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Iridium-Catalyzed Asymmetric Ring-Opening of Azabicyclic Alkenes with Phenols

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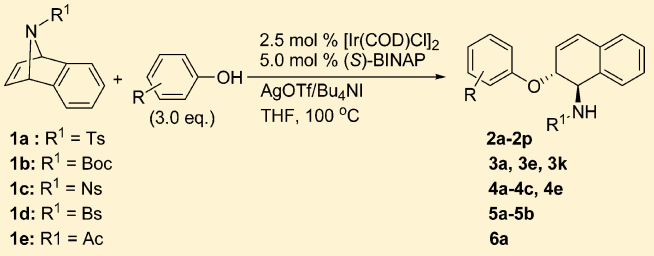
Supporting Information

ABSTRACT: The asymmetric ring-opening of azabicyclic alkenes with a variety of phenols is investigated using an iridium catalyst generated in situ from 2.5 mol % of $[Ir(COD)Cl]_2$ and 5.0 mol % of (*S*)-BINAP, which afforded the corresponding 1,2-*trans*-phenoxyamino products in excellent yield (up to 92%) with moderate to good enantioselectivities (up to 98% ee). The *trans*-configuration of the product **4b** was confirmed by X-ray crystallography.



INTRODUCTION

Oxa- and azabicyclic olefins are valuable precursors in asymmetric synthesis due to their potentials to generate multiple chiral centers in a single step via asymmetric ring-opening reactions.[1] Transition metal-catalyzed asymmetric ring-opening reactions of oxa- and azabicyclic olefins have been investigated for many years, including a variety of metal catalysts such as Pd,[2] Rh,[3] Cu,[4] Ni,[5] Fe,[6] and Ru.[7] Many nucleophiles have been used for these reactions, including, not limited to, amines,[1c,3,8] Grignard reagents,[4b,c,6,9] organoboronic acids,[2c,10] alcohol,[3a,11] carboxylates,[12] dialkylzincs,[1a,f,g,2a,b,4a,13] alkynes,[5a,b,14] organic halides,[15] sulfur,[16] phenols,[17] and others.[18]

Lautens and co-workers[17] had previously reported the Rh-catalyzed highly efficient asymmetric ring-opening of oxabicyclic alkenes with phenols. However, similar asymmetric ring-opening reactions of azabicyclic olefins with phenol as nucleophiles remain unknown.

In our previous work,[19] we explored asymmetric ring-opening reactions of oxa- and azabicyclic olefins with amines including aliphatic amines and aromatic amines in the presence of iridium catalyst, which afforded the desired products in good yields with excellent enantioselectivities. To expand the scope of this novel Ir-catalyzed reaction, we are interested in studying the asymmetric ring-opening of oxa- and azabicyclic olefins with oxygen-based nucleophiles in the presence of an iridium catalyst. Meanwhile, we also tried to optimize the catalytic system by using some new additives such as $AgOTf/Bu_4NI$ in the reaction. In this paper, we report the first Ir-catalyzed asymmetric ring-opening of N-substituted azabenzonorbornadienes with a variety of phenols. Compared to that of Rh, the ring-opening reactions catalyzed by Ir were observed to have better yields and enantioselectivities.

RESULTS AND DISCUSSION

The N-substituted substrates **1a**, **1b**, **1c**, **1d**, and **1e** were prepared on the basis of literature procedures.[8a,b] In our initial experiments, we used DPPF (5.0 mol %) to validate the catalytic activity of the iridium complex in the ring-opening reactions of *N*-Ts-azabenzonorbornadiene (**1a**) with *p*-chlorophenol as a nucleophile in THF at 80 °C in the presence of 2.5 mol % of $[Ir(COD)Cl]_2$ with 5.0 mol % ligand. The desired product **2a** was obtained in 40% yield (Table 1, entry 1). Inspired by these results, we subsequently used several chiral ligands to optimize the reaction conditions.

Among these chiral ligands, we found only (*S*)-BINAP offered better results, with yields of 69% and 61% ee (Table 1, entry 2). All other ligands gave poor results (Table 1, entries 3−6). Therefore, we decided to choose (*S*)-BINAP as a ligand for the reactions. Then we studied the impact of catalyst loading (Table 1, entries 7−10). It was found that with the increased iridium catalyst loading the enantioselectivities were also increased. However, it was further found that 2.5 mol % of $[Ir(COD)Cl]_2$ with 5.0 mol % (*S*)-BINAP would be a more suitable loading in terms of the product yield and ee value.

To optimize the reaction and to get better yields and higher enantioselectivities, we next investigated the effects of different parameters including solvents, temperature, and additives on reactivity and enantioselectivity for the reaction (Table 2). At the beginning, we screened several commonly used solvents (Table 2, entries 1−7). It was found that the reaction in THF gave a good yield with moderate ee (Table 2, entry 1). In other solvents, such as toluene, DME, dioxane, and THP, the reactions offered excellent ee with low yields (Table 2, entries 3/4 and 6/7), and both CH_2Cl_2 and CH_3CN gave low yields and ee (Table 2, entries 2 and 5). The impact of reaction

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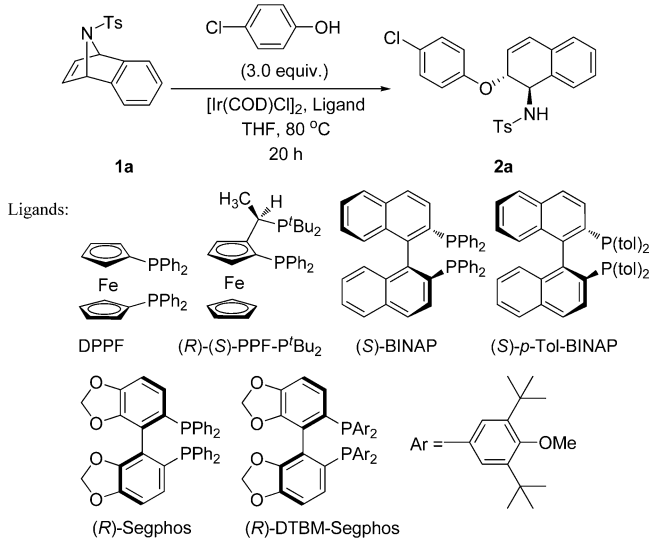
Table 1. Identification of the Optimal Chrial Ligand for Iridium-Catalyzed Asymmetric Ring-Opening of *N*-Ts-Azabenzonorbornadiene (1a) with *p*-Chlorophenol[a]



entry	ligand (mol %)	$[Ir(COD)Cl]_2$ (mol %)	yield (%)[b]	ee (%)[c]
1	5.0 DPPF	2.5	40	0
2	5.0 (*S*)-BINAP	2.5	69	61
3	5.0 (*R*)-(*S*)-PPF-P^{t}Bu$_2$	2.5	61	12
4	5.0 (*S*)-*tol*-BINAP	2.5	51	19
5	5.0 (*R*)-Segphos	2.5	36	42
6	5.0 (*R*)-DTBM-Segphos	2.5	45	41
7	2.0 (*S*)-BINAP	1.0	64	47
8	3.0 (*S*)-BINAP	1.5	61	51
9	4.0 (*S*)-BINAP	2.0	34	59
10	8.0 (*S*)-BINAP	4.0	54	67

[a]The reaction was carried out with **1a** (0.2 mmol) and 3.0 equiv of *p*-chlorophenol (0.6 mmol) in THF (2.0 mL) at 80 °C (oil bath temperature). [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC with a Chiralcel AD-H column.

temperature was also examined. It was found that there were no reactions at 0 and 25 °C (Table 2, entries 8 and 9). At 100 °C, it was observed that the reaction gave a better ee with moderate yield (Table 2, entry 10). At higher temperature, such as 120 °C, it was found that the ee was up to 92%, but yield was down to 36% (Table 2, entry 10). The role of ammonium halide additives was also explored. It was observed that they had little positive impact on the reaction (Table 2, entries 12−14). It was also worth pointing out that in the case of using NH_4I the isolated product was product **2aa** with 64% yield (Table 2, entry 15). To further optimize the reaction, we tested the impact of silver salts such as AgOTf on the reactions. It was found that it could facilitate the reaction.[3c,4a,13f] It was surprising that the yield and ee value were significantly improved when AgOTf and Bu_4NI were added as additives to the ring-opening reaction (Table 2, entry 17). We also tried using Rh complex instead of Ir complex to catalyze the ring-opening reaction under optimal conditions. It was found that **2a** was obtained only as a racemic product (Table 2, entry 18).

The scope of the reaction with the catalytic system was examined by using a number of phenols with different substituted groups. The results were shown in Table 3, from which it could be seen that the position of the substituent on the benzene ring of phenol had a significant impact on both yields and enantioselectivities. Among monosubstituted phenols (Table 3, entries 1−9), *meta*-substituted phenols were found to give better yields than that of *ortho*- and *para*-substituted phenols. It was further found that *para*-substituted phenols gave higher ee than that of *ortho*- and *meta*-substituted. Moreover, phenol with no substituent group gave the expected product with reasonable yield and moderate ee value (Table 3, entry 7). It was also worth pointing out that when the substitute group R was *p*-NO_2 or *p*-OCH_3, it was found that the yields and ee values were sharply decreased, which was probably due to the electronic effects (Table 3, entries 8 and 9). Despite the unfavorable steric and electronic effects in the case of phenols with multisubstituted groups, it was found that the ring-opening reactions gave acceptable yields and ee values (Table 3, entries 10−16). However, it was observed that, treating **1a** with 4-chloro-3-methylphenol (Table 3, entry 15), the desired product was obtained in high yield (89%) with low ee value (30%). In the case of 2-naphthol, which has unfavorable steric hindrance greater than other chosen nucleophiles (Table 3, entry 16), the desired product gave a low yield (33%) with moderate ee value (63%).

In order to extend the scope of this reaction to other substrates, we then investigated several other substrates such as N-substituted azabenzonorbornadienes, where the N-substituted group was −Boc (**1b**), −Ns (**1c**), −Bs (**1d**), and −Ac (**1e**) (Table 4). The results showed that the nature of the substitutent groups affected the steric hindrance and electron-withdrawing effects; these protective groups on the nitrogen atom were found to negatively impact the reactivity. In those cases, longer reaction times were observed with remarkably

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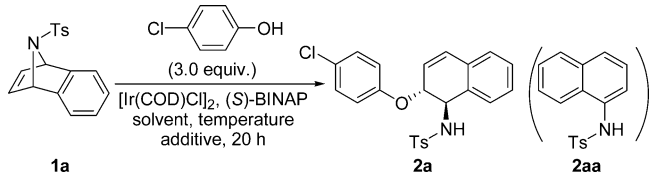
Table 2. Condition Screening for the Iridium-Catalyzed Asymmetric Ring-Opening Reaction of *N*-Ts-Azabenzonorbornadiene (1a) with *p*-Chlorophenol[a]



1a 2a 2aa

entry	solvent	additive[b]	yield (%)[c]	ee (%)[d]
1	THF		69	61
2	CH_2Cl_2		27	4
3	toluene		32	80
4	DME		22	92
5	CH_3CN		49	12
6	dioxane		17	89
7	THP		8	89
8	THF[e]		n.r.	
9	THF[f]		n.r.	
10	THF[g]		61	77
11	THF[h]		36	92
12	THF	NH_4F	9	71
13	THF	NH_4Cl	n.r.	
14	THF	NH_4Br	n.r.	
15	THF	NH_4I	trace[i]	
16	THF	Bu_4NI	56	65
17	THF	AgOTf/Bu_4NI[j]	74	88
18	THF[k]	AgOTf/Bu_4NI	71	3

[a]The reaction was carried out with **1a** (0.2 mmol) and 3.0 equiv of *p*-chlorophenol (0.6 mmol) in solvent (2.0 mL) at 80 °C (oil bath temperature) in the presence of $[Ir(COD)Cl]_2$ (2.5 mol %) and (*S*)-BINAP (5.0 mol %). [b]1.0 equiv of additive. [c]Isolated yield after silica gel column chromatography (0.2 mmol). [d]Determined by HPLC with a Chiralcel AD-H column. [e]Oil temperature was 0 °C. [f]Oil temperature was room temperature. [g]Oil temperature was 100 °C. [h]Oil temperature was 120 °C. [i]Yield of **2aa** was 64%. [j]The loading of AgOTf was 10.0 mol %, and Bu_4NI was 20.0 mol %. [k]The catalyst was 2.5 mol % $[Rh(COD)Cl]_2$.

lower yields and enantioselectivities. We even did not find any trace of products **3k** and **6a** formed (Table 4, entries 3 and 10). However, product **3e** was obtained with an acceptable ee value (61%) with low yield (24%) (Table 4, entry 2), and product **5a** was also obtained with an acceptable ee value (62%) with moderate yield (57%) (Table 4, entry 8). Moreover, product **4a** was obtained in higher yield (82%) with lower ee value (39%) than those of product **2a** (Table 4, entry 4). It is also worth pointing out that *m*-chlorophenol reacted with **1c** to afford the expected product **4b** with acceptable yield (69%) and high ee value (98%) (Table 4, entry 5).

The absolute configuration of ring-opened product **4b** was demonstrated by X-ray crystallography. The single crystal was obtained by solvent evaporation from a solution consisting of dichloromethane, petroleum ether, and ethyl acetate. Its configuration was assigned as (1*R*, 2*R*) and confirmed as the 1,2-*trans*-configuration, as shown in Figure 1. It is obvious that the reaction favors the formation of 1,2-*trans*-phenoxyamino products.

On the basis of our observations on the reaction, we could propose the reaction mechanism as outlined in Scheme 1. The chiral dimeric iridium complex **A** was first formed. The nitrogen atom and the double bond of *N*-Ts-azabenzonorbornadiene (**1a**) then reversibly coordinate to the iridium center of the catalyst to give the intermediate **B**. Oxidative insertion of the iridium into the C−N bond of **B** forms **C**. Then, phenol nucleophile attack with configuration inversion was proposed to occur in an S_N2 displacement of the iridium catalyst. The 1,2-*trans*-phenoxyamino product **2a** was subsequently released, and the iridium complex **A** was regenerated.

CONCLUSIONS

In summary, we have investigated the iridium-catalyzed asymmetric ring-opening of N-substituted azabicyclic alkenes with a variety of phenols, which afforded the corresponding products in good yield with excellent enantioselectivities for the first time. The reaction results showed that the nature of the chiral ligand had significant impact on the ring-opening. Future study will focused on the biological and pharmaceutical activities of the products. Studies on further expansion of the scope of this Ir-catalyzed method are also in progress in our laboratory.

EXPERIMENTAL SECTION

General Procedure (I) for the Asymmetric Ring-Opening Reactions of *N*-Ts-Azabenzonorbornadiene (1a) with Phenols. A 5 mL round-bottom flask fitted with a reflux condenser was flame-dried under a stream of nitrogen and cooled to room temperature. $[Ir(COD)Cl]_2$ (3.5 mg, 2.5 mol %) and (*S*)-BINAP (6.5 mg, 5.0 mol %) were simultaneously added and followed by addition of anhydrous tetrahydrofuran (2.0 mL). After they were stirred for 10 min, silver trifluoromethanesulfonate (5.2 mg, 10.0 mol %) was added; then 10 min later, additive Bu_4NI (14.8 mg, 20.0 mol %) was added. After they were stirred for another 10 min, *N*-Ts-azabenzonorbornadiene (**1a**) (59.4 mg, 0.20 mmol) was added and the resulting mixture was heated to reflux. At the first sign of reflux, phenol nucleophile (3 equiv to **1a**) was added. Then the temperature was continuously increased to 100 °C until the reaction was completed as judged by thin-layer

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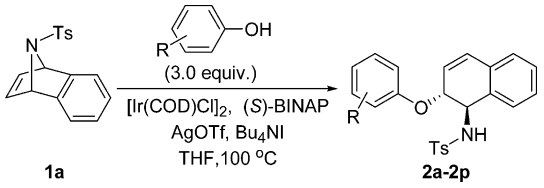
Table 3. Scope of Asymmetric Ring-Opening Reactions of *N*-Ts-Azabenzonorbornadiene (1a) with Phenol and Substituted Phenols[a]

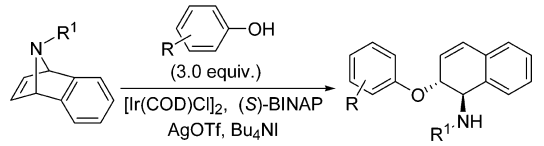


1a **2a-2p**

entry	R	time (h)	product	yield (%)[b]	ee (%)[c]
1	4-Cl	18	**2a**	74	88
2	3-Cl	18	**2b**	92	67
3	2-Cl	21	**2c**	85	47
4	4-CH_3	18	**2d**	34	75
5	3-CH_3	17	**2e**	66	73
6	2-CH_3	18	**2f**	45	53
7	H	20	**2g**	61	67
8	4-NO_2	22	**2h**	51	36
9	4-OCH_3	24	**2i**	16	37
10	2,4-dibromo	24	**2j**	64	18
11	2-bromo-4-chloro	36	**2k**	28	49
12	4-bromo-2-fluoro	30	**2l**	75	65
13	3,4-difluoro	21	**2m**	65	66
14	2,6-dichloro	23	**2n**	45	55
15	4-chloro-3-methyl	24	**2o**	89	30
16	2-naphthyl	24	**2p**	33	63

[a]The reaction was carried out with **1a** (0.2 mmol) and 3.0 equiv of substituted phenols (0.6 mmol), 10.0 mol % of AgOTf, and 20.0 mol % of Bu_4NI as additive in THF (2.0 mL) at 100 °C (oil bath temperature) in the presence of $[Ir(COD)Cl]_2$ (2.5 mol %) and (*S*)-BINAP (5.0 mol %). [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC with a Chiralcel AD-H column or OD-H column.

Table 4. Scope of Asymmetric Ring-Opening Reactions of Azabicyclic Alkenes 1b, 1c, 1d, and 1e with Different Substituted Phenols[a]



1b: R^1 = Boc
1c: R^1 = Ns
1d: R^1 = Bs
1e: R1 = Ac

3a, 3e, 3k
4a-4c, 4e
5a-5b
6a

entry	R^1	R	time (h)	product	yield (%)[b]	ee (%)[c]
1	Boc	4-Cl	54	**3a**	22	32
2	Boc	3-CH_3	58	**3e**	24	61
3	Boc	2-bromo-4-chloro	61	**3k**	trace	
4	Ns	4-Cl	45	**4a**	82	39
5	Ns	3-Cl	64	**4b**	69	98
6	Ns	2-Cl	67	**4c**	40	33
7	Ns	3-CH_3	58	**4e**	25	38
8	Bs	4-Cl	48	**5a**	57	62
9	Bs	3-Cl	30	**5b**	66	42
10	Ac	4-Cl	71	**6a**	n.r.	

[a]The reaction was carried out with substrate **1b** or **1c** or **1d** or **1e** (0.2 mmol) and 3.0 equiv of substituted phenols (0.6 mmol), 10.0 mol % of AgOTf, and 20.0 mol % of Bu_4NI as additive in THF (2.0 mL) at 100 °C (oil bath temperature) in the presence of $[Ir(COD)Cl]_2$ (2.5 mol %) and (*S*)-BINAP (5.0 mol %). [b]Isolated yield after silica gel column chromatography. [c]Determined by HPLC with a Chiralcel AD-H column or OD-H column.

chromatography. The solvent was removed in vacuo, and the crude mixture was purified by column chromatography on silica gel (ethyl acetate/petroleum ether, 1:10, v/v) to give the target product.

(1*R*,2*R*)-*N*-[2-(4-Chlorophenoxy)-1,2-dihydronaphthalen-1-yl]-4-methylbenzenesulfonamide, 2a. Following the above general procedure, **2a** was obtained as a crystalline solid (62.6 mg, 74%), R_f = 0.22 on silica gel (ethyl acetate/petroleum ether, 1:4, v/v), mp 106−108 °C. The ee was determined to be 88% using HPLC analysis on a Chiralcel AD-H column (hexane/2-propanol. 90:10, 1.0 mL/min, λ = 254 nm); retention times were 22.95 min (minor) and 26.72 min (major); $[\alpha]^{20}_D$ = −209.2 (*c* 1.00, $CHCl_3$); IR (KBr, cm^{-1}) 3261(m), 3053(w), 2924(m), 2852(w), 1594(w), 1488(s), 1452(w),

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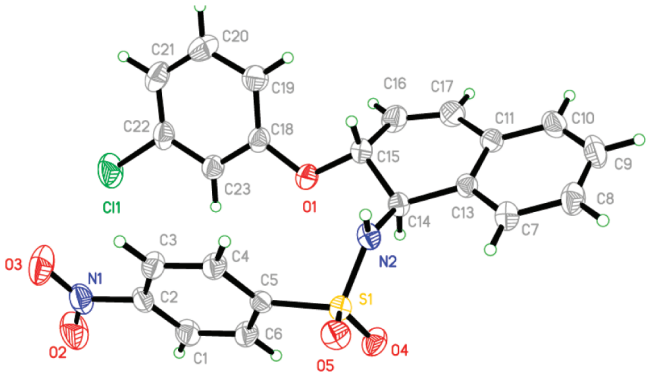
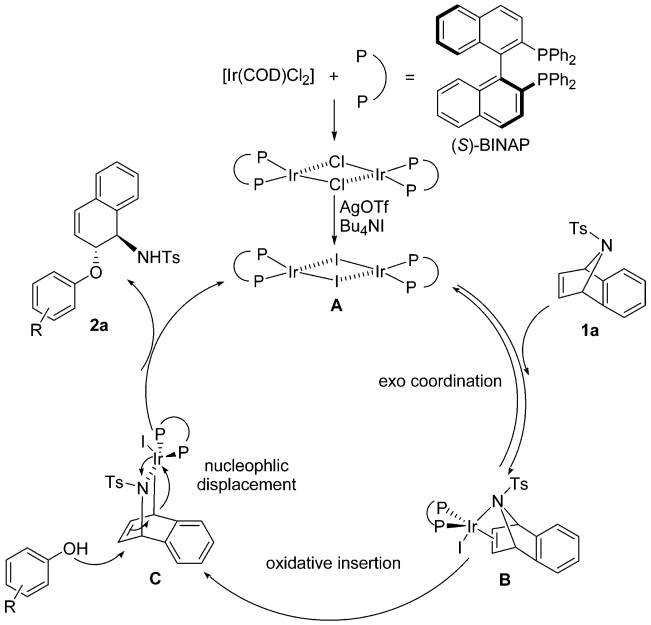


Figure 1. ORTEP plot for **4b**.

Scheme 1. Working Hypothesis for the Asymmetric Ring-Opening of *N*-Ts-Azabenzonorbornadiene (1a) with Phenol Nucleophiles



1326(m), 1234(s), 1158(s), 1093(w), 999(w), 920(w), 820(m), 663(m), 571(w), 545(m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.30−7.26 (m, 3H), 7.20−7.10 (m, 4H), 6.81 (d, J = 7.6 Hz, 1H), 6.73 (d, J = 8.8 Hz, 2H), 6.67 (d, J = 10.0 Hz, 1H), 6.04 (dd, J = 4.4, 9.6 Hz, 1H), 4.96 (dd, J = 4.4, 4.4 Hz, 1H), 4.70−4.60 (m, 2H), 2.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 143.9, 137.5, 132.3, 131.7, 131.4, 129.9, 129.5, 129.2, 128.8, 128.3, 127.7, 127.5, 126.4, 123.8, 117.3, 73.7, 54.3, 21.7; MS (ESI) calcd for $C_{23}H_{20}ClNO_3S$ (M^+) 425.09, found 448.27 (M + Na)$^+$. Anal. Calcd for $C_{23}H_{20}ClNO_3S$: C, 64.86; H, 4.73; N, 3.29; S, 7.53. Found: C, 64.79; H, 4.80; N, 3.43; S, 7.46.

The asymmetric ring-opening reactions of *N*-Ts-azabenzonorbornadiene (**1a**), *N*-Boc-azabenzonorbornadiene (**1b**), *N*-Ns-azabenzonorbornadiene (**1c**), *N*-Bs-azabenzonorbornadiene (**1d**), and *N*-Ac-azabenzonorbornadiene (**1e**) with phenols are the same as the above representative procedure. See Supporting Information for details of the syntheses of the new compounds **2a**−**2p**, **3a**, **3e**, **4a**−**4c**, **4e**, **5a**, and **5b**.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and full characterization data for all new products including optical rotations, IR, MS, ^{1}H and ^{13}C NMR, elemental analysis, and X-ray structure data for compound **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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