Convergent Azaspirocyclization of Bromoarenes with *N*-Tosylhydrazones by a Palladium Catalyst

Aika Yanagimoto,[†a] Yota Uwabe,[†a] Qikun Wu,[a] Kei Muto,[*b] and Junichiro Yamaguchi[*a]

[a] Department of Applied Chemistry, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan

[b] Waseda Institute for Advanced Study, Waseda University, 513 Wasedatsurumakicho, Shinjuku, Tokyo 162-0041, Japan

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ABSTRACT: 1-Azaspirocyclic compounds have gained attention in chemistry and drug discovery fields. In this manuscript, the development of a Pd-catalyzed dearomative azaspirocyclization of bromoarenes bearing an aminoalkyl group with *N*-tosylhydrazones is described. The present method enables azaspirocyclization with the introduction of carbon substituents, achieving the convergent synthesis of 1-azaspirocycles. This method allowed furan, thiophene, and naphthalene cores to generate the corresponding 1-azaspirocycles. The obtained azaspirocycles from furans were further elaborated *via* an acid-catalyzed rearrangement to afford 1-azaspirocyclopentenones.

Spirocyclic compounds have found wide use ranging from bioactive compounds to molecular catalysts.[1] 1-Azaspirocycles, one of the representative spirocyclic compounds, are often seen in natural products and pharmaceuticals (Figure 1A). Because of their three-dimensionality and rigidity, embedding an azaspirocycle into molecules is beneficial in medicinal chemistry, often leading to increased solubility and decreased conformational entropy of compounds. This skeletal feature also allows functional groups to be configured at fixed positions in a three-dimensional space, making spirocyclic compounds useful for *in-silico* fragment-based screening. Additionally, 1-azaspirocyclic compounds can function as organocatalysts, achieving asymmetric reactions.[2] The use of 1-azaspirocycles as ligands to metal catalysts was also reported, showing further application of these skeletons in a broad area.[3]

With these attractive features, chemists have sought to design efficient synthetic methods of 1-azaspirocycles. Cyclization of aliphatic compounds is one of the strategies to access these skeletons.[4] Dearomative synthesis of 1-azaspirocycles was also exploited as a powerful method.[5] Among dearomative methods, many C–N bond forming spirocyclizations have been reported. Hypervalent iodine-mediated and/or catalyzed oxidative C–N bond formation of phenol derivatives is known as a reliable method.[6] Comparable to this example, other dearomative azaspirocyclizations of phenols through the generation of electrophilic nitrogen species such as metal-nitrenoids and *O*-tosylhydroxylamines have emerged.[7,8] Reactions using heteroles have also been employed to synthesize [4.4]-1-azaspirocycles (Figure 1B).[5a–5d] One of the representative examples is the aza-Piancatelli reaction, which can transform furfuryl alcohols with a pendant aminoalkyl group to azaspirocyclopentenones under acidic conditions.[9,10] In most of the above cases, the substituents on the azaspirocycle should be installed before these dearomative reactions, resulting in a linear synthesis.

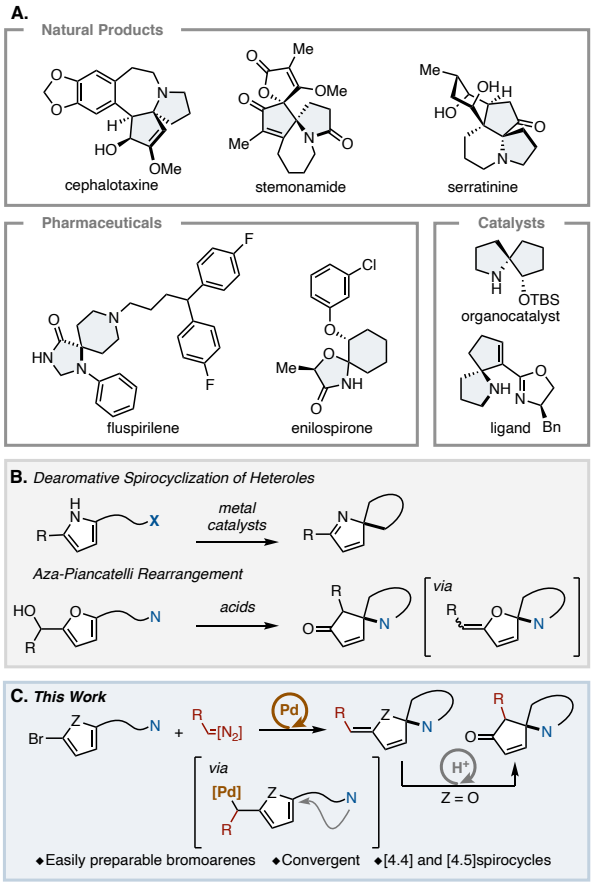
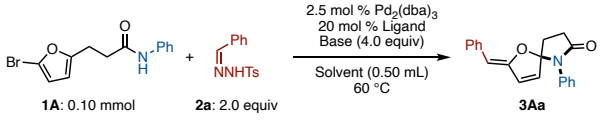


Figure 1. (A) 1-Azaspirocycles in bioactive compounds and catalysts. (B) Dearomative azaspirocyclization of heteroles. (C) This work.

Meanwhile, we have reported the Pd-catalyzed dearomative functionalization of haloarenes, diazo compounds, and carbon nucleophiles.[11] This methodology is advantageous because of the high availability of haloarenes as a starting material and the convergency of the reaction. The key finding in these reactions was the generation of a benzyl–Pd intermediate[12,13] by the action of haloarenes and diazo compounds such as TMS diazomethane and *N*-tosylhydrazones.[14] We envisaged that this type of reaction can be applied to the synthesis of 1-azaspirocycles using bromoarenes bearing an aminoalkyl chain through an intramolecular C–N bond formation on a benzyl–Pd species. The introduction of carbon functional groups *via* a diazo species could enable the convergent synthesis of substituted azaspirocyclic compounds. Herein, we report a Pd-catalyzed dearomative azaspirocyclization of bromo(hetero)arenes with *N*-tosylhydrazones (Figure 1C).

We first evaluated the reaction conditions by using bromofuran **1A** with *N*-tosylhydrazone **2a** as a diazo equivalent in the presence of $Pd_2(dba)_3$ and Cs_2CO_3 in DME (Table 1). Initially, we tested the effect of ligands. To our delight, we found that this reaction proceeds by using simple PPh_3 as a ligand, furnishing the desired azaspirocycle **3Aa** in good yield with a *Z*/*E* ratio of 78:22 (Table 1, Entry 1). Changing PPh_3 to electron-donating tri(*p*-tolyl)phosphine as well as electron-deficient P(*p*-$CF_3C_6H_4$)$_3$ maintained the catalytic activity, generating **3Aa** in comparable yields (Table 1, Entries 2 and 3). When DPEphos was used, the yield of **3Aa** increased to 95% (Table 1, Entry 4). However, another bidentate phosphine, dppe did not work (Table 1, Entry 5). Without ligands, the yield of **3Aa** remained in 5% (Table 1, Entry 6). Next, the influence of base was examined. When we used K_2CO_3, this reaction did not proceed at all (Table 1, Entry 7). Strong bases such as LiO^{t}Bu and NaH resulted in low yields of **3Aa** (Table 1, Entries 8 and 9). Next, various solvents were examined. It was found that

Table 1. Optimization of reaction conditions.



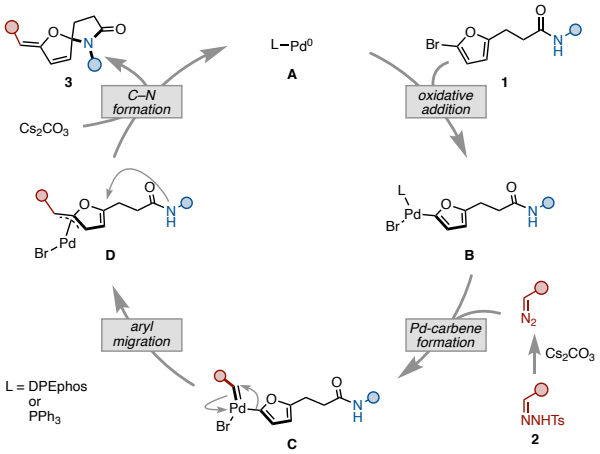
Entry	Ligand	Base	Solvent	**3Aa**/%[a]	*Z*/*E*
1	PPh_3	Cs_2CO_3	DME	85	78:22
2	P(*p*-tolyl)$_3$	Cs_2CO_3	DME	75	73:27
3	P(*p*-$CF_3C_6H_4$)$_3$	Cs_2CO_3	DME	80	80:20
4	DPEphos[b]	Cs_2CO_3	DME	95	70:30
5	dppe[b]	Cs_2CO_3	DME	2	62:38
6	none	Cs_2CO_3	DME	5	43:57
7	PPh_3	K_2CO_3	DME	trace	–
8	PPh_3	LiO^{t}Bu	DME	33	82:18
9	PPh_3	NaH	DME	trace	–
10	PPh_3	Cs_2CO_3	THF	87	76:24
11	PPh_3	Cs_2CO_3	dioxane	74	84:16
12	PPh_3	Cs_2CO_3	toluene	36	75:25

Conditions: **1A** (0.10 mmol), **2a** (0.20 mmol), $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), ligand (20 mol %), base (4.0 equiv), solvent (0.50 mL), 60 °C, 12 h. [a] Yield was determined by ^{1}H NMR analysis. [b] 10 mol % of ligand was used.

THF and 1,4-dioxane can be used as alternatives to DME, furnishing **3Aa** in good yields (Table 1, Entries 10 and 11). A less polar solvent such as toluene was ineffective (Table 1, Entry 12). With these studies, we identified the optimized conditions with $Pd_2(dba)_3$/DPEphos (or PPh_3) as a catalyst and Cs_2CO_3 in DME at 60 °C (Table 1, Entries 1 and 4).

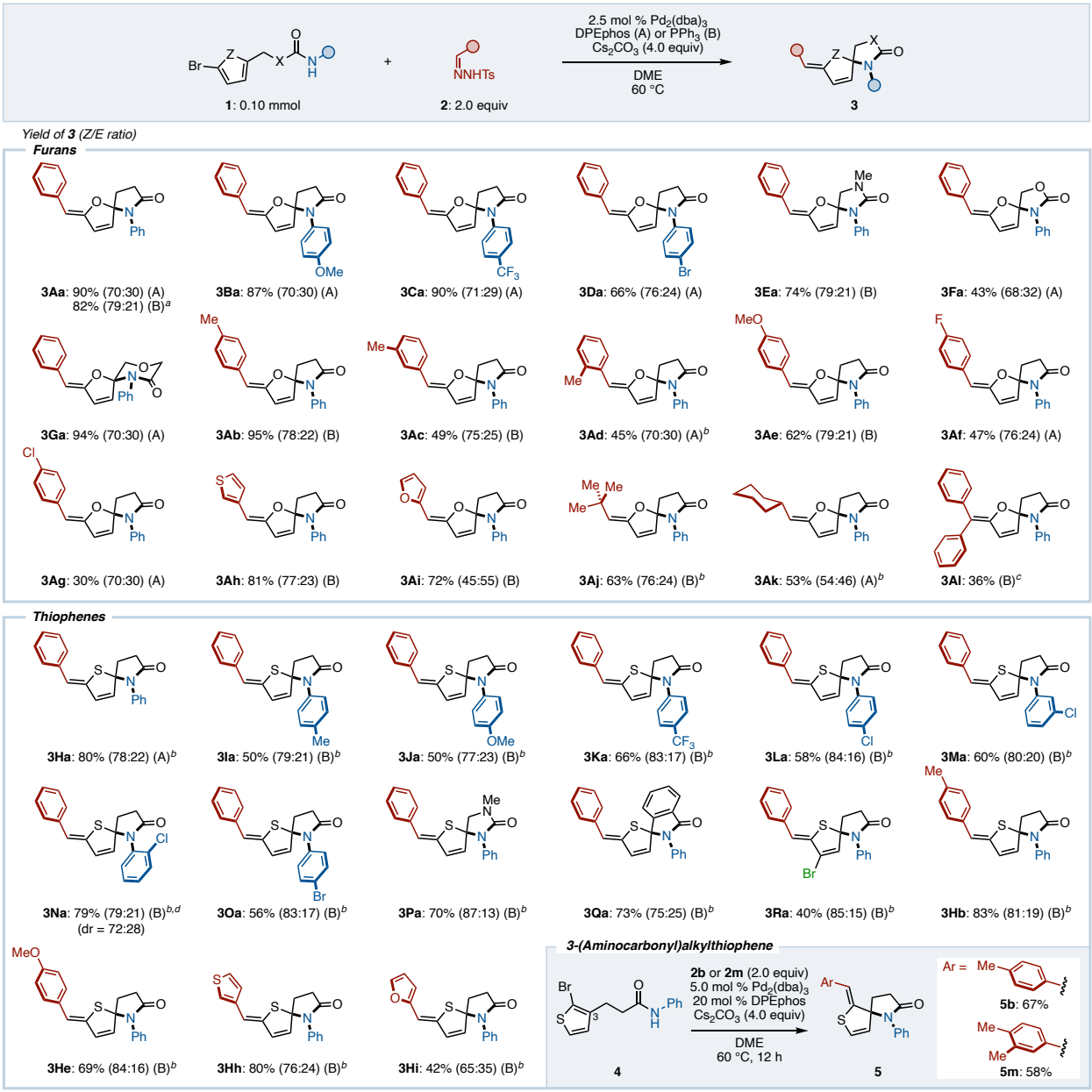
A plausible catalytic cycle is shown in Scheme 1. Initiated by an oxidative addition of bromoarenes **1** to Pd(0) species **A**, the reaction of an aryl–Pd species **B** with an *in situ* generated diazo compound affords a Pd-carbene species **C**. Subsequently an aryl migration generates a benzyl–Pd intermediate **D**. Finally, a base-assisted intramolecular C–N bond formation takes place to give 1-azaspirocycle **3** with the regeneration of Pd(0) **A**.

Scheme 1. A plausible catalytic cycle.



With the optimized conditions in hand, we evaluated the substrate scope of this reaction (Scheme 2). We first examined the anilide moiety of **1**. Various anilides were applicable to this reaction, as phenyl (**1A**), *p*-anisyl (**1B**), and *p*-trifluoromethylphenyl amides (**1C**) furnished the corresponding products (**3Aa**, **3Ba**, and **3Ca**) in good yields. The bromo atom on the anilide (**3Da**) was tolerated, showing that the oxidative addition of the C–Br bond selectively occurs on the bromoheterole. In addition to amides, urea **1E** and carbamate **1F** successfully furnished **3Ea** and **3Fa**. This methodology also enabled six-membered ring formation, where we obtained morpholinone spirocycle **3Ga** in excellent yield. Next, we evaluated the scope of *N*-tosylhydrazones. *p*-Tolyl tosylhydrazone **2b** smoothly reacted to give **3Ab** in 95% yield, whereas the reactions of *m*- and *o*-tolyl tosylhydrazones delivered **3Ac** and **3Ad** in moderate yields. It was found that electron-donating anisyl-substituted *N*-tosylhydrazone delivers spirocyclic product **3Ae** in a good yield. On the contrary, *N*-tosylhydrazones bearing electron-deficient fluoro- and chlorophenyl gave the corresponding products in lower yields (**3Af**, **3Ag**). Heteroarenes such as thiophene (**3Ah**) and furan (**3Ai**) can be installed on an azaspirocycle by using the corresponding *N*-tosylhydrazones **2h** and **2i** in good yields. Delightfully, alkyl-substituted 1-azaspirocycles **3Aj** and **3Ak** were synthesized in moderate yields by using *N*-tosylhydrazones derived from alkyl aldehydes. In the case of cyclohexyl **2k**, a competing β-hydride elimination on the benzyl–Pd intermediate did not occur.[15] Ketone-derived *N*-tosylhydrazone **2l** was also reacted under the modified conditions using KF as an additive to give **3Al** albeit in 36% yield.

Scheme 2. Substrate scope.



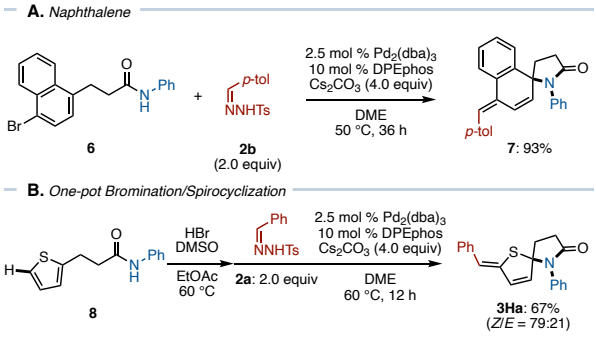
Conditions: **1** (0.10 mmol), **2** (0.20 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %), DPEphos (10 mol %, A) or PPh_3 (20 mol %, B), Cs_2CO_3 (4.0 equiv), DME (0.50 mL), 60 °C, 12 h. [a] 1.0 mmol scale. [b] 70 °C [c] Using KF (1.0 equiv) as an additive, 36 h. [d] 0.18 mmol scale.

Pleasingly, the present method allowed the transformation of thiophene cores, which have higher aromatic stability than furans (Scheme 2). When bromothiophene **1H** was reacted with **2a** at 70 °C, desired 1-azaspirocycle **3Ha** was obtained in 80% yield. In the case of thiophenes, various substituents on the anilide such as methyl (**1I**), methoxy (**1J**), CF_3 (**1K**), chloro (**1L**–**1N**), and bromo (**1O**) groups were also compatible with this reaction, affording the corresponding 1-azaspirocycles in good yields. When *o*-chloroanilide **1N** was used, **3Na** was obtained in a good yield, albeit as a mixture of atropisomers. Urea **3Pa** was also synthesized in a good yield. A phenylene linker was also suitable in this reaction, giving isoindolinone spirocycle **3Qa** in 73% yield. Interestingly, 2,3-dibromothiophene **1R** was applicable to give bromo-bearing azaspirocycle **3Ra** in 40% yield. In the case of thiophenes, various *N*-tosylhydrazones including heteroaryl *N*-tosylhydrazones can participated in this reaction to give the corresponding products (**3Hb**, **3He**, **3Hh**, and **3Hi**). Additionally, we found that 3-(aminocarbonyl)alkyl-2-bromothiophenes **4** can be applied to this reaction, furnishing relatively rare 7-thia-1-azaspirocyclic skeleton **5b** and **5m**.

This catalytic system allowed the use of challenging benzenoid cores (Scheme 3A). Bromonaphthalene **6** was transformed to azaspirocycle **7** in an excellent yield. In this case, a longer reaction

time was required because of the high aromatic stability of naphthalene. Next, we tried to establish a one-pot[16] bromination/azaspirocyclization protocol using thiophene **8** (Scheme 3B). Seeking a suitable bromination protocol, we found that Jiao's bromination conditions using HBr and DMSO was suitable for this purpose.[17] After treating **8** with HBr and DMSO, the generated volatile side-products were removed *in vacuo*. The present dearomative azaspirocyclization was then performed in the same flask to give **3Ha** in 67% yield.

Scheme 3. (A) Azaspirocyclization of naphthalene 6. (B) One-pot bromination/azaspirocyclization of 8.

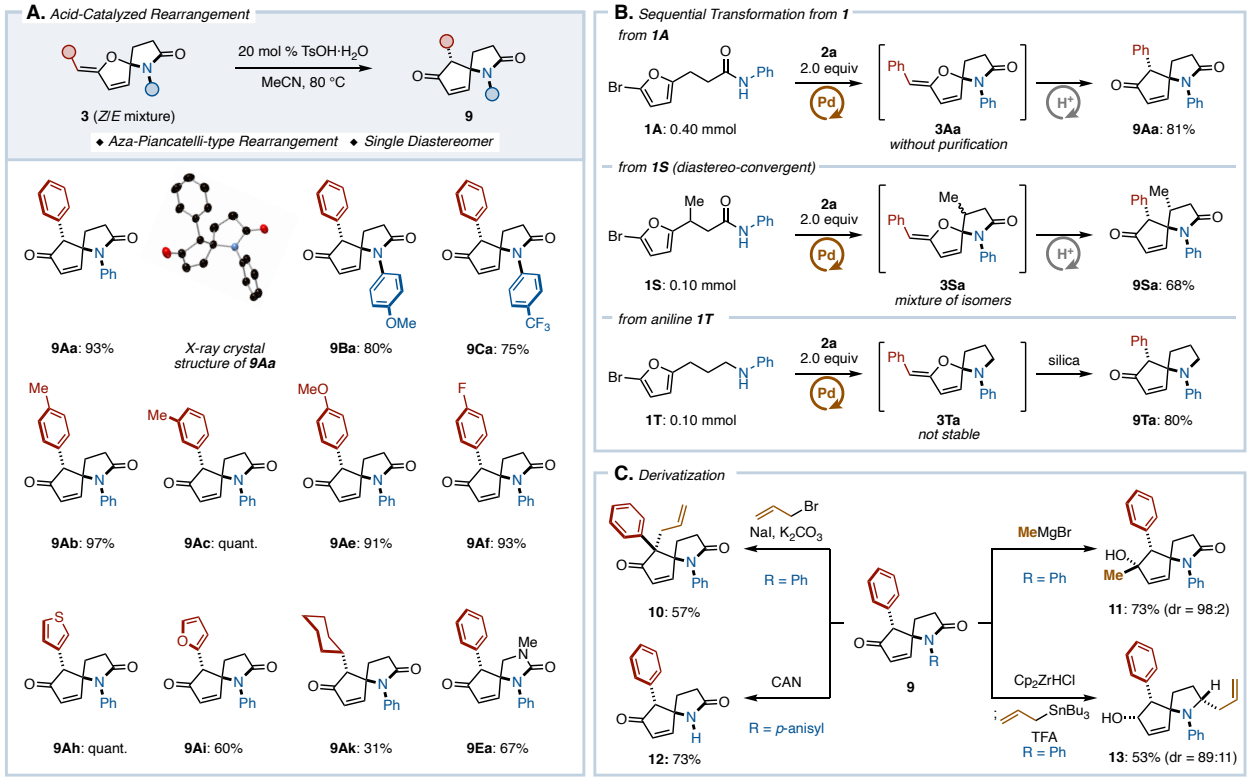


1-Azaspirocycles **3** derived from furan can be structurally elaborated through an aza-Piancatelli-type rearrangement to valuable 1-azaspirocyclopentenones (Scheme 4A). By using a catalytic amount of TsOH in MeCN at 80 °C, this rearrangement reaction smoothly proceeded to generate azaspirocyclopentenones **9**. Even when a *Z*/*E* mixture of **3Aa** was used for this reaction, product **9Aa** was obtained as a sole diastereoisomer. The relative stereochemistry of **9Aa** was assigned by ^{1}H NMR and X-ray crystallographic analyses, confirming the *anti* configuration of the anilide and the carbonyl α-substituent. *p*-Methoxy (**3Ba**) and *p*-CF_3phenyl (**3Ca**) lactams were efficiently converted to the corresponding cyclopentenones **9** in good yields. Azaspirocyclopentenones bearing a variety of substituents at the carbonyl α-position were generated in excellent yields (**9Ab**, **9Ac**, **9Ae**, **9Af**, **9Ah**), whereas furyl (**9Ai**) and cyclohexyl (**9Ak**) were obtained in lower yields. Urea **9Ea** was successfully synthesized.

A sequential transformation of Pd-catalyzed dearomative spirocyclization and acid-catalyzed rearrangement was possible (Scheme 4B). As demonstrated using **1A**, azaspirocyclopentenone **9Aa** was obtained in 81% yield over two steps without the purification of intermediate **3Aa**. Moreover, a diastereo-convergent synthesis of **9Sa** was successful. Although dearomative azaspirocyclization of **1S** generated **3Sa** as mixture of isomers (*Z*/*E* = 71:29, dr = 55:45), the subsequent acid-catalyzed reaction proceeded in a diastereoconvergent manner, giving **9Sa** in 68% yield. Aniline **1T** was also a suitable substrate to generated **3Ta**, which rapidly converted to cyclopentenone **9Ta** by treating with silica gel.

Further structural elaborations of **9** were performed (Scheme 4C). By treating **9Aa** with allyl bromide in the presence of NaI and K_2CO_3, **10** was obtained as a single diastereomer. 1,2-Addition with a Grignard reagent was also achieved, generating **11** in 73% yield with a high diastereoselectivity. Furthermore, the *p*-anisyl group on **9Ba** was removed by using CAN to give **12** in 73% yield. Finally, Sato and Chida's amide reductive allylation conditions[18] furnished **14** in 53% yield with a moderate diastereoselectivity. Overall, we succeeded in installing substituents on **9** in various vectors, which

Scheme 4. (A) Acid-catalyzed rearrangement. (B) Sequential transformations from 1. (C) Derivatization of 9.



would be useful in drug discovery research.

In conclusion, we developed a Pd-catalyzed dearomative azaspirocyclization of bromoarenes with *N*-tosylhydrazones. This dearomative reaction can be applied to not only bromoheteroles, but also to benzenoids. Although the typical aza-Piancatelli rearrangement of furfuryl alcohols does not allow the use of amides nucleophiles, this method can utilize both amides and anilines. We believe that this method will find use in the synthesis of bioactive compounds and catalysts containing a 1-azaspirocyclic core. Further studies demonstrating this method's application to the synthesis of natural products are ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectroscopic data for compounds including ^{1}H-, ^{13}C-, and ^{19}F-NMR spectra and crystallographic data (PDF). CCDC 2086786 contains the supplementary crystallographic data for this paper.

AUTHOR INFORMATION

Corresponding Author

* keimuto@aoni.waseda.jp (KM)
* junyamaguchi@waseda.jp (JY)

ORCID

Kei Muto: 0000-0001-8301-4384
Junichiro Yamaguchi: 0000-0002-3896-5882

Author Contributions

† These authors contributed equally to this work.

Notes

The authors declare no competing financial interest.

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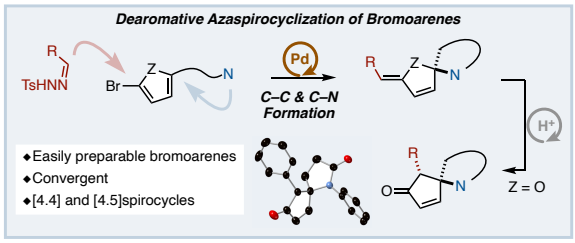
Dearomative Azaspirocyclization of Bromoarenes
R
TsHNN
Br
Z
N
Pd
C–C & C–N
Formation
R
Z
N
H+
Z = O
R
O
N
◆Easily preparable bromoarenes
◆Convergent
◆[4.4] and [4.5]spirocycles