equiv.)	90 h/room temp.	–[d]
4	K_2CO_3 (2 equiv.)	48 h/room temp.	–[d]
5	$CsCO_3$ (2 equiv.)	48 h/room temp.	–[d]
6	KOH (2 equiv.)	20 h/room temp.	35
7	KOH (2 equiv.)	20 h/80 [°C][b]	36
8	Et_3N (2 equiv.)	0.5 h/80 °C/MW[c]	38
9	Et_3N (5 equiv.)	0.5 h/80 °C/MW[c]	33
10	KOH (2 equiv.)	0.5 h/80 °C/MW[c]	54
11	KOH (5 equiv.)	0.5 h/80 °C/MW[c]	85
12	KOH (5 equiv.)	3 h/80 °C/MW[c]	43

[a] Isolated yield based on **1a**. [b] Preheated oil bath. [c] MW: microwave. [d] No reaction.

Many recent reports have indicated that microwave procedures can optimize various chemical transformations,[12] so we also examined the potential to activate the catalytic process by use of a microwave-promoted methodology.[13] Microwave irradiation at 80 °C for 0.5 h was capable of inducing the reaction, even in the presence of Et_3N (2–5 equiv.) as a base, to give **1d** in acceptable yields (Table 2; Runs 8 and 9). The reaction was more efficient in the presence of KOH (2 equiv.) as a base with microwave heating for 0.5 h, leading to **1d** in 54% yield, whereas the optimal product yield (85%) was obtained by increasing the amount of KOH (5 equiv.). On the other hand, extending the reaction time (3 h) resulted in significant decreases in the yield, possibly due to cleavage of the amide bond under these conditions (Table 2; Runs 10–12).

Success having been achieved in optimization of the Cu-catalyzed *N*-phenylation process under microwave irradiation conditions, compound **1a** was then subjected to the same reaction conditions with various arylboronic acids, leading to products **2a**–**2j** in moderate to good yields (Table 3).

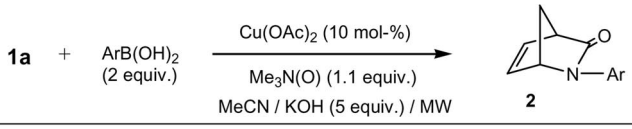
It was also of interest to examine whether the oxirane-fused compound **3**[14] (Scheme 2) and the dibrominated compound **4**[15] would tolerate the optimized conditions. Treatment of **3** or **4** with phenylboronic acid under microwave irradiation conditions proceeded smoothly within 1 h, giving the corresponding *N*-phenyl derivative **5** or **6** in 78% or 74% yields, respectively.

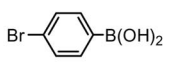
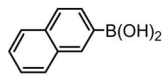
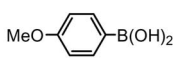
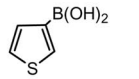
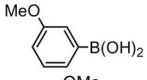
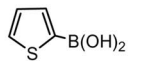
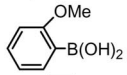
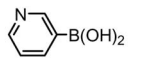
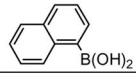
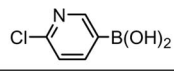


Scheme 2.

A number of metal-catalyzed procedures for the introduction of various aryl groups have been developed to date; however, metal-catalyzed arylation at the double bonds of compounds **1** is scarcely known. Recently, Pd-catalyzed arylation of **1a** through a reductive Heck reaction has emerged.[16] In view of the successful use of $ArB(OH)_2$ as the source of the aryl group for catalytic *N*-arylation,[17] we

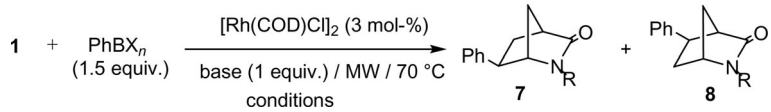
Table 3. Cu-Catalyzed *N*-arylation of **1a**.



$ArB(OH)_2$	Time	Yield (%) of **2**[a]	$ArB(OH)_2$	Time	Yield (%) of **2**[a]
	1.5 h	69 (**2a**)		0.5 h	54 (**2f**)
	0.5 h	72 (**2b**)		1 h	76 (**2g**)
	0.5 h	83 (**2c**)		1 h	59 (**2h**)
	1 h	58 (**2d**)		2 h	85 (**2i**)
	1 h	70 (**2e**)		1 h	80 (**2j**)

[a] Isolated yield based on **1a**.

Table 4. Rh-catalyzed *C*-phenylation of **1**.



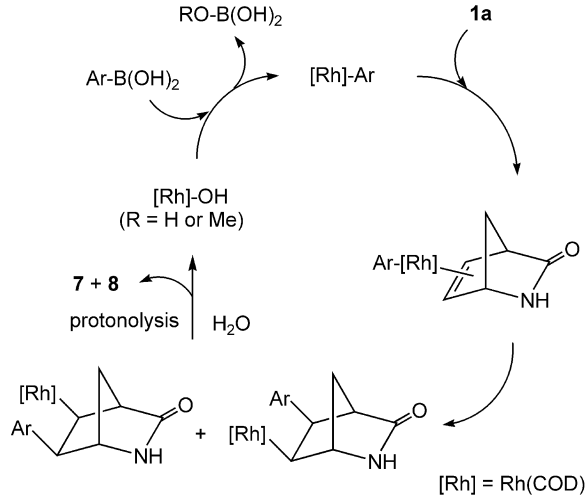
Run	R	PhBX$_n$	Base	Conditions	Yield [%][a] (**7**/**8**)
1	Bn	PhB(OH)$_2$	KOH	MeOH/H$_2$O (10:1)/48 h[b]	–[c]
2	Bn	PhB(OH)$_2$	KOH	MeOH/H$_2$O (10:1)/0.5 h	72 (**7b/8b** 60:40)
3	PMB	PhB(OH)$_2$	KOH	MeOH/H$_2$O (10:1)/0.5 h	40 (**7c/8c** 80:20)
4	Ph	PhB(OH)$_2$	KOH	MeOH/H$_2$O (10:1)/0.5 h	29 (**7d/8d** 60:40)
5	Me	PhB(OH)$_2$	KOH	MeOH/H$_2$O (10:1)/1 h	71 (**7e/8e** 70:30)
6	H	PhB(OH)$_2$	KOH	MeOH/H$_2$O (10:1)/0.5 h	80 (**7a/8a** 75:25)
7	H	PhB(OH)$_2$[d]	KOH	MeOH/H$_2$O (10:1)/0.5 h	80 (**7a/8a** 70:30)
8	H	PhB(OH)$_2$[e]	KOH	MeOH/H$_2$O (10:1)/2 h	72 (**7a/8a** 70:30)
9	H	PhB(OH)$_2$	KOH	MeOH/1 h	70 (**7a/8a** 70:30)
10	H	PhB(OH)$_2$	KOH	EtOH/H$_2$O (10:1)/4 h	16 (**7a/8a** 70:30)
11	H	PhB(OH)$_2$	KOH	2-PrOH/H$_2$O (10:1)/2 h	57 (**7a/8a** 70:30)
12	H	PhB(OH)$_2$	CsF	MeOH/H$_2$O (10:1)/0.5 h	50 (**7a/8a** 75:25)
13	H	PhB(OH)$_2$	Cs$_2$CO$_3$	MeOH/H$_2$O (10:1)/0.5 h	80 (**7a/8a** 70:30)
14	H	PhB(OH)$_2$	K$_2$CO$_3$	MeOH/H$_2$O (10:1)/3 h	74 (**7a/8a** 70:30)
15	H	PhB(OH)$_2$	Et$_3$N	MeOH/H$_2$O (10:1)/0.5 h	70 (**7a/8a** 70:30)
16	H	(PhBO)$_3$[f]	KOH	MeOH/H$_2$O (10:1)/0.5 h	80 (**7a/8a** 70:30)
17	H	[PhBF$_3$]$^-$ K$^+$	KOH	MeOH/H$_2$O (10:1)/4 h	34 (**7a/8a** 70:30)

[a] Combined yield based on **1**. [b] Preheated oil bath. [c] No isolable products. [d] 5 equiv. [e] 1.1 equiv. [f] 0.5 equiv.

were interested in developing a catalytic procedure in which ArB(OH)$_2$ could also be used for the *C*-arylation of **1**. Rhodium catalysts have frequently been used for the activation of arylboronic acids, which prompted us to select a rhodium catalyst for the *C*-arylation reaction.[18] Our initial attempt to arylate **1b** with phenylboronic acid (2 equiv.) by use of [Rh(COD)Cl]$_2$ (3 mol-%) in the presence of KOH in MeOH/H$_2$O (10:1) at 70 °C for 48 h resulted in the formation of complex mixtures without any isolable products (Table 1, Run 1). In view of its successful application in Cu-catalyzed *N*-arylation, microwave irradiation was therefore also considered (Table 4).

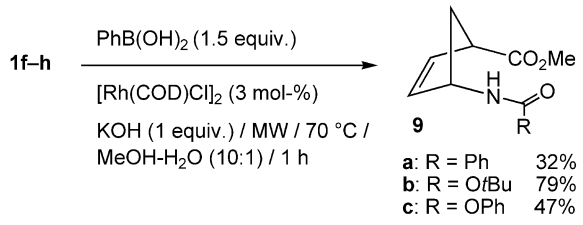
As expected, the reaction was dramatically improved under microwave irradiation conditions. A pair of phenylated products – compounds **7b** and **8b** – were obtained in 72% combined yield on treatment of **1b** with PhB(OH)$_2$ (2 equiv.) in the presence of [Rh(COD)Cl]$_2$ (3 mol-%) and KOH (1 equiv.) in MeOH/H$_2$O (10:1) for 0.5 h under microwave heating conditions at 70 °C (Table 4; Runs 1 and 2). Reactions performed with **1a** and **1c**–**e** also took place, giving the regioisomers **7** and **8**, with **7** favored (Table 4; Runs 3–6). The product yields in the reactions of **1c** and **1e** were smaller, whereas **1a** gave the best yield: **7a/8a** (75:25) in 80% combined yield. Solvents, bases, and quantities of phenylboronic acid were optimized to determine suitable conditions. Of the solvents screened, MeOH/H$_2$O (10:1) gave the best results (Table 4; Runs 9–11). Although KOH, Cs$_2$CO$_3$, and K$_2$CO$_3$ were all efficient in relation to CsF, KOH was elected as the base for further reactions due to the optimal yield and its ready availability (Table 4; Runs 12–15). Use of a smaller amount of PhB(OH)$_2$ (1.1 equiv.) decreased the yield slightly, whereas increasing the amount to 5 equiv. did not change the yield (Table 4; Runs 7 and 8). Moreover, (PhBO)$_3$ was also compatible with the transformation and a satisfactory yield was obtained, whereas in the reaction performed with [PhBF$_3$]K the yield was markedly decreased (Table 4; Runs 16 and 17). Finally, the best reaction conditions were determined to be **1** (1 equiv.), PhB(OH)$_2$ (1.5 equiv.), [Rh(COD)Cl]$_2$ (3 mol-%), and KOH (1 equiv.) in MeOH/H$_2$O (10:1) at 70 °C under microwave irradiation conditions.

The following common mechanistic scheme, involving the generation of the hydroxorhodium complex [Rh(COD)-OH] as an active catalyst from [Rh(COD)Cl] and H$_2$O in situ (Scheme 3), might account for the Rh-catalyzed *C*-arylation reaction.[18]



Scheme 3.

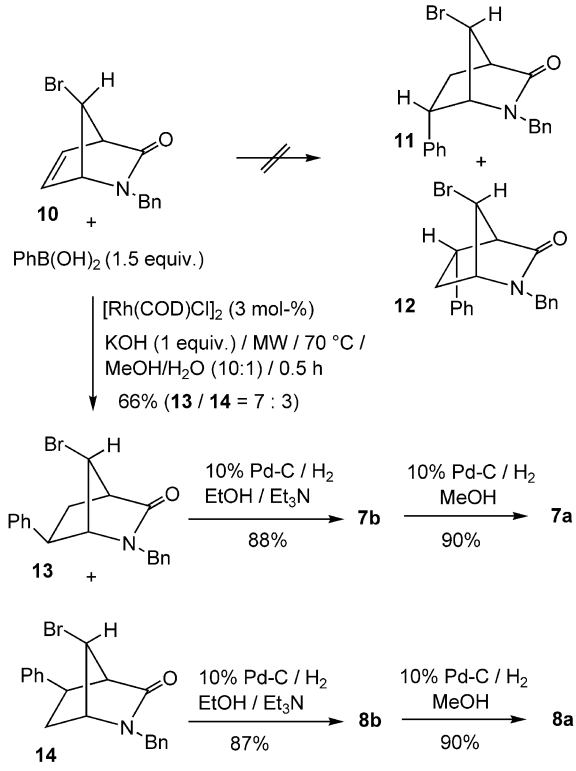
On the other hand, treatment of **1f**–**h**, with *N*-acyl groups (Scheme 4), under the optimized conditions led to the exclusive isolation of the ring-opening products **9a**–**c**, resulting from the solvolysis of the amide bond, without the phenylated products.



Scheme 4.

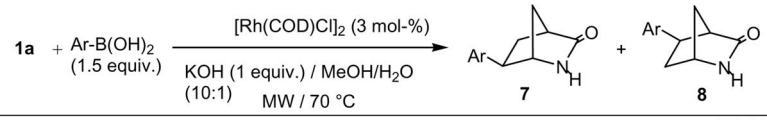
Treatment of **1a** with various arylboronic acids was also examined under these conditions (Table 5). Treatment of **1a** with phenylboronic acid derivatives afforded the phenylated products **7f**–**k** and **8f**–**k** in moderate to good yields (Table 5; Runs 1–6), whereas attempted reactions with heteroarylboronic acids were troublesome. Furanboronic acids gave no isolable products (Table 5; Runs 7 and 8), due to the instability of the furan ring under the conditions. In the case of thiophenboronic acids, the products were obtained in low yields and required longer reaction times (Table 5; Runs 9 and 10). In contrast with the lack of product from pyridineboronic acid, 2-chloropyridine gave **7n** and **8n** in 65% combined yield (Table 5; Runs 11 and 12).

All reactions of **1** with arylboronic acids proceeded in a highly *exo*-selective fashion, giving the compounds **7** and **8** exclusively.[19] We were also interested in the *endo*-phenylated products **11** and **12** (Scheme 5). Anticipating the possibility of obtaining *endo*-phenyl adducts, presumably as a result of the steric bulkiness of the Br group,[20] we examined the reaction between **10** and $PhB(OH)_2$ under the opti-



Scheme 5.

Table 5. Rh-catalyzed *C*-arylation of **1**.

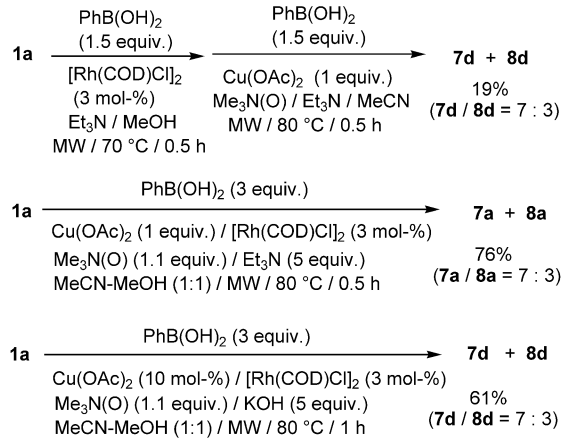


Run	Ar	Time	Yield (%)[a] (**7** / **8**)	Run	Ar	Time	Yield (%)[a] (**7** / **8**)
1		0.5 h	77 (**7f** / **8f** = 70 : 30)	7	 (5 equiv.)	3 h	-----[b]
2		1.5 h	84 (**7g** / **8g** = 80 : 20)	8	 (5 equiv.)	3 h	-----[b]
3		1.5 h	84 (**7h** / **8h** = 74 : 26)	9		6 h	41 (**7l** / **8l** = 98 : 2)
4		2.5 h	70 (**7i** / **8i** = 77 : 23)	10		6 h	52 (**7m** / **8m** = 98 : 2)
5		3 h	48 (**7j** / **8j** = 74 : 26)	11		3 h	-----[b]
6		2 h	53 (**7k** / **8k** = 85 : 15)	12		2 h	65 (**7n** / **8n** = 75 : 25)

[a] Combined yield based on **1a**. [b] No isolable products.

mized conditions. Treatment of **10** with $PhB(OH)_2$ in the presence of a catalytic amount of $[Rh(COD)Cl]_2$ and of KOH in MeOH/H_2O (10:1) resulted only in the isolation of **13** and **14** in 66% combined yield, without the *endo*-adducts **11** and **12**. The structures of **13** and **14** were later confirmed chemically by transformation into **7a** and **8a**, respectively. Catalytic hydrogenation of **13** and **14** in the presence of Pd/C (10%) and Et_3N produced **7b** and **8b**. Subsequently, the benzyl groups of **7b** and **8b** were removed by catalytic hydrogenolysis by further use of Pd/C (10%), giving **7a** and **8a**. The structure of **7a** was unequivocally established by X-ray structure analysis.[21]

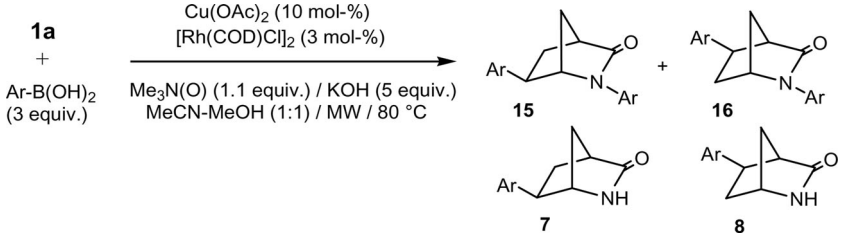
Moreover, we also investigated the possibility of developing a one-pot procedure for *N*- and *C*-diphenylation of **1a**.[22] We first examined sequential one-pot treatment of **1a** with $PhB(OH)_2$ by treatment with $[Rh(COD)Cl]_2$ and then $Cu(OAc)_2$ (Scheme 6). A mixture of **1a**, $PhB(OH)_2$ (1.5 equiv.), Et_3N (1 equiv.), and $[Rh(COD)Cl]_2$ (3 mol-%) in MeOH was heated for 0.5 h at 70 °C under microwave irradiation conditions. Additional $PhB(OH)_2$ (1.5 equiv.), $Cu(OAc)_2$ (1 equiv.), Et_3N (1 equiv.), $Me_3N(O)$ (1 equiv.), and MeCN were then added, and the whole mixture was further heated under microwave irradiation at 80 °C for 0.5 h. The *N*-,*C*-diphenylated products **7d** and **8d** were isolated, but only in low yields. This result prompted us to investigate a one-pot treatment of **1a** with $PhB(OH)_2$ in the presence both of $Cu(OAc)_2$ and of $[Rh(COD)Cl]_2$. Microwave irradiation was performed with **1a**, $PhB(OH)_2$ (3 equiv.), $Cu(OAc)_2$ (1 equiv.), $[Rh(COD)Cl]_2$ (3 mol-%), Et_3N (5 equiv.), and $Me_3N(O)$ (1.1 equiv.) in MeOH and MeCN at 80 °C for 0.5 h. It was of interest that the only isolated materials were the *C*-phenylated products **7a** and **8a** in 76% combined yield, without diphenylated products. After identification of suitable conditions, it was found that the diphenylated products **7d** and **8d** were obtained in 61% combined yield on replacement of Et_3N (5 equiv.) and stoichiometric amounts of $Cu(OAc)_2$ with KOH (5 equiv.) and a catalytic amount of $Cu(OAc)_2$.



Scheme 6.

The potential for one-pot diarylation with various arylboronic acids was also examined (Table 6). When the reaction was carried out with 4-bromophenylboronic acid, the diarylated products **15a** and **16a** were obtained in 40% combined yield along with small amounts of *C*-arylated products **7o** and **8o** (12% combined yield). In contrast, only the *N*-arylated product **2k** was isolated, in 48% yield, on treatment with 2-bromophenylboronic acid, with the bulky Br group at the 2-position (Table 6; Runs 1 and 2). Because we were interested in the role of Cu and Rh catalysts in the reaction, application of the Cu-catalyzed *N*-arylation and the Rh-catalyzed *C*-arylation reactions, respectively, to **1a** and 2-bromophenylboronic acid was then examined (Scheme 7). Although **1a** did not react with 2-bromophenylboronic acid under the Rh-catalyzed *C*-arylation conditions with microwave heating at 70 °C for 6 h, exclusive formation of the *N*-arylated product **2k** (70%) was found in the Cu-catalyzed *N*-arylation reaction under microwave irradiation conditions at 80 °C for 2 h. On the other hand, subjection of 4-methoxyphenylboronic acid to the reaction with **1a** gave rise to the formation of **15b** and **16b** in 36%

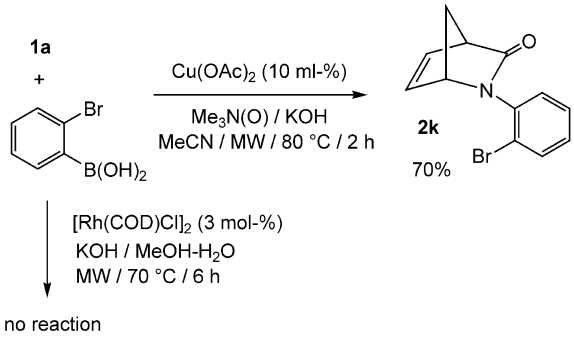
Table 6. One-pot reactions between **1a** and arylboronic acids.



Run	Ar	Time	Yield [%][a] (**15/16**)
1	4-bromophenyl	3 h	40 (**15a/16a** 7:3)[b]
2	2-bromophenyl	4 h	–[c]
3	4-methoxyphenyl	2 h	36 (**15b/16b** 7:3)[d]
4	2-methoxyphenyl	3 h	31 (**15c/16c** 7:3)
5	3-methoxyphenyl	3 h	45 (**15d/16d** 7:3)
6	6-chloropyridin-3-yl	3 h	–[e]

[a] Combined yield based on **1a**. [b] Along with **7o** (Ar = 4-bromophenyl) and **8o** (Ar = 4-bromophenyl) (**7o/8o** 7:3) in 12% combined yield. [c] Isolation of **2k** in 48% yield. [d] Along with **7g** and **8g** (**7g/8g** 7:3) in 15% combined yield. [e] Complex mixtures.

combined yield along with **7g** and **8g** in 15% combined yield (Table 6; Run 3). Moreover, 2-methoxyphenylboronic and 3-methoxyphenylboronic acids reacted with **1a** to provide **15c** and **16c** in 31% combined yield and **15d** and **16d** in 45% combined yield, respectively (Table 6; Runs 4 and 5). The reaction with (6-chloropyridin-3-yl)boronic acid was troublesome, however, resulting in complex mixtures (Table 6; Run 6).



Scheme 7.

Conclusions

In summary, we have disclosed the recent results of our investigations of metal-catalyzed *N*- or *C*-arylation of the 2-azabicyclo[2.2.1]hept-5-en-3-ones **1** with arylboronic acids. In contrast to the known procedure with use of stoichiometric amounts of $Cu(OAc)_2$, we have established that under microwave irradiation conditions catalytic amounts of $Cu(OAc)_2$ (10 mol-%) were sufficient to catalyze the *N*-arylation reactions in good yields. Moreover, microwave irradiation was also significant when catalytic amounts of $[Rh(COD)Cl]_2$ (3 mol-%) were used to promote catalytic additions of arylboronic acids to the double bonds of compounds **1**, leading to the *C*-arylated products **7** and **8**.

Experimental Section

General: Melting points were recorded with a Yamato MP21 instrument and are uncorrected. MS and HRMS spectra were recorded with a Micromass AutoSpec 3100 mass spectrometer. IR spectra were measured with a Shimadzu IRAffinity-1 FT-IR spectrophotometer. The NMR experiments were performed with a Jeol JNM-ECA500 (500 MHz) spectrometer, and chemical shifts are expressed in ppm (δ) with TMS as an internal reference. Column chromatography was performed on silica gel (silica gel 60*N*, Kanto Chemical Co., Ltd.). Microwave irradiation was performed with a Green-Motif I (IMCR-25003) monomode microwave reactor (IDX Corporation). All microwave (MW) irradiation experiments were carried out in glass tubes with microwave power from 0–300 W, depending on the microwave-absorbing capability of the reaction mixture.

Treatment of 1a with Phenylboronic Acid in the Presence of Stoichiometric Amounts of $Cu(OAc)_2$: $Cu(OAc)_2$ (73 mg, 0.4 mmol) was added to a mixture of **1a** (44 mg, 0.4 mmol), phenylboronic acid (98 mg, 0.8 mmol), and Et_3N (81 mg, 0.8 mmol) in MeCN (2 mL). The mixture was stirred at room temperature for 5 min, and then heated under reflux for 36 h. After cooling, the mixture was diluted with AcOEt, and insoluble materials were removed by filtration with suction. The filtrate was concentrated, and the residue was separated by silica gel column chromatography with hexane/AcOEt (10:1) to give **1d** (68 mg, 92%).

***rel*-(1*S*,4*R*)-2-Phenyl-2-azabicyclo[2.2.1]hept-5-en-3-one (1d):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.27 (dd, *J* = 2.3, 8.0 Hz, 1 H), 2.48 (dd, *J* = 3.4, 8.0 Hz, 1 H), 3.50 (s, 1 H), 4.77 (s, 1 H), 6.72 (m, 1 H), 7.02 (m, 1 H), 7.09 (m, 1 H), 7.32–7.35 (m, 2 H), 7.37–7.39 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.8, 57.3, 64.7, 118.7, 124.0, 129.0, 138.5, 139.1, 157.3, 177.4 ppm. IR (neat): $\tilde{\nu}$ = 1698 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{11}NO$ $[M]^+$ 185.0841; found 185.0845.

General Procedure for Treatment of 1a, 3, or 4 with Arylboronic Acids in the Presence of a Catalytic Amount of $Cu(OAc)_2$: $Cu(OAc)_2$ (7.3 mg, 0.04 mmol) was added to a mixture of **1a**, **3** or **4** (0.4 mmol), an arylboronic acid (0.8 mmol), trimethylamine *N*-oxide (0.44 mmol), and pulverized KOH (112 mg, 2.0 mmol) in MeCN (2 mL). The mixture was stirred at room temperature for 5 min, and then heated at 80 °C under microwave irradiation conditions (reaction time noted in Tables 2 and 3). After the mixture had cooled, insoluble materials were removed by filtration. The filtrate was concentrated in vacuo, and the residue was diluted with AcOEt. The mixture was washed with aq. NaOH (10%) and brine and dried with $MgSO_4$. The solvent was removed, and the residue was separated by silica gel column chromatography with hexane/AcOEt (10:1) to give compounds **2** (Table 3), **5** (78%), or **6** (74%).

***rel*-(1*S*,4*R*)-2-(4-Bromophenyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2a):** Yield 73 mg (69%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.28 (dd, *J* = 1.2, 8.1 Hz, 1 H), 2.47 (d, *J* = 8.0 Hz, 1 H), 3.50 (s, 1 H), 4.75 (s, 1 H), 6.71 (m, 1 H), 7.00 (dd, *J* = 1.1, 5.1 Hz, 1 H), 7.28 (d, *J* = 9.2 Hz, 2 H), 7.43 (d, *J* = 9.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.6, 57.1, 64.5, 116.7, 120.1, 131.9, 138.7, 138.7, 138.8, 177.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1700 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{10}NOBr$ $[M]^+$ 262.9946 and 264.9925; found 263.0001 and 264.9914.

***rel*-(1*S*,4*R*)-2-(4-Methoxyphenyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2b):** Yield 62 mg (72%); colorless crystals; m.p. 72–73 °C (hexane/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.25 (d, *J* = 8.0 Hz, 1 H), 2.48 (d, *J* = 8.0 Hz, 1 H), 3.48 (s, 1 H), 3.77 (s, 3 H), 4.67 (d, *J* = 1.8 Hz, 1 H), 6.72 (m, 1 H), 6.87 (d, *J* = 9.1 Hz, 2 H), 7.00 (dd, *J* = 1.7, 5.2 Hz, 1 H), 7.24 (d, *J* = 9.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.6, 55.6, 57.8, 65.5, 114.3, 120.8, 132.9, 138.5, 139.3, 156.5, 177.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1690 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{13}NO_2$ $[M]^+$ 215.0946; found 215.0931. $C_{13}H_{13}NO_2$ (215.09): calcd. C 72.54, H 6.09, N 6.51; found C 72.43, H 6.19, N 6.40.

***rel*-(1*S*,4*R*)-2-(3-Methoxyphenyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2c):** Yield 72 mg (83%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.26 (d, *J* = 8.0 Hz, 1 H), 2.46 (d, *J* = 8.0 Hz, 1 H), 3.49 (s, 1 H), 3.80 (s, 3 H), 4.77 (d, *J* = 1.8 Hz, 1 H), 6.65 (dd, *J* = 2.3, 8.0 Hz, 1 H), 6.71 (m, 1 H), 6.91 (dd, *J* = 1.8, 7.4 Hz, 1 H), 7.01 (dd, *J* = 2.3, 5.8 Hz, 1 H), 7.06 (t, *J* = 2.3 Hz, 1 H), 7.23 (t, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.9, 55.4, 57.2, 64.7, 104.9, 109.5, 110.6, 129.7, 138.6, 139.1, 140.9, 160.2, 177.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1692 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{13}NO_2$ $[M]^+$ 215.0946; found 215.0936.

***rel*-(1*S*,4*R*)-2-(2-Methoxyphenyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2d):** Yield 50 mg (58%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.25 (dt, *J* = 1.7, 7.5 Hz, 1 H), 2.60 (dt, *J* = 1.7, 7.5 Hz, 1 H), 3.46 (s, 1 H), 3.84 (s, 3 H), 4.68 (dd, *J* = 1.7, 3.5 Hz, 1 H),

6.76 (m, 1 H), 6.87 (dd, *J* = 1.8, 5.2 Hz, 1 H), 6.91–6.94 (m, 2 H), 7.12 (dd, *J* = 1.8, 8.6 Hz, 1 H), 7.16 (dt, *J* = 1.7, 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.1, 55.7, 58.8, 66.9, 111.9, 121.0, 126.0, 127.2, 127.9, 138.3, 140.7, 154.1, 179.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1686 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{13}NO_2$ $[M]^+$ 215.0946; found 215.0932.

***rel*-(1*S*,4*R*)-2-(1-Naphthyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2e):** Yield 67 mg (70%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.39 (d, *J* = 8.0 Hz, 1 H), 2.85 (d, *J* = 7.5 Hz, 1 H), 3.63 (s, 1 H), 4.61 (d, *J* = 1.7 Hz, 1 H), 6.88 (m, 1 H), 7.00 (dd, *J* = 1.7, 5.7 Hz, 1 H), 7.09 (d, *J* = 7.4 Hz, 1 H), 7.43 (t, *J* = 8.0 Hz, 1 H), 7.49–7.54 (m, 2 H), 7.76 (d, *J* = 8.0 Hz, 1 H), 7.85–7.87 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.8, 58.6, 68.3, 121.2, 123.2, 125.7, 126.4, 126.5, 127.5, 128.4, 130.3, 134.6, 136.7, 138.2, 140.3, 179.5 ppm. IR (neat): $\tilde{\nu}$ = 1696 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{13}NO$ $[M]^+$ 239.0997; found 239.0998.

***rel*-(1*S*,4*R*)-2-(2-Naphthyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2f):** Yield 52 mg (54%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.33 (dd, *J* = 1.7, 8.0 Hz, 1 H), 2.55 (d, *J* = 8.1 Hz, 1 H), 3.55 (s, 1 H), 4.92 (d, *J* = 1.7 Hz, 1 H), 6.76 (m, 1 H), 7.10 (dd, *J* = 1.7, 5.2 Hz, 1 H), 7.39 (t, *J* = 8.0 Hz, 1 H), 7.45 (dt, *J* = 1.2, 6.9 Hz, 1 H), 7.67 (s, 1 H), 7.69 (dd, *J* = 1.8, 8.6 Hz, 1 H), 7.78 (d, *J* = 8.6 Hz, 2 H), 7.81 (d, *J* = 8.6 Hz, 1 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 54.8, 57.4, 64.9, 114.9, 119.2, 125.0, 126.4, 127.5, 127.6, 128.8, 130.4, 133.7, 137.3, 138.7, 139.1, 177.5 ppm. IR (neat): $\tilde{\nu}$ = 1700 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{13}NO$ $[M]^+$ 239.0997; found 239.0983.

***rel*-(1*S*,4*R*)-2-(Thiophen-3-yl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2g):** Yield 58 mg (76%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.27 (d, *J* = 8.1 Hz, 1 H), 2.48 (d, *J* = 8.1 Hz, 1 H), 3.47 (s, 1 H), 4.76 (d, *J* = 1.7 Hz, 1 H), 6.72 (ddd, *J* = 1.7, 3.5, 5.2 Hz, 1 H), 6.96 (dd, *J* = 1.7, 5.2 Hz, 1 H), 7.04 (dd, *J* = 1.7, 2.9 Hz, 1 H), 7.25–7.28 (m, 2 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 54.3, 57.5, 65.2, 107.3, 120.0, 125.3, 138.4, 139.0, 139.1, 176.8 ppm. IR (neat): $\tilde{\nu}$ = 1701 cm^{-1}. HRMS (EI): calcd. for $C_{10}H_9NOS$ $[M]^+$ 191.0405; found 191.0407.

***rel*-(1*S*,4*R*)-2-(Thiophen-2-yl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2h):** Yield 45 mg (59%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.31 (d, *J* = 8.1 Hz, 1 H), 2.51 (d, *J* = 8.1 Hz, 1 H), 3.53 (s, 1 H), 4.83 (d, *J* = 1.7 Hz, 1 H), 6.57 (dd, *J* = 1.7, 2.9 Hz, 1 H), 6.72–6.74 (m, 1 H), 6.83–6.86 (m, 2 H), 6.97 (dd, *J* = 2.3, 5.2 Hz, 1 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 53.7, 57.2, 66.1, 110.2, 117.4, 124.7, 139.1, 139.3, 142.0, 176.0 ppm. IR (neat): $\tilde{\nu}$ = 1701 cm^{-1}. HRMS (EI): calcd. for $C_{10}H_9NOS$ $[M]^+$ 191.0405; found 191.0410.

***rel*-(1*S*,4*R*)-2-(Pyridin-3-yl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2i):** Yield 63 mg (85%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.22 (d, *J* = 7.5 Hz, 1 H), 2.39 (d, *J* = 7.5 Hz, 1 H), 3.21 (s, 1 H), 4.33 (s, 1 H), 6.77 (dd, *J* = 1.8, 5.2 Hz, 1 H), 7.02 (dd, *J* = 1.7, 5.2 Hz, 1 H), 7.25 (dd, *J* = 4.6, 8.1 Hz, 1 H), 7.89 (dd, *J* = 1.2, 8.0 Hz, 1 H), 8.32 (d, *J* = 4.6 Hz, 1 H), 8.55 (d, *J* = 2.9 Hz, 1 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 54.3, 57.2, 64.1, 123.5, 126.2, 136.2, 138.8, 138.9, 139.3, 145.0, 177.7 ppm. IR (neat): $\tilde{\nu}$ = 1707 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{10}N_2O$ $[M]^+$ 186.0793; found 186.0800.

***rel*-(1*S*,4*R*)-2-(6-Chloropyridin-3-yl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2j):** Yield 70 mg (80%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.35 (dt, *J* = 1.7, 8.0 Hz, 1 H), 2.50 (dt, *J* = 1.7, 8.0 Hz, 1 H), 3.53 (s, 1 H), 4.82 (dt, *J* = 1.7, 1.8 Hz, 1 H), 6.73 (ddd, *J* = 1.7, 3.5, 5.2 Hz, 1 H), 7.01 (dd, *J* = 1.7, 5.2 Hz, 1 H), 7.25–7.29 (m, 1 H), 7.96 (dd, *J* = 2.9, 8.6 Hz, 1 H), 8.31 (s, 1 H) ppm. ^{13}C NMR (500 MHz, $CDCl_3$): δ = 54.2, 57.0, 64.1, 124.2, 129.1, 138.4, 138.7, 138.9, 177.5 ppm. IR (neat): $\tilde{\nu}$ = 1713 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_9ClN_2O$ $[M]^+$ 220.0403 and 222.0374; found 220.0415 and 222.0365.

***rel*-(1*R*,2*S*,4*R*,5*S*)-3-Oxa-6-phenyl-6-azatricyclo[3.2.1.0^{2,4}]heptan-7-one (5):** Yield 63 mg (78%); colorless crystals; m.p. 82–83 °C (hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.81 (d, *J* = 10.3 Hz, 1 H), 1.97 (d, *J* = 10.3 Hz, 1 H), 3.15 (t, *J* = 1.1 Hz, 1 H), 3.71 (d, *J* = 2.3 Hz, 1 H), 3.93 (d, *J* = 3.4 Hz, 1 H), 4.53 (s, 1 H), 7.11 (t, *J* = 7.4 Hz, 1 H), 7.36 (t, *J* = 7.4 Hz, 2 H), 7.42 (d, *J* = 7.9 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 29.2, 48.5, 51.6, 54.5, 61.4, 119.1, 124.4, 129.2, 138.4, 175.2 ppm. IR (neat): $\tilde{\nu}$ = 1690 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{11}NO_2$ $[M]^+$ 201.0790; found 201.0742. $C_{12}H_{11}NO_2$ (201.07): calcd. C 71.63, H 5.51, N 6.96; found C 71.45, H 5.65, N 6.88.

***rel*-(1*S*,4*S*,6*S*,7*R*)-6,7-Dibromo-2-phenyl-2-azabicyclo[2.2.1]heptan-3-one (6):** Yield 101 mg (74%); colorless crystals; m.p. 152.0–153.5 °C (hexane/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.68 (dd, *J* = 8.6, 14.3 Hz, 1 H), 2.81 (dt, *J* = 4.1, 14.3 Hz, 1 H), 3.11 (d, *J* = 11.2 Hz, 1 H), 4.14 (dd, *J* = 1.7, 8.0 Hz, 1 H), 4.48 (s, 1 H), 4.61 (s, 1 H), 7.18 (m, 1 H), 7.38 (d, *J* = 3.5 Hz, 4 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 34.3, 40.5, 46.9, 53.6, 68.8, 119.8, 125.5, 129.5, 136.0, 170.6 ppm. IR (neat): $\tilde{\nu}$ = 1708 cm^{-1}. HRMS: calcd. for $C_{12}H_{11}NOBr_2$ $[M]^+$ 342.9207 and 344.9187; found 342.9193 and 344.9188. $C_{12}H_{11}NOBr_2$ (342.91 and 344.91): calcd. C 41.77, H 3.21, N, 4.06; found C 41.88, H 3.13, N 3.99.

General Procedure for Treatment of Compounds 1 and 10 with Arylboronic Acids in the Presence of Catalytic Amounts of [Rh(COD)Cl]$_2$: Pulverized KOH (0.4 mmol) was added to a solution of a compound **1** or **10** (0.4 mmol), an arylboronic acid (0.6 mmol), and $[Rh(COD)Cl]_2$ (0.012 mmol) in MeOH/H_2O (10:1, 2 mL). The mixture was stirred at room temperature for 5 min, and then irradiated in a microwave reactor at 70 °C for a suitable time (noted in Tables 4 and 5). After cooling, the reaction mixture was diluted with AcOEt and washed with aq. NaOH solution (10%) and brine. The organic layer was dried with $MgSO_4$. The solvent was removed, and the residue was separated by silica gel column chromatography with hexane/AcOEt (3:1) to give a pair of compounds **7** and **8** (Table 4) or a pair of compounds **13** and **14** (94 mg, 66% combined yield).

***rel*-(1*S*,4*S*,6*R*)-6-Phenyl-2-azabicyclo[2.2.1]heptan-3-one (7a):** Colorless crystals; m.p. 86–87 °C (EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.78 (dd, *J* = 1.8, 9.7 Hz, 1 H), 1.95 (dt, *J* = 1.7, 10.3 Hz, 1 H), 2.08 (dt, *J* = 4.5, 13.2 Hz, 1 H), 2.16 (ddd, *J* = 2.1, 9.3, 13.0 Hz, 1 H), 2.83 (d, *J* = 2.9 Hz, 1 H), 3.26 (dd, *J* = 5.7, 7.9 Hz, 1 H), 3.90 (s, 1 H), 6.18 (br. s, 1 H), 7.21–7.24 (m, 3 H), 7.33 (t, *J* = 7.4 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.9, 38.5, 45.0, 48.7, 60.6, 126.6, 127.4, 128.7, 142.1, 181.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3432, 3196, 1690 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{13}NO$ $[M]^+$ 187.0997; found 187.0982. $C_{12}H_{13}NO$ (187.09): calcd. C 75.39, H 7.47, N, 7.99; found C 75.33, H 7.49, N 7.88.

***rel*-(1*R*,4*R*,5*R*)-5-Phenyl-2-azabicyclo[2.2.1]heptan-3-one (8a):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.82 (dd, *J* = 1.2, 10.3 Hz, 1 H), 1.99 (d, *J* = 11.5 Hz, 1 H), 2.05 (ddd, *J* = 2.3, 4.5, 12.4 Hz, 1 H), 2.25 (ddd, *J* = 2.2, 9.0, 12.5 Hz, 1 H), 2.88 (s, 1 H), 3.33 (dd, *J* = 5.2, 8.6 Hz, 1 H), 4.02 (s, 1 H), 5.61 (br. s, 1 H), 7.22 (m, 1 H), 7.24–7.25 (m, 2 H), 7.32 (t, *J* = 8.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.7, 38.9, 41.5, 51.3, 55.8, 126.6, 127.2, 128.74 142.8, 180.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 3204, 1682 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{13}NO$ $[M]^+$ 187.0997; found 187.1013.

***rel*-(1*S*,4*S*,6*R*)-2-Benzyl-6-phenyl-2-azabicyclo[2.2.1]heptan-3-one (7b):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.72 (d, J = 9.7 Hz, 1 H), 1.86 (dt, J = 1.7, 9.8 Hz, 1 H), 2.08 (dt, J = 4.6, 12.6 Hz, 1 H), 2.17 (ddd, J = 2.3, 8.5, 13.1 Hz, 1 H), 2.95 (d, J = 2.3 Hz, 1 H), 3.10 (dd, J = 5.1, 8.5 Hz, 1 H), 3.69 (d, J = 0.9 Hz, 1 H), 4.12 (d, J = 15.3 Hz, 1 H), 4.74 (d, J = 15.3 Hz, 1 H), 7.10 (d, J = 7.4 Hz, 2 H), 7.19 (t, J = 7.6 Hz, 1 H), 7.26–7.31 (m, 5 H), 7.33–7.37 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.0, 37.5, 44.4, 45.5, 45.8, 64.1, 126.6, 127.4, 127.8, 128.3, 128.9, 137.2, 142.1, 178.2 ppm. IR (neat): $\tilde{\nu}$ = 1692 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{19}NO$ $[M]^+$ 277.1467; found 277.1467.

***rel*-(1*R*,4*R*,5*R*)-2-Benzyl-5-phenyl-2-azabicyclo[2.2.1]heptan-3-one (8b):** ^{1}H NMR ($CDCl_3$): δ = 1.74 (d, J = 9.7 Hz, 1 H), 1.89 (dd, J = 2.3, 12.6 Hz, 1 H), 1.90 (ddd, J = 2.3, 4.6, 7.5 Hz, 1 H), 2.10 (ddd, J = 2.3, 9.2, 12.6 Hz, 1 H), 2.99 (d, J = 1.1 Hz, 1 H), 3.28 (dd, J = 5.1, 8.5 Hz, 1 H), 3.79 (s, 1 H), 4.04 (d, J = 14.7 Hz, 1 H), 4.73 (d, J = 14.7 Hz, 1 H), 7.20–7.25 (m, 3 H), 7.28–7.31 (m, 5 H), 7.32–7.36 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.5, 37.6, 42.5, 44.7, 52.1, 59.2, 126.5, 127.2, 127.6, 128.1, 128.7, 128.8, 137.2, 142.9, 177.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1680 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{19}NO$ $[M]^+$ 277.1467; found 277.1466.

***rel*-(1*S*,4*S*,6*R*)-2-(4-Methoxybenzyl)-6-phenyl-2-azabicyclo[2.2.1]-heptan-3-one (7c):** Colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.70 (d, J = 9.2 Hz, 1 H), 1.82 (dd, J = 1.8, 8.6 Hz, 1 H), 2.07 (m, 1 H), 2.14 (m, 1 H), 2.93 (s, 1 H), 3.08 (d, J = 5.2 Hz, 1 H), 3.68 (s, 1 H), 3.80 (s, 3 H), 4.09 (dd, J = 2.9, 14.9 Hz, 1 H), 4.64 (dd, J = 2.9, 14.9 Hz, 1 H), 6.87–6.88 (m, 2 H), 7.11 (d, J = 5.7 Hz, 2 H), 7.20–7.28 (m, 5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.2, 37.5, 43.8, 45.5, 45.9, 55.4, 63.9, 114.2, 126.5, 127.3, 128.7, 129.1, 129.5, 142.1, 159.2, 178.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1672 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{21}NO_2$ $[M]^+$ 307.1572; found 307.1561.

***rel*-(1*R*,4*R*,5*R*)-2-(4-Methoxybenzyl)-5-phenyl-2-azabicyclo[2.2.1]-heptan-3-one (8c):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.72 (d, J = 9.7 Hz, 1 H), 1.85 (m, 1 H), 1.87 (ddd, J = 2.3 5.2, 13.2 Hz, 1 H), 2.07 (ddd, J = 2.2, 9.0, 11.4 Hz, 1 H), 2.97 (d, J = 1.2 Hz, 1 H), 3.26 (dd, J = 5.1, 9.1 Hz, 1 H), 3.77 (s, 1 H), 3.81 (s, 3 H), 4.02 (d, J = 14.8 Hz, 1 H), 4.62 (d, J = 14.8 Hz, 1 H), 6.87 (d, J = 9.1 Hz, 2 H), 7.19–7.25 (m, 5 H), 7.30 (t, J = 5.6 Hz, 2 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 35.5, 37.7, 42.4, 44.2, 52.2, 55.4, 59.1, 114.2, 126.5, 127.2, 128.7, 129.2, 129.4, 143.0, 159.1, 177.8 ppm. IR (neat): $\tilde{\nu}$ = 1672 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{21}NO_2$ $[M]^+$ 307.1572; found 307.1571.

***rel*-(1*S*,4*S*,6*R*)-2,6-Diphenyl-2-azabicyclo[2.2.1]heptan-3-one (7d):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.92 (d, J = 9.7 Hz, 1 H), 2.07 (dt, J = 1.7, 10.2 Hz, 1 H), 2.21 (dt, J = 4.5, 13.0 Hz, 1 H), 2.32 (ddd, J = 2.2, 9.0, 13.1 Hz, 1 H), 3.05 (d, J = 1.7 Hz, 1 H), 3.48 (t, J = 7.4 Hz, 1 H), 4.45 (s, 1 H), 7.13 (t, J = 7.3 Hz, 1 H), 7.28 (t, J = 7.4 Hz, 1 H), 7.31 (d, J = 7.4 Hz, 2 H), 7.37 (t, J = 7.3 Hz, 4 H), 7.58 (d, J = 7.9 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.5, 36.7, 46.0, 47.2, 65.7, 119.0, 124.0, 126.9, 127.3, 128.9, 129.2, 138.1, 141.9, 176.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1684 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{17}NO$ $[M]^+$ 263.1310; found 263.1274.

***rel*-(1*R*,4*R*,5*R*)-2,5-Diphenyl-2-azabicyclo[2.2.1]heptan-3-one (8d):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.93 (d, J = 9.7 Hz, 1 H), 2.09 (dt, J = 9.7 Hz, 1 H), 2.16 (ddd, J = 2.3, 5.2, 12.6 Hz, 1 H), 2.51 (ddd, J = 2.3, 9.1, 12.0 Hz, 1 H), 3.09 (s, 1 H), 3.43 (dd, J = 5.1, 9.1 Hz, 1 H), 4.55 (s, 1 H), 7.12 (t, J = 7.5 Hz, 1 H), 7.24–7.29 (m, 4 H), 7.33 (t, J = 7.4 Hz, 1 H), 7.37 (t, J = 7.4 Hz, 2 H), 7.54 (d, J = 7.4 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.2, 37.0, 42.5, 53.41, 61.2, 119.1, 124.0, 126.7, 127.2, 128.8, 129.1, 138.3, 142.82, 176.0 ppm. IR (neat): $\tilde{\nu}$ = 1696 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{17}NO$ $[M]^+$ 263.1310; found 263.1229.

***rel*-(1*S*,4*S*,6*R*)-2-Methyl-6-phenyl-2-azabicyclo[2.2.1]heptan-3-one (7e):** Colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.72 (d, J = 9.7 Hz, 1 H), 1.88 (dd, J = 1.8, 9.7 Hz, 1 H), 2.07 (dd, J = 4.1, 5.2 Hz, 1 H), 2.12 (dd, J = 1.8, 9.7 Hz, 1 H), 2.84 (s, 3 H), 2.86 (s, 1 H), 3.20 (dd, J = 5.8, 9.2 Hz, 1 H), 3.72 (s, 1 H), 7.22–7.26 (m, 3 H), 7.32–7.35 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.4, 32.3, 37.2, 44.9, 45.6, 66.6, 126.6, 127.4, 128.8, 142.1, 178.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1682 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{15}NO$ $[M]^+$ 201.1154; found 201.1160.

***rel*-(1*R*,4*R*,5*R*)-2-Methyl-5-phenyl-2-azabicyclo[2.2.1]heptan-3-one (8e):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.77 (m, 1 H), 1.97 (m, 1 H), 2.04 (dd, J = 4.1, 5.2 Hz, 1 H), 2.15 (dd, J = 1.8, 9.7 Hz, 1 H), 2.80 (s, 3 H), 2.90 (s, 1 H), 3.24 (dd, J = 5.1, 8.6 Hz, 1 H), 3.81 (s, 1 H), 7.22–7.26 (m, 3 H), 7.32–7.35 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.8, 34.8, 37.2, 42.4, 51.9, 61.7, 126.5, 128.3, 128.7, 142.9, 178.5 ppm. IR (neat): $\tilde{\nu}$ = 1680 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{15}NO$ $[M]^+$ 201.1154; found 201.1147.

***rel*-(1*S*,4*S*,6*R*)-6-(4-Fluorophenyl)-2-azabicyclo[2.2.1]heptan-3-one (7f):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.75 (dd, J = 1.8, 9.8 Hz, 1 H), 1.97 (dt, J = 1.7, 9.8 Hz, 1 H), 2.03 (dt, J = 4.6, 13.2 Hz, 1 H), 2.18 (ddd, J = 2.3, 9.2, 13.2 Hz, 1 H), 2.84 (d, J = 3.4 Hz, 1 H), 3.23 (dd, J = 5.7, 8.0 Hz, 1 H), 3.86 (s, 1 H), 5.72 (br. s, 1 H), 7.02 (d, J = 8.6 Hz, 2 H), 7.19 (dd, J = 5.2, 9.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.2, 38.4, 44.9, 48.1, 60.6, 115.5, 115.6, 128.7, 128.8, 137.7, 1601.5, 180.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 1690 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{12}FNO$ $[M]^+$ 205.0903; found 205.0905.

***rel*-(1*R*,4*R*,5*R*)-5-(4-Fluorophenyl)-2-azabicyclo[2.2.1]heptan-3-one (8f):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.78 (d, J = 9.7 Hz, 1 H), 1.98–2.04 (m, 2 H), 2.25 (ddd, J = 1.8, 8.6, 12.1 Hz, 1 H), 2.83 (s, 1 H), 3.30 (dd, J = 5.2, 9.2 Hz, 1 H), 4.02 (s, 1 H), 5.51 (br. s, 1 H), 7.01 (t, J = 8.6 Hz, 2 H), 7.21 (dd, J = 5.2, 9.0 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.8, 39.0, 40.8, 51.3, 55.8, 115.4, 115.6, 128.6, 128.6, 136.1, 138.4, 161.6, 180.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3444, 1686 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{12}FNO$ $[M]^+$ 205.0903; found 205.0899.

***rel*-(1*S*,4*S*,6*R*)-6-(4-Methoxyphenyl)-2-azabicyclo[2.2.1]heptan-3-one (7 g):** Colorless crystals; m.p. 80–81 °C (hexane/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73 (dd, J = 1.7, 9.7 Hz, 1 H), 1.93–1.98 (m, 2 H), 2.13 (ddd, J = 2.3, 9.2, 1 3.2 Hz, 1 H), 2.81 (d, J = 2.9 Hz, 1 H), 3.44 (dd, J = 6.3, 8.6 Hz, 1 H), 3.84 (s, 3 H), 3.89 (s, 1 H), 5.56 (br. s, 1 H), 6.88 (d, J = 8.1 Hz, 1 H), 6.93 (t, J = 8.0 Hz, 1 H), 7.11 (d, J = 7.5 Hz, 1 H), 7.23 (dd, J = 1.8, 8.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.1, 38.6, 42.3, 44.9, 55.4, 59.2, 110.3, 120.3, 125.8, 127.6, 130.6, 157.4, 181.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 1694 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{15}NO_2$ $[M]^+$ 217.1103; found 217.1104. $C_{13}H_{15}NO_2$ (217.11): calcd. C 71.86, H 6.96, N 7.45; found C 71.77, H 7.08, N 7.33.

***rel*-(1*R*,4*R*,5*R*)-5-(4-Methoxyphenyl)-2-azabicyclo[2.2.1]heptan-3-one (8 g):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.80 (dd, J = 1.7, 10.3 Hz, 1 H), 1.97 (d, J = 9.8 Hz, 1 H), 2.02 (ddd, J = 2.9, 5.1, 13.2 Hz, 1 H), 2.21 (ddd, J = 2.2, 8.5, 11.9 Hz, 1 H), 2.81 (s, 1 H), 3.28 (dd, J = 5.1, 8.5 Hz, 1 H), 3.79 (s, 3 H), 4.01 (s, 1 H), 5.48 (br. s, 1 H), 6.86 (d, J = 9.0 Hz, 2 H), 7.17 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.7, 38.8, 40.8, 51.6, 55.4, 55.8, 114.1, 128.2, 134.7, 158.2, 180.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3432, 1692 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{15}NO_2$ $[M]^+$ 217.1103; found 217.1095.

***rel*-(1*S*,4*S*,6*R*)-6-(3-Methoxyphenyl)-2-azabicyclo[2.2.1]heptan-3-one (7h):** Colorless crystals; m.p. 210–212 °C (hexane/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.79 (dd, J = 1.7, 9.7 Hz, 1 H), 1.96 (dt, J = 1.8, 9.7 Hz, 1 H), 2.06 (dt, J = 4.6, 13.2 Hz, 1 H), 2.16 (ddd, J = 2.3, 8.6, 13.2 Hz, 1 H), 2.83 (s, 1 H), 3.22 (dd, J = 5.2, 8.6 Hz, 1 H), 3.81 (s, 3 H), 3.89 (s, 1 H), 5.68 (br. s, 1 H), 6.76 (s, 1 H), 6.77 (m, 1 H), 6.81 (d, J = 7.5 Hz, 1 H), 7.25 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.0, 38.6, 44.9, 48.7, 55.3, 60.5, 111.4, 113.8, 119.6, 129.7, 143.8, 159.9, 181.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 1694 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{15}NO_2$ [M]$^+$ 217.1103; found 217.1104. $C_{13}H_{15}NO_2$ (217.11): calcd. C 71.86, H 6.96, N 7.45; found C 71.67, H 7.05, N 7.33.

***rel*-(1*S*,4*S*,6*R*)-5-(3-Methoxyphenyl)-2-azabicyclo[2.2.1]heptan-3-one (8h):** Colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.81 (d, J = 10.3 Hz, 1 H), 1.97 (dt, J = 1.8, 10.3 Hz, 1 H), 2.04 (m, 1 H), 2.23 (ddd, J = 2.3, 9.2, 12.0 Hz, 1 H), 2.86 (s, 1 H), 3.30 (dd, J = 5.2, 9.2 Hz, 1 H), 3.79 (s, 3 H), 4.01 (s, 1 H), 5.70 (br. s, 1 H), 6.76 (m, 1 H), 6.81 (d, J = 7.5 Hz, 1 H), 6.84 (d, J = 8.1 Hz, 1 H), 7.23 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.7, 38.9, 41.5, 51.3, 55.3, 55.8, 111.5, 113.5, 119.5, 129.7, 144.5, 159.8, 180.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3432, 1698 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{15}NO_2$ [M]$^+$ 217.1103; found 217.1103.

***rel*-(1*S*,4*S*,6*R*)-6-(2-Methoxyphenyl)-2-azabicyclo[2.2.1]heptan-3-one (7i):** Colorless crystals; m.p. 80–81 °C (hexane/CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73 (dd, J = 1.7, 9.7 Hz, 1 H), 1.93–1.98 (m, 2 H), 2.13 (ddd, J = 2.3, 9.2, 1 3.2 Hz, 1 H), 2.81 (d, J = 2.9 Hz, 1 H), 3.44 (dd, J = 6.3, 8.6 Hz, 1 H), 3.84 (s, 3 H), 3.89 (s, 1 H), 5.56 (br. s, 1 H), 6.88 (d, J = 8.1 Hz, 1 H), 6.93 (t, J = 8.0 Hz, 1 H), 7.11 (d, J = 7.5 Hz, 1 H), 7.23 (dd, J = 1.8, 8.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.1, 38.6, 42.3, 44.9, 55.4, 59.2, 110.3, 120.3, 125.8, 127.6, 130.6, 157.4, 181.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 1694 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{15}NO_2$ [M]$^+$ 217.1103; found 217.1104. $C_{13}H_{15}NO_2$: calcd. C 71.86, H 6.96, N 7.45; found C 71.96, H 6.77, N 7.23.

***rel*-(1*R*,4*R*,5*R*)-5-(2-Methoxyphenyl)-2-azabicyclo[2.2.1]heptan-3-one (8i):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.80–1.84 (m, 2 H), 2.00 (m, 1 H), 2.26 (ddd, J = 2.3, 9.2, 13.2 Hz, 1 H), 2.89 (s, 1 H), 3.50 (dd, J = 4.0, 8.6 Hz, 1 H), 3.84 (s, 3 H), 3.97 (s, 1 H), 5.44 (br. s, 1 H), 6.87 (d, J = 8.0 Hz, 1 H), 6.92 (t, J = 6.9 Hz, 1 H), 7.12 (dd, J = 1.2, 6.9 Hz, 1 H), 7.22 (td, J = 1.2, 8.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 35.5, 38.7, 39.3, 49.0, 55.4, 55.81, 110.3, 120.2, 125.2, 127.5, 131.4, 132.1, 181.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 3348, 1694 cm^{-1}. HRMS (EI): calcd. for $C_{13}H_{15}NO_2$ [M]$^+$ 217.1103; found 217.1106.

***rel*-(1*S*,4*S*,6*R*)-6-(1-Naphthyl)-2-azabicyclo[2.2.1]heptan-3-one (7j):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.94 (m, 1 H), 2.06 (m, 1 H), 2.10 (m, 1 H), 2.46 (m, 1 H), 3.09 (s, 1 H), 3.96 (dd, J = 5.0, 13.7 Hz, 1 H), 4.06 (s, 1 H), 5.56 (br. s, 1 H), 7.32 (d, J = 7.5 Hz, 1 H), 7.43 (t, J = 7.4 Hz, 1 H), 7.50–7.58 (m, 2 H), 7.75 (d, J = 8.6 Hz, 1 H), 7.87 (d, J = 8.6 Hz, 1 H), 8.08 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.0, 39.4, 39.5, 49.9, 55.8, 121.6, 123.8, 125.3, 125.9, 126.4, 127.4, 128.9, 132.1, 134.1, 138.5, 181.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3488, 3416, 1700 cm^{-1}. HRMS (EI) *m*/*z*: calcd. for $C_{16}H_{15}NO$ [M]$^+$ 237.1154; found 237.1090.

***rel*-(1*R*,4*R*,5*R*)-5-(1-Naphthyl)-2-azabicyclo[2.2.1]heptan-3-one (8j):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.97 (d, J = 8.1 Hz, 1 H), 1.99 (dd, J = 5.2, 8.0 Hz, 1 H), 2.13 (dt, J = 1.8, 9.7 Hz, 1 H), 2.46 (ddd, J = 1.8, 9.7, 21.8 Hz, 1 H), 2.88 (d, J = 3.5 Hz, 1 H), 3.82 (dd, J = 5.8, 8.6 Hz, 1 H), 4.21 (s, 1 H), 5.66 (br. s, 1 H), 7.25 (m, 1 H), 7.43 (t, J = 8.6 Hz, 1 H), 7.50–7.57 (m, 2 H), 7.75 (d, J = 8.6 Hz, 1 H), 7.87 (d, J = 8.6 Hz, 1 H), 7.99 (d, J = 8.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.4, 39.4, 44.9, 59.0, 121.8, 123.6, 125.3, 125.9, 126.4, 127.3, 129.1, 131.9, 134.0, 138.8, 181.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 3348, 1696, 1622 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{15}NO$ [M]$^+$ 237.1154; found 237.1134.

***rel*-(1*S*,4*S*,6*R*)-6-(2-Naphthyl)-2-azabicyclo[2.2.1]heptan-3-one (7k):** Colorless crystals; m.p. 140–142 °C (propan-2-ol). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.95 (dd, J = 1.7, 10.3 Hz, 1 H), 2.01 (dt, J = 1.7, 10.3 Hz, 1 H), 2.19–2.28 (m, 2 H), 2.89 (s, 1 H), 3.42 (t, J = 6.9 Hz, 1 H), 4.02 (s, 1 H), 5.64 (br. s, 1 H), 7.36 (dd, J = 1.7, 8.6 Hz, 1 H), 7.44–7.50 (m, 2 H), 7.63 (s, 1 H), 7.81 (t, J = 9.7 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.9, 38.5, 45.0, 48.9, 60.4, 124.9, 125.9, 126.4, 126.5, 127.6, 127.7, 128.5, 132.2, 133.4, 139.5, 181.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 1696, 1652 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{15}NO$ [M]$^+$ 237.1154; found 237.1079. $C_{16}H_{15}NO$ (237.10): calcd. C 80.98, H 6.37, N 5.90; found C 80.79, H 6.44, N 5.81.

***rel*-(1*R*,4*R*,5*R*)-5-(2-Naphthyl)-2-azabicyclo[2.2.1]heptan-3-one (8k):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.89 (d, J = 9.8 Hz, 1 H), 2.03 (m, 1 H), 2.18 (ddd, J = 2.3, 5.1, 12.5 Hz, 1 H), 2.32 (ddd, J = 2.3, 9.1, 11.3 Hz, 1 H), 2.99 (s, 1 H), 3.49 (dd, J = 5.1, 9.0 Hz, 1 H), 4.07 (s, 1 H), 5.55 (br. s, 1 H), 7.39 (dd, J = 1.7, 8.5 Hz, 1 H), 7.46 (dq, J = 1.7, 7.4 Hz, 2 H), 7.66 (s, 1 H), 7.80 (t, J = 8.5 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.6, 38.9, 41.6, 53.5, 55.9, 124.58, 125.8, 126.3, 126.7, 127.6, 127.7, 128.4, 132.2, 133.4, 140.2, 180.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3432, 1698 cm^{-1}. HRMS (EI): calcd. for $C_{16}H_{15}NO$ [M]$^+$ 237.1154; found 237.1090.

***rel*-(1*S*,4*S*,6*R*)-6-(3-Thiophenyl)-2-azabicyclo[2.2.1]heptan-3-one (7l):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.72 (dd, J = 1.1, 9.7 Hz, 1 H), 1.95 (dd, J = 1.7, 9.7 Hz, 1 H), 2.03 (dt, J = 4.6, 13.2 Hz, 1 H), 2.16 (ddd, J = 1.7, 8.6, 10.9 Hz, 1 H), 2.81 (d, J = 2.3 Hz, 1 H), 3.25 (dd, J = 5.2, 8.6 Hz, 1 H), 3.87 (s, 1 H), 6.07 (br. s, 1 H), 6.98 (d, J = 4.0 Hz, 2 H), 7.30 (t, J = 4.6 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.1, 38.9, 44.4, 44.6, 61.6, 123.8, 124.1, 127.1, 146.3, 180.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3430, 1695 cm^{-1}. HRMS (EI): calcd. for $C_{10}H_{11}NOS$ [M]$^+$ 193.0561; found 193.0566.

***rel*-(1*R*,4*R*,5*R*)-5-(3-Thiophenyl)-2-azabicyclo[2.2.1]heptan-3-one (8l):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.74 (dd, J = 1.2, 9.7 Hz, 1 H), 1.97 (d, J = 9.7 Hz, 1 H), 2.03 (ddd, J = 2.3, 4.6, 12.6 Hz, 1 H), 2.21 (ddd, J = 2.3, 9.2, 12.0 Hz, 1 H), 2.83 (s, 1 H), 3.33 (dd, J = 5.2, 9.2 Hz, 1 H), 4.00 (d, J = 1.2 Hz, 1 H), 5.60 (br. s, 1 H), 7.00 (dd, J = 1.8, 2.9 Hz, 1 H), 7.01 (dd, J = 1.7, 5.2 Hz, 1 H), 7.30 (dd, J = 2.9, 5.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.5, 38.8, 39.0, 51.6, 55.7, 119.9, 126.2, 127.8, 143.9, 180.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3463, 1683 cm^{-1}. HRMS (EI): calcd. for $C_{10}H_{11}NOS$ [M]$^+$ 193.0561; found 193.0557.

***rel*-(1*S*,4*S*,6*R*)-6-(2-Thiophenyl)-2-azabicyclo[2.2.1]heptan-3-one (7m):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.84 (dd, J = 1.8, 11.5 Hz, 1 H), 1.99 (dt, J = 1.7, 10.3 Hz, 1 H), 2.08 (dt, J = 4.6, 13.2 Hz, 1 H), 2.25 (ddd, J = 2.3, 5.6, 13.2 Hz, 1 H), 2.83 (d, J = 2.9 Hz, 1 H), 3.43 (dd, J = 4.6, 8.6 Hz, 1 H), 3.87 (s, 1 H), 5.74 (br. s, 1 H), 6.86 (m, 1 H), 6.96 (dd, J = 3.4, 5.2 Hz, 1 H), 7.18 (dd, J = 1.2, 5.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.1, 38.8, 44.4, 44.6, 61.6, 123.8, 124.1, 127.1, 146.3, 180.6 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3467, 1690 cm^{-1}. HRMS (EI): calcd. for $C_{10}H_{11}NOS$ [M]$^+$ 193.0561; found 193.0560.

***rel*-(1*R*,4*R*,5*R*)-5-(2-Thiophenyl)-2-azabicyclo[2.2.1]heptan-3-one (8m):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.88 (dd, J = 1.5, 10.0 Hz, 1 H), 2.02 (m, 1 H), 2.08 (ddd, J = 1.8, 4.6, 12.6 Hz, 1 H), 2.30 (ddd, J = 2.9, 9.2, 12.6 Hz, 1 H), 2.86 (s, 1 H), 3.53 (dd, J = 5.2, 8.6 Hz, 1 H), 4.02 (d, J = 2.9 Hz, 1 H), 5.48 (br. s, 1 H),

6.88 (dt, J = 1.2, 3.5, Hz, 1 H), 6.95 (dd, J = 3.5, 5.2 Hz, 1 H), 7.16 (dd, J = 1.2, 5.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 37.6, 39.2, 40.6, 52.9, 55.5, 123.7, 124.1, 127.0, 147.2, 179.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3445, 1685 cm^{-1}. HRMS (EI): calcd. for $C_{10}H_{11}NOS$ $[M]^+$ 193.0561; found 193.0573.

***rel*-(1*S*,4*S*,6*R*)-6-(6-Chloropyridin-3-yl)-2-azabicyclo[2.2.1]heptan-3-one (7n):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.70 (dd, J = 3.4, 10.3 Hz, 1 H), 1.98 (dd, J = 2.3, 5.2 Hz, 1 H), 2.00–2.06 (m, 1 H), 2.24 (ddd, J = 2.3, 9.2, 11.5 Hz, 1 H), 2.86 (d, J = 2.3 Hz, 1 H), 3.25 (dd, J = 5.2, 13.8 Hz, 1 H), 4.06 (s, 1 H), 6.35 (br. s, 1 H), 7.28 (d, J = 6.3 Hz, 1 H), 7.52 (ddd, J = 2.3, 8.0, 10.9 Hz, 1 H), 8.29 (d, J = 2.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 30.8, 38.6, 45.1, 45.7, 60.1, 124.2, 137.5, 137.8, 148.8, 149.5, 181.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 1696, 1652 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{11}ClN_2O$ $[M]^+$ 222.0560 and 224.0530; found 222.0550 and 224.0532.

***rel*-(1*R*,4*R*,5*R*)-5-(6-Chloropyridin-3-yl)-2-azabicyclo[2.2.1]heptan-3-one (8n):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.73 (dd, J = 3.0, 10.3 Hz, 1 H), 2.02 (dt, J = 2.3, 8.6 Hz, 1 H), 2.00–2.06 (m, 1 H), 2.31 (ddd, J = 2.3, 9.2, 12.1 Hz, 1 H), 2.84 (s, 1 H), 3.31 (dd, J = 5.2, 9.2 Hz, 1 H), 3.90 (s, 1 H), 6.20 (br. s, 1 H), 7.31 (d, J = 6.3 Hz, 1 H), 7.52 (ddd, J = 2.3, 8.0, 10.9 Hz, 1 H), 8.31 (d, J = 2.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.7, 38.8, 39.0, 50.9, 55.8, 124.2, 137.3, 137.6, 148.6, 149.9, 180.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 1696 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_{11}ClN_2O$ $[M]^+$ 222.0560 and 224.0530; found 222.0574 and 224. 0522.

Methyl *rel*-(1*R*,4*S*)-4-(Benzoylamino)cyclopent-2-ene-1-carboxylate (9a):[23] Yield 32 mg (32%); colorless crystals; m.p. 145–146 °C (EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.98 (m, 1 H), 2.60 (m, 1 H), 3.57 (m, 1 H), 3.68 (s, 3 H), 4.99 (br. s, 1 H), 5.11 (m, 1 H), 5.90 (m, 1 H), 5.99 (dt, J = 1.7, 5.7 Hz, 1 H), 7.41 (t, J = 7.5 Hz, 2 H), 7.49 (t, J = 4.9 Hz, 1 H), 7.79 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 33.8, 49.1, 51.4, 55.3, 127.0, 128.2, 132.0, 133.0, 168.1, 174.9, 176.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3378, 1708, 1644 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{15}NO_3$ $[M]^+$ 245.1052; found 245.1047. $C_{14}H_{15}NO_3$ (245.10): calcd. C 68.55, H 6.16, N 5.71; found C 68.39, H 6.20, N 5.58.

Methyl *rel*-(1*R*,4*S*)-4-[(*tert*-Butoxycarbonyl)amino]cyclopent-2-ene-1-carboxylate (9b):[24] Yield 76 mg (79%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 1. 84 (dt, J = 8.0, 14.3 Hz, 1 H), 2.48 (dt, J = 8.5, 14.2 Hz, 1 H), 3.46 (dd, J = 4.0, 7.9 Hz, 1 H), 3.69 (s, 3 H), 4.76 (m, 1 H), 4.91 (br. d, J = 7.9 Hz, 1 H), 5.83–5.88 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.5, 34.6, 49.2, 52.2, 55.8, 79.4, 131.2, 134.9, 155.2, 175.0 ppm. IR (neat): $\tilde{\nu}$ = 3364, 1682 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{19}NO_4$ $[M]^+$ 241.1314; found 241.1310.

Methyl *rel*-(1*R*,4*S*)-4-[(Phenoxycarbonyl)amino]cyclopent-2-ene-1-carboxylate (9c): Yield 49 mg (47%); colorless crystals; m.p. 78–79 °C (EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.00 (dt, J = 3.5, 14.3 Hz, 1 H), 2.53 (dt, J = 8.6, 13.8 Hz, 1 H), 3.53 (d, J = 5.8 Hz, 1 H), 3.73 (s, 3 H), 4.89 (t, J = 8.0 Hz, 1 H), 5.55 (br. d, J = 8.0 Hz, 1 H), 5.93 (m, 1 H), 5.96 (m, 1 H), 7.12 (d, J = 7.5 Hz, 2 H), 7.18 (t, J = 7.5 Hz, 1 H), 7.34 (t, J = 7.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 34.4, 49.3, 52.4, 56.5, 121.7, 125.3, 129.3, 131.9, 134.4, 151.1, 154.0, 175.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3428, 1698 cm^{-1}. HRMS (EI): calcd. for $C_{14}H_{15}NO_4$ $[M]^+$ 261.1001; found 261.0982. $C_{14}H_{15}NO_4$ (261.10): calcd. C 64.36, H 5.78, N 5.36; found C 64.41, H 5.77, N 5.20.

***rel*-(1*R*,4*R*,6*R*,7*R*)-2-Benzyl-7-bromo-6-phenyl-2-azabicyclo[2.2.1]heptan-3-one (13):** Colorless oil. ^{1}H NMR ($CDCl_3$): δ = 2.37 (dd, J = 9.2, 12.6 Hz, 1 H), 2.74 (ddd, J = 2.3, 6.3, 9.2 Hz, 1 H), 3.06 (t, J = 1.8 Hz, 1 H), 3.26 (t, J = 7.5 Hz, 1 H), 4.06 (d, J = 14.9 Hz, 1 H), 4.12 (t, J = 1.7 Hz, 1 H), 4.23 (s, 1 H), 4.83 (d, J = 14.9 Hz, 1 H), 7.17–7.19 (m, 3 H), 7.25–7.27 (m, 2 H), 7.29–7.32 (m, 2 H), 7.35 (m, 1 H), 7.38–7.41 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.3, 44.3, 44.9, 50.1, 52.1, 65.8, 126.2, 127.0, 128.2, 128.4, 129.2, 136.0, 140.5, 173.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1690 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{18}BrNO$ $[M]^+$ 355.0572 and 357.0551; found 355.0580 and 357.0562.

***rel*-(1*R*,4*R*,5*R*,7*R*)-2-Benzyl-7-bromo-5-phenyl-2-azabicyclo[2.2.1]-heptan-3-one (14):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.21 (dd, J = 9.2, 12.6 Hz, 1 H), 2.63 (ddd, J = 2.3, 6.3, 13.2 Hz, 1 H), 3.41 (dd, J = 6.3, 9.2 Hz, 1 H), 3.51 (t, J = 1.7 Hz, 1 H), 3.85 (s, 1 H), 4.22 (s, 1 H), 4.26 (d, J = 14.9 Hz, 1 H), 4.62 (d, J = 14.9 Hz, 1 H), 7.25–7.30 (m, 6 H), 7.33–7.38 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.1, 41.7, 45.2, 49.8, 54.9, 64.1, 126.2, 127.2, 128.1, 128.2, 128.3, 129.1, 136.3, 141.0, 173.9 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1685 cm^{-1}. HRMS (EI): calcd. for $C_{19}H_{18}BrNO$ $[M]^+$ 355.0572 and 357.0551; found 355.0566 and 357.0553.

Conversion of 13 and 14 into 7b and 8b: A mixture of **13** (36 mg, 0.1 mmol), Et_3N (101 mg, mmol), and Pd on C (10%, 36 mg) in EtOH (5 mL) was stirred for 6 h under hydrogen (atmospheric pressure). Insoluble materials were removed by filtration, and the filtrate was concentrated in vacuo. The residue was separated by silica gel column chromatography with hexane/AcOEt (3:1) to give **7b** (24 mg, 88%). The same treatment of **14** (30 mg, 0.08 mmol) produced **8b** (19 mg, 87%).

Conversion of 7b and 8b into 7a and 8a: Catalytic hydrogenation of **7b** (27 mg) with Pd on C (10%, 27 mg) in MeOH (5 mL) was carried out under hydrogen (atmospheric pressure) for 6 h. Insoluble materials were removed by filtration, and the filtrate was concentrated in vacuo. The residue was separated by silica gel column chromatography with hexane/AcOEt (3:1) to give **7a** (17 mg, 90%). The same treatment of **8b** (20 mg, 0.07 mmol) produced **8a** (12 mg, 90%).

Sequential One-Pot Treatment of 1a with Phenylboronic Acid: Et_3N (40 mg, 0.4 mmol) was added to a solution of **1a** (44 mg, 0.4 mmol), phenylboronic acid (73 mg, 0.6 mmol), and $[Rh(COD)Cl]_2$ (6 mg, 0.012 mmol) in MeOH/H_2O (10:1, 2 mL). The mixture was stirred at room temperature for 5 min, and irradiated in a microwave reactor with magnetic stirring for 0.5 h at 70 °C. After it had cooled, additional phenylboronic acid (73 mg, 0.6 mmol), $Cu(OAc)_2$ (73 mg, 0.4 mmol), Et_3N (40 mg, 0.4 mmol), $Me_3N(O)$ (33 mg, 0.44 mmol), and MeCN (2 mL) were added. The mixture was stirred at room temperature for 5 min and irradiated in a microwave reactor with magnetic stirring for 0.5 h at 80 °C. After cooling, the reaction mixture was diluted with AcOEt, and insoluble materials were removed by filtration with suction. The filtrate was concentrated and the residue was diluted with AcOEt and washed with aq. NaOH solution (10%), H_2O, and brine. The organic layer was dried with $MgSO_4$. The solvent was removed in vacuo, and the residue was separated by silica gel column chromatography with hexane/AcOEt (3:1) to give **7d** and **8d** (20 mg, 19% combined yield).

One-Pot Treatment of 1a with Phenylboronic Acid in the Presence of Stoichiometric Amounts of $Cu(OAc)_2$ and Catalytic Amounts of $[Rh(cod)Cl]_2$: Et_3N (202 mg, 2.0 mmol) was added to a solution of **1a** (44 mg, 0.4 mmol), phenylboronic acid (146 mg, 1.2 mmol), $[Rh(COD)Cl]_2$ (6 mg, 0.012 mmol), $Cu(OAc)_2$ (73 mg, 0.4 mmol), and $Me_3N(O)$ (33 mg, 0.44 mmol) in MeOH/MeCN (1:1, 2 mL). The mixture was stirred at room temperature for 5 min and irradiated in a microwave reactor with magnetic stirring for 0.5 h at

80 °C. After cooling, the reaction mixture was diluted with AcOEt, and insoluble materials were removed by filtration with suction. The filtrate was concentrated and the residue was diluted with AcOEt and washed with aq. NaOH solution (10%), H_2O, and brine. The organic layer was dried with $MgSO_4$. The solvent was removed in vacuo, and the residue was separated by silica gel column chromatography with hexane/AcOEt (3:1) to give **7a** and **8a** as a pair (57 mg, 76% combined yield).

General Procedure for One-Pot Treatment of 1a with Arylboronic Acids in the Presence of Catalytic Amounts of $Cu(OAc)_2$ and $[Rh(COD)Cl]_2$: Pulverized KOH (112 mg, 2.0 mmol) was added to a solution of **1a** (44 mg, 0.4 mmol), an arylboronic acid (1.2 mmol), $[Rh(COD)Cl]_2$ (6 mg, 0.012 mmol), $Cu(OAc)_2$ (7.3 mg, 0.04 mmol), and $Me_3N(O)$ (33 mg, 0.44 mmol) in MeOH/MeCN (1:1, 2 mL). The mixture was stirred at room temperature for 5 min and irradiated in a microwave reactor with magnetic stirring for 1 h at 80 °C. After cooling, the reaction mixture was diluted with AcOEt, and insoluble materials were removed by filtration with suction. The filtrate was concentrated and the residue was diluted with AcOEt and washed with aq. NaOH solution (10%), H_2O, and brine. The organic layer was dried with $MgSO_4$. The solvent was removed in vacuo, and the residue was separated by silica gel column chromatography with hexane/AcOEt (3:1) to give pairs variously of **7d** and **8d** (63 mg, 61% combined yield), **15a** and **16a** (67 mg, 40% combined yield) along with **7o** and **8o** (12 mg, 12% combined yield), **15b** and **16b** (47 mg, 36% combined yield) along with **7g** and **8g** (13 mg, 15% combined yield), **15c** and **16c** (40 mg, 31% combined yield), and **15d** and **16d** (58 mg, 45% combined yield). The same treatment of **1a** with 2-bromophenylboronic acid afforded **2k**.

***rel*-(1*S*,4*S*,6*R*)-2,6-Bis(4-bromophenyl)-2-azabicyclo[2.2.1]heptan-3-one (15a):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.86 (d, J = 10.3 Hz, 1 H), 2.07 (m, 1 H), 2.13 (dt, J = 4.6, 13.7 Hz, 1 H), 2.32 (ddd, J = 2.3, 9.2, 13.2 Hz, 1 H), 3.04 (d, J = 1.7 Hz, 1 H), 3.36 (dd, J = 5.8, 8.6 Hz, 1 H), 4.37 (s, 1 H), 7.16 (d, J = 8.6 Hz, 2 H), 7.46 (d, J = 8.6 Hz, 4 H), 7.49 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.7, 36.5, 45.5, 47.0, 116.9, 120.5, 120.9, 132.1, 132.2, 137.0, 140.7, 176.2 ppm. IR (neat): $\tilde{\nu}$ = 1705 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{15}Br_2NO$ $[M]^+$ 418.9520, 420.9500, and 422.9479; found 418.9519, 420.9498, and 422.9480.

***rel*-(1*S*,4*S*,6*R*)-2,5-Bis(4-bromophenyl)-2-azabicyclo[2.2.1]heptan-3-one (16a):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (d, J = 9.8 Hz, 1 H), 2.07–2.10 (m, 2 H), 2.46 (dt, J = 4.6, 13.7 Hz, 1 H), 3.05 (d, J = 1.7 Hz, 1 H), 3.36 (dd, J = 5.2, 9.2 Hz, 1 H), 4.83 (s, 1 H), 6.71 (d, J = 8.6 Hz, 2 H), 7.32 (d, J = 8.6 Hz, 2 H), 7.42–7.48 (m, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.0, 37.0, 41.9, 53.1, 61.4, 117.4, 120.8, 128.9, 129.5, 131.9, 132.2, 132.5, 137.0, 141.3, 176.3 ppm. IR (neat): $\tilde{\nu}$ = 1700 cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{15}Br_2NO$ $[M]^+$ 418.9520, 420.9500, and 422.9479; found 418.9522, 420.9506, and 422.9479.

***rel*-(1*S*,4*S*,6*R*)-2,6-Bis(4-methoxyphenyl)-2-azabicyclo[2.2.1]-heptan-3-one (15b):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.86 (d, J = 9.8 Hz, 1 H), 2.04 (dt, J = 1.7, 10.3 Hz, 1 H), 2.14 (dt, J = 4.0, 13.8 Hz, 1 H), 2.28 (ddd, J = 1.8, 9.2, 12.6 Hz, 1 H), 3.00 (d, J = 1.7 Hz, 1 H), 3.40 (dd, J = 5.2, 8.6 Hz, 1 H), 3.79 (s, 3 H), 3.81 (s, 3 H), 4.29 (d, J = 1.7 Hz, 1 H), 6.89 (d, J = 7.5 Hz, 2 H), 6.91 (d, J = 7.5 Hz, 2 H), 7.20 (d, J = 9.2 Hz, 2 H), 7.46 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.5, 36.8, 45.3, 47.0, 55.4, 55.6, 66.6, 114.2, 114.4, 121.0, 128.4, 131.4, 134.0, 156.3, 158.4, 176.4 ppm. IR (neat): $\tilde{\nu}$ = 1695 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{21}NO_3$ $[M]^+$ 323.1521; found 323.1516.

***rel*-(1*S*,4*S*,6*R*)-2,5-Bis(4-methoxyphenyl)-2-azabicyclo[2.2.1]-heptan-3-one (16b):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.87 (d, J = 9.7 Hz, 1 H), 2.07 (dt, J = 2.3, 7.5 Hz, 1 H), 2.08 (ddd, J = 2.9, 5.2, 15.5 Hz, 1 H), 2.44 (ddd, J = 2.5, 11.3, 12.6 Hz, 1 H), 3.00 (d, J = 1.2 Hz, 1 H), 3.37 (dd, J = 4.6, 8.6 Hz, 1 H), 3.70–3.80 (3 × s, 6 H), 4.44 (s, 1 H), 6.86 (d, J = 8.6 Hz, 2 H), 6.90 (d, J = 8.6 Hz, 2 H), 7.19 (d, J = 9.2 Hz, 2 H), 7.42 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.3, 37.1, 41.8, 53.6, 55.4, 55.6, 61.8, 114.1, 114.4, 121.2, 128.2, 131.7, 134.9, 156.4, 158.3, 176.0 ppm. IR (neat): $\tilde{\nu}$ = 1693 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{21}NO_3$ $[M]^+$ 323.1521; found 323.1520.

***(rel)*-(1*S*,4*S*,6*R*)-2,6-Bis(2-methoxyphenyl)-2-azabicyclo[2.2.1]-heptan-3-one (15c):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.75 (ddd, J = 2.3, 5.2, 13.2 Hz, 1 H), 1.85 (d, J = 9.2 Hz, 1 H), 2.21 (d, J = 9.2 Hz, 1 H), 2.47 (ddd, J = 2.3, 8.6, 12.1 Hz, 1 H), 3.07 (s, 1 H), 3.67 (dd, J = 5.8, 9.2 Hz, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 4.31 (s, 1 H), 6.88 (d, J = 8.0 Hz, 1 H), 6.93 (t, J = 7.5 Hz, 1 H), 6.95–6.99 (m, 2 H), 7.17 (d, J = 7.4 Hz, 1 H), 7.21–7.25 (m, 2 H), 7.33 (dd, J = 1.8, 9.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 36.1, 36.4, 38.2, 50.2, 55.5, 55.8, 63.5, 110.4, 112.2, 120.3, 121.0, 125.4, 126.4, 127.4, 127.8, 128.0, 131.9, 154.6, 157.7, 177.6 ppm. IR (neat): $\tilde{\nu}$ = 1694 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{21}NO_3$ $[M]^+$ 323.1521; found 323.1519.

***(rel)*-(1*R*,4*R*,5*R*)-2,5-Bis(2-methoxyphenyl)-2-azabicyclo[2.2.1]-heptan-3-one (16c):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.79 (dt, J = 1.7, 9.8 Hz, 1 H), 1.95 (ddd, J = 4.6, 5.2, 13.2 Hz, 1 H), 2.19 (dt, J = 21.7, 9.8 Hz, 1 H), 2.38 (ddd, J = 2.3, 9.2, 15.5 Hz, 1 H), 2.96 (d, J = 2.3 Hz, 1 H), 3.60 (dd, J = 5.2, 9.2 Hz, 1 H), 3.71 (s, 3 H), 3.84 (s, 3 H), 4.34 (d, J = 1.2 Hz, 1 H), 6.81 (dd, J = 1.2, 8.0 Hz, 1 H), 6.90 (td, J = 1.2, 7.5 Hz, 1 H), 6.94 (dd, J = 3.4, 8.6 Hz, 1 H), 6.97 (td, J = 1.2, 7.5 Hz, 1 H), 7.10 (d, J = 8.0 Hz, 1 H), 7.17–7.24 (m, 2 H), 7.37 (dd, J = 1.8, 8.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.7, 38.0, 39.8, 46.4, 55.3, 55.8, 66.3, 110.3, 112.2, 120.3, 120.9, 125.6, 126.1, 127.4, 127.6, 127.9, 131.5, 154.6, 157.5, 177.8 ppm. IR (neat): $\tilde{\nu}$ = 1693 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{21}NO_3$ $[M]^+$ 323.1521; found 323.1524.

***(rel)*-(1*S*,4*S*,6*R*)-2,6-Bis(3-methoxyphenyl)-2-azabicyclo[2.2.1]-heptan-3-one (15d):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.91 (d, J = 9.8 Hz, 1 H), 2.07 (d, J = 10.4 Hz, 1 H), 2.13 (ddd, J = 2.3, 4.6, 12.6 Hz, 1 H), 2.47 (ddd, J = 2.3, 9.2, 12.6 Hz, 1 H), 3.06 (d, J = 1.7 Hz, 1 H), 3.39 (dd, J = 5.2, 9.2 Hz, 1 H), 3.81 (s, 3 H), 3.83 (s, 3 H), 4.52 (s, 1 H), 6.67 (d, J = 1.7, 8.0 Hz, 1 H), 6.79 (dt, J = 2.3, 8.0 Hz, 1 H), 6.81 (t, J = 1.7 Hz, 1 H), 6.86 (dd, J = 1.7, 8.6 Hz, 1 H), 7.04–7.08 (m, 2 H), 7.24–7.28 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.8, 36.2, 37.0, 42.6, 53.6, 55.4, 61.2, 105.4, 109.5, 111.1, 111.6, 113.5, 119.4, 129.7, 129.8, 139.6, 144.5, 159.9, 160.2, 176.0 ppm. IR (neat): $\tilde{\nu}$ = 1701 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{21}NO_3$ $[M]^+$ 323.1521; found 323.1527.

***(rel)*-(1*R*,4*R*,5*R*)-2,5-Bis(3-methoxyphenyl)-2-azabicyclo[2.2.1]-heptan-3-one (16d):** Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.90 (dt, J = 1.8, 9.7 Hz, 1 H), 2.04 (dt, J = 1.7, 10.3 Hz, 1 H), 2.17 (dt, J = 4.0, 13.2 Hz, 1 H), 2.30 (ddd, J = 1.7, 8.6, 10.9 Hz, 1 H), 3.02 (d, J = 1.7 Hz, 1 H), 3.43 (dd, J = 5.8, 7.6 Hz, 1 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 4.43 (d, J = 1.2 Hz, 1 H), 6.78 (dd, J = 2.3, 8.1 Hz, 1 H), 6.81 (dd, J = 2.3, 8.1 Hz, 1 H), 6.83 (t, J = 2.3 Hz, 1 H), 6.89 (dd, J = 1.2, 8.0 Hz, 1 H), 7.06 (dd, J = 1.1, 8.0 Hz, 1 H), 7.27 (d, J = 10.5 Hz, 1 H), 7.29 (d, J = 10.5 Hz, 1 H), 7.32 (t, J = 2.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 32.6, 36.7, 46.0, 47.2, 55.3, 55.4, 65.7, 105.3, 109.6, 110.9, 111.4, 114.0, 129.9, 130.0, 139.3, 143.6, 160.0, 160.3, 176.5 ppm. IR (neat): $\tilde{\nu}$ =

1699 cm^{-1}. HRMS (EI): calcd. for $C_{20}H_{21}NO_3$ $[M]^+$ 323.1521; found 323.1521.

(*rel*)-(1*S*,4*S*,6*R*)-6-(4-Bromophenyl)-2-azabicyclo[2.2.1]heptan-3-one (7o): Colorless crystals; m.p. 197–199 °C (EtOH). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.73 (dd, J = 1.2, 9.7 Hz, 1 H), 1.98 (dt, J = 1.8, 9.7 Hz, 1 H), 2.02 (dt, J = 4.6, 13.2 Hz, 1 H), 2.18 (ddd, J = 1.7, 9.1, 12.6 Hz, 1 H), 2.84 (s, 1 H), 3.21 (dd, J = 5.2, 8.6 Hz, 1 H), 3.87 (s, 1 H), 5.71 (br. s, 1 H), 7.10 (d, J = 8.5 Hz, 2 H), 7.45 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 31.1, 38.5, 44.9, 48.3, 60.4, 120.5, 129.1, 141.1, 180.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3436, 1696 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{12}BrNO$ $[M]^+$ 265.0102 and 267.0082; found 265.0113 and 267.0082. $C_{12}H_{12}BrNO$ (265.01 and 267.00): calcd. C 54.16, H 4.54, N 5.26; found C 53.98, H 4.66, N 5.20.

(*rel*)-(1*R*,4*R*,5*R*)-5-(4-Bromophenyl)-2-azabicyclo[2.2.1]heptan-3-one (8o): Colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.76 (dd, J = 1.1, 10.3 Hz, 1 H), 1.96–2.03 (m, 2 H), 2.25 (ddd, J = 2.3, 9.1, 11.9 Hz, 1 H), 2.84 (s, 1 H), 3.27 (dd, J = 5.1, 11.8 Hz, 1 H), 4.02 (s, 1 H), 5.51 (br. s, 1 H), 7.12 (d, J = 8.5 Hz, 2 H), 7.44 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 38.9, 41.1, 51.1, 55.8, 120.4, 128.9, 131.8, 141.8, 180.45 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3432, 1702 cm^{-1}. HRMS (EI): calcd. for $C_{12}H_{12}BrNO$ $[M]^+$ 265.0102 and 267.0082; found 265.0105 and 267.0080.

(*rel*)-(1*S*,4*R*)-2-(2-Bromophenyl)-2-azabicyclo[2.2.1]hept-5-en-3-one (2k): Yield 51 mg (48%); colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 2.30 (d, J = 7.5 Hz, 1 H), 2.73 (d, J = 8.0 Hz, 1 H), 3.52 (s, 1 H), 4.69 (d, J = 1.7 Hz, 1 H), 6.81–6.83 (m, 1 H), 6.89 (dd, J = 2.3, 4.6 Hz, 1 H), 6.97 (dd, J = 1.7, 8.1 Hz, 1 H), 7.12 (dt, J = 1.2, 8.0 Hz, 1 H), 7.28 (dt, J = 1.7, 8.0 Hz, 1 H), 7.61 (dd, J = 1.8, 8.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 54.2, 58.2, 67.4, 127.1, 128.5, 133.5, 138.7, 138.9, 139.7, 139.9, 178.9 ppm. IR (neat): $\tilde{\nu}$ = 1715 cm^{-1}. HRMS (ESI): calcd. for $C_{12}H_{11}BrNO$ $[M\ H]^+$ 264.0024 and 266.0004; found 264.0021 and 265.9998.

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