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Palladium-Catalyzed Chemoselective Oxidative Addition of Allyloxy-Tethered Aryl Iodides: Synthesis of Medium-Sized Rings and Mechanistic Studies

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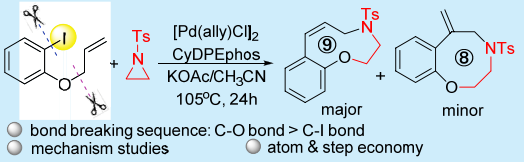
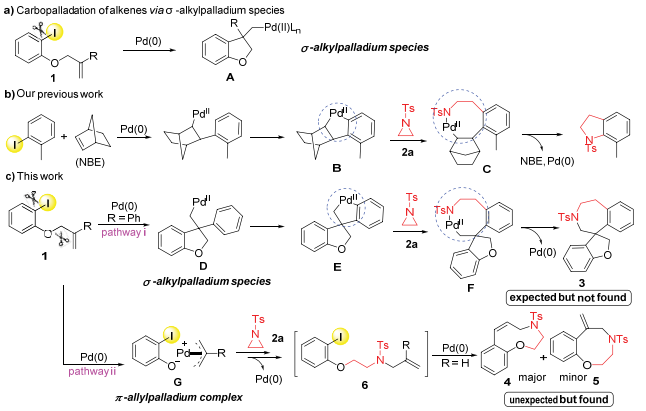
ABSTRACT: This Letter describes a Pd-catalyzed Tsuji−Trost-type/Heck reaction with allyloxy-tethered aryl iodides and aziridines. The strategy provides efficient access to benzannulated medium-sized rings via intermolecular cyclization. The substrate aryl iodide has two oxidative addition sites, that is, the aromatic C−I bond and the allyl−oxygen bond. The chemoselective oxidative addition of allyl−oxygen bonds is favored, followed by the activation of aromatic C−I bonds. Aziridine plays a key role. Mechanistic studies shed light on the reaction pathway.



Medium-sized rings (8- to 11-membered rings) are commonly found in a range of bioactive natural products.[1] Some important natural products containing the medium-sized ring system include (+)-laurencin, heliannuol A, brazilone, and rhazinilam, and so on.[2−5] Although medium-sized rings have much promise in medicinal chemistry and the pharmaceutical industry, the construction of the frameworks is still challenging owing to unfavorable entropic factors and transannular interactions.[6] To overcome these difficulties, many excellent synthetic strategies have been developed, such as transition-metal-catalyzed cyclization, ring expansion, ring-closing metathesis, lactonization and lactamization, and so on.[1,7] Among the studies of transition-metal-catalyzed cyclization,[7a,c,f,k] many transformations proceed via intramolecular cyclization within a single molecule. Thus substrates must be carefully designed, and they usually bear a long tether. Herein a novel synthesis of benzannulated medium-sized rings by palladium-catalyzed intermolecular cyclization with readily accessible allyloxy-tethered aryl iodides and three-membered aziridines heterocycles was studied.

In the past 30 years, alkene-tethered aryl iodides have been exploited as substrates via palladium-catalyzed intramolecular Heck-type reactions and C−H bond activations in domino processes.[8] Among these reports, numerous seminal works have been published by Shi,[9] Lautens,[10] and others[11] that used iodoarenes with alkyl ether moieties (**1**) as substrates (Scheme 1a) to synthesize valuable heterocyclic and fused polycyclic compounds. The previously mentioned reports are generally triggered by the Heck-type reaction to generate σ-alkylpalladium species **A** first, and this can be further functionalized (Scheme 1a). On the basis of our interest in the field[11b] and our previous report on the synthesis of indolines (Scheme 1b),[12] we envisioned that the migration of aziridine **2a** to give the five-membered palladacycle **E** (similar to palladacycle **B**) then gives the eight-membered palladacycle **F** (similar to palladacycle **C**) followed by reductive elimination to produce the spiro-fused benzoazepine derivative **3** (pathway i, Scheme 1c). To probe this conjecture, we carried out experimental explorations. Interestingly and unexpectedly, nine- and eight-membered medium-sized heterocyclic compounds **4** and **5** were isolated in a one-pot process (Scheme 1c) rather than the expected compound **3**. It is likely that Pd(0) reacts with allyl−oxygen bonds to generate the π-allylpalladium species **G** first;

Scheme 1. Project Background and Pd-Catalyzed Oxidative Addition of Allyloxy-Tethered Aryl Iodides



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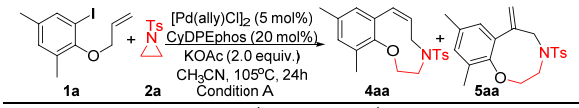
then, in the presence of aziridine **2a**, the allylamine compound **6** is formed via a Tsuji−Trost-type reaction, which is followed by a Heck reaction to produce heterocyclic compounds (pathway ii, Scheme 1c).

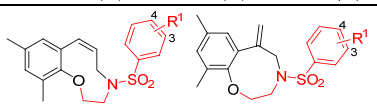
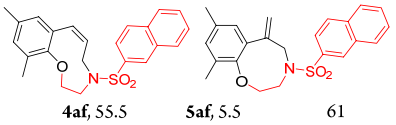
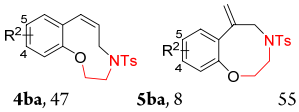
However, the development of such a transformation faces a considerable challenge. The substrate aryl iodide **1** has two oxidative addition sites, that is, the aromatic C−I bond and the allyl−oxygen bond. The direct oxidative Heck-type reaction is a strongly competitive process (Scheme 1a). Aryl iodide **1** itself could easily produce a carboiodination product (R ≠ H),[10] spiro-fused benzocyclobutene (R = aryl),[11c] or Heck-type product (R = H)[13] via a σ-alkylpalladium species. On the other hand, aryl iodide **1** is also an allyl compound. In the presence of a suitable nucleophile, a substrate containing a leaving group in the allylic position can proceed via the Tsuji−Trost reaction to provide a new substituted allyl compound.[14] According to the results of this palladium-catalyzed chemoselective oxidative addition of allyloxy-tethered aryl iodides (pathway ii, Scheme 1c), the addition of aziridine **2a** is helpful in the formation of a π-allylpalladium species to produce allylamine product **6**. Aziridine itself is an electrophilic reagent.[15] However, when its three-membered ring is opened by the nucleophilic 2-iodophenolate ion, the newly generated amino group can act as a nucleophilic reagent to complete the Tsuji−Trost reaction. In addition, with the retention of aromatic C−I bonds, studies about Pd-catalyzed deprotection of allyl ethers of phenols have been reported.[16]

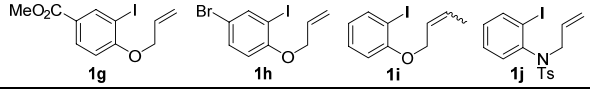
Aryl iodide **1a** and 1-tosylaziridine **2a** were used as starting substrates to explore this palladium-catalyzed chemoselective oxidative addition reaction. (See the Supporting Information (SI), Table S1.) After a series of reaction parameters was used, the desired heterocyclic compounds were observed in up to 61% yield (**4aa** + **5aa**). We found that the nine-membered ring product **4aa**, formed through a 9-endo-trig cyclization, accounted for the higher proportion (**4aa**/**5aa** 12.5:1).[17] Of the phosphine ligands examined, the use of bidentate phosphine ligands was found to be crucial, and CyDPEphos gave the best yields (Table S1). The scope for one-pot annulations with aryl iodides **1** and aziridines **2** was then investigated under Condition A (Table 1). Considering the regioselectivity of the products, the dimethyl-substituted substrate **1a** was the best choice (12.5:1) compared with substrates **1b**−**1f** (entries 1 and 7−11). The configurations of products **4ba** and **5ba** were determined by X-ray analysis. (See the SI.) A gram-scale reaction with **1b** (5 mmol) and **2a** was carried out, and the desired products **4ba** and **5ba** were isolated in 46% yield (**4ba**/**5ba** 5:1; for detailed information, see the SI). With **1a** as the aryl iodide partner, the transformations of several aziridines with different aryl sulfonyl groups on the nitrogen atom were also studied (entries 2−6). They all performed well and afforded the respective cyclization products in moderate yields with good selectivity. In particular, when aziridines **2c** and **2e** were involved, only single isomers of the nine-membered ring products **4ac** and **4ae** were generated, respectively (entries 3 and 5, >20:1). However, when the phenyl ring bore electron-withdrawing groups, such as **1g** and **1h**, only Tsuji−Trost-type products were isolated.[18] In addition, reactions of aryl iodide **1i** and allylamine **1j** did not proceed well.

When the temperature was lowered to 80 °C, in addition to cyclization products **4ba** and **5ba**, allylamine derivative **6ba** with reactive functional groups (Ar−I and C=C bonds) was observed (72%, Scheme 2). A new optimization was

Table 1. Substrate Scope for Annulation with 1 and 2[a]

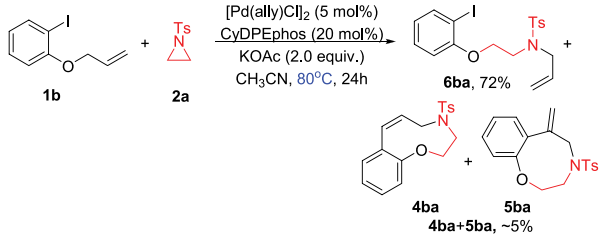


Entry		4[b] Yield (%)	5[b] Yield (%)	4+5[c] Yield (%)	Ratio[d] 4:5
					
1	R^1 = H	**4aa**, 56.5	**5aa**, 4.5	61	12.5:1
2	R^1 = 3-OMe	**4ab**, 56.6	**5ab**, 3.4	60	16.7:1
3	R^1 = 3-F	**4ac**, 54	**5ac**, 2	56	>20:1
4	R^1 = 4-Br	**4ad**, 50	**5ad**, 3	53	16.7:1
5	R^1 = 4-NO_2	**4ae**, 50	**5ae**, 2	52	>20:1
					
6		**4af**, 55.5	**5af**, 5.5	61	10:1
					
7	R^2 = H (X-ray)	**4ba**, 47	**5ba**, 8	55	5.9:1
8	R^2 = 5-Me	**4ca**, 43	**5ca**, 8	51	5.3:1
9	R^2 = 4-Me	**4da**, 49.6	**5da**, 7.4	57	6.7:1
10	R^2 = 5-^{t}Bu	**4ea**, 41	**5ea**, 15	56	2.7:1
11	R^2 = 5-Ph	**4fa**, 43.4	**5fa**, 9.6	53	4.5:1



[a]Condition A: **1** (0.2 mmol, 1.0 equiv), **2** (1.5 equiv), $[Pd(allyl)Cl]_2$ (5 mol %), CyDPEphos (20 mol %), and KOAc (2.0 equiv) in CH_3CN (4 mL) at 105 °C in an oil bath for 24 h. [b]Yields were calculated by ratio. [c]Isolated yields. [d]Ratios were determined by ^1H NMR.

Scheme 2. Synthesis of Allylamine 6ba at Low Temperature



performed, and the results are detailed in Table S2. The use of a bidentate phosphine ligand was crucial for the allyl amination reaction, and dppe was proven to be the best ligand. Allylamine products **6aa** and **6ba** were isolated in 85 and 90% yields, respectively (Table 2). The configuration of product **6ba** was unambiguously determined by X-ray analysis. Substituted groups at the two-position of the allyl bonds of the substrates (**1k** and **1l**) were also tolerated, and good yields resulted (**6ka**, 70%; **6la**, 74%).[19]

To understand the reaction mechanism, we carried out a series of control experiments (Scheme 3). When substrate **6ba** proceeded under Condition A, cyclization products **4ba** and **5ba** were isolated in up to 59% yield (**4ba**/**5ba** 5:1, Scheme 3a). Combined with the results in Schemes 2 and 3a, it is reasonable to state that the intermolecular cyclization reaction

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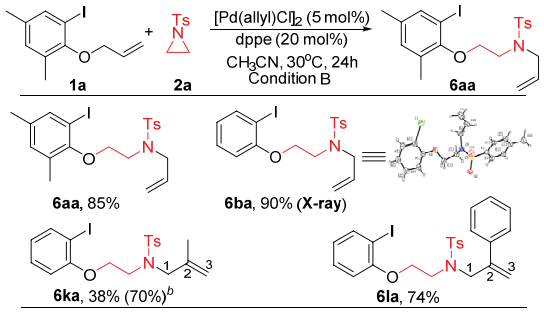
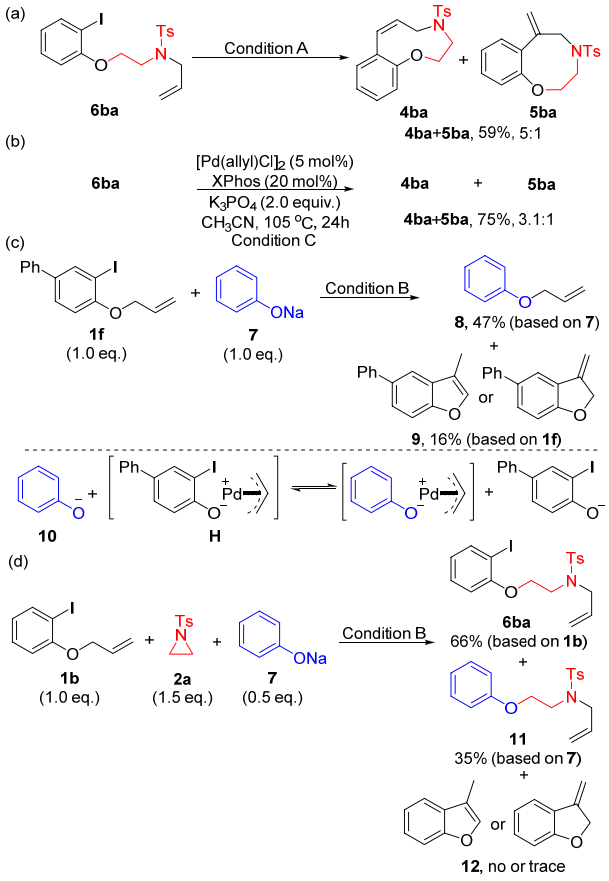
Table 2. Scope of Allylamine Derivatives 3[a]



[a]Condition B: **1** (0.2 mmol, 1.0 equiv), **2a** (1.5 equiv), $[Pd(allyl)Cl]_2$ (5 mol %), and dppe (20 mol %) in CH_3CN (2 mL) at 30 °C in an oil bath for 24 h. Isolated yields. [b]DtBPF was used as the phosphine ligand. DtBPF = 1,1′-bis(di*tert*-butylphosphino) ferrocene.

Scheme 3. Control Experiments



proceeds via a sequential Tsuji−Trost-type reaction (**6ba**) and Heck reaction (**4ba** and **5ba**). After experimental exploration (Table S3), the desired cyclization products were obtained in up to 75% yield when XPhos was utilized (**4ba**/**5ba** 3.1:1, Scheme 3b). After considering the results in Tables S1−S3, we found that bidentate phosphine ligands were beneficial for the Tsuji−Trost-type reaction, whereas Buchwald phosphine ligands favored the Heck reaction. Next, aryl iodide **1f** and sodium phenolate (**7**) were mixed under Condition B (Scheme 3c). Not only was the anion exchange product allyl phenyl ether **8** isolated (via a π-allylpalladium species) but also Heck cyclization products **9** were observed (via a σ-alkylpalladium species).[20] One can speculate that (1) the transformation (Scheme 3c) involved a chemical equilibrium between phenol ion **10** and π-allylpalladium species **H** and (2) under certain circumstances, π-allylpalladium species and σ-alkylpalladium species can exist in the same reaction system. Moreover, 0.5 equiv of sodium phenolate **7** was added to the allyl amination reaction under Condition B (Scheme 3d), and in addition to allylamine derivative **6ba** (66% yield, based on **1b**), the new allylamine product **11** was obtained (35% yield, based on **7**). Furthermore, when 5.0 equiv of **7** was added, virtually only product **11** was isolated (96%, based on **1b**, Scheme S2). No amount or trace amounts of Heck cyclization products **12** were observed (Scheme 3d and Scheme S2). Combined with the results in Scheme 3c,d, these results indicated that the addition of aziridine **2a** was helpful in the formation of a π-allylpalladium species to produce allylamine products.

Inspired by Le Floch's report,[21] density functional theory (DFT) was used to understand the mechanism of the Tsuji−Trost-type reaction and Heck cyclization with aryl iodide **1b** in Figure 1. Aryl iodide **1b** coordinates with palladium through the C═C (**i1A**) or C−I (**i1B**) bond. **i1A** is more stable than

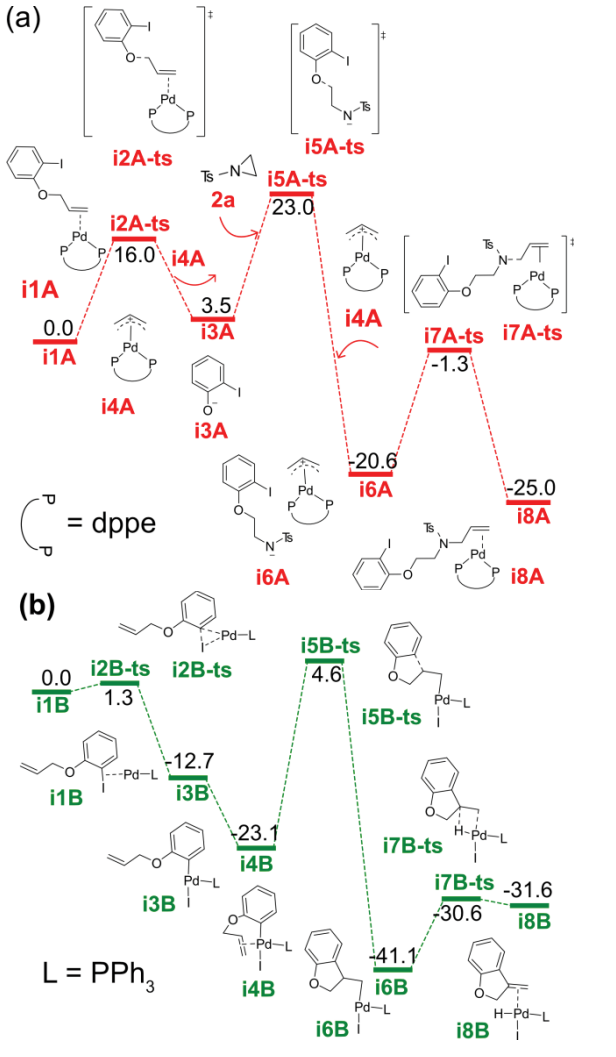


Figure 1. Computed free-energy profile. (a) The red path represents the palladium-catalyzed Tsuji−Trost-type reaction with aziridine. (b) The green path represents the β-H elimination pathway. The energies are in kilocalories per mole.

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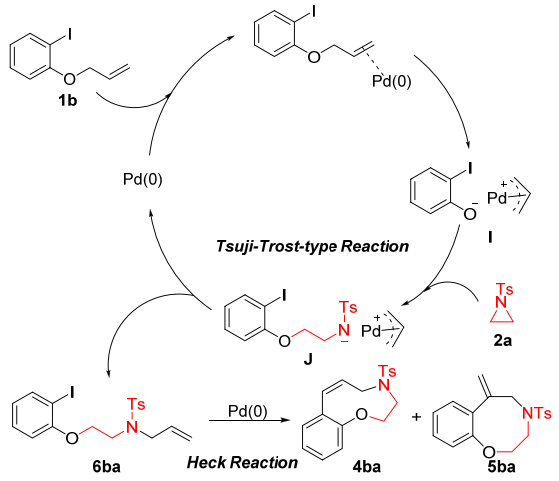
i1B, with a 7.2 kcal/mol energy difference. For the palladium-catalyzed Tsuji–Trost-type reaction (red path, Figure 1a), the C–O bond of **i1A** breaks with a barrier of 16.0 kcal/mol, forming **i3A** and **i4A**. The O atom of **i3A** attacks the three-membered ring compound **2a** with a barrier of 19.5 kcal/mol. The C–N bond of **i8A** forms with barrier of 19.3 kcal/mol. The rate-determining step (rds) is that from **i1A** to **i5A-ts**, with a barrier of 23.0 kcal/mol. For comparison, the monodentate ligand PPh_3 was used to calculate the β-H elimination path (green path, Figure 1b). The oxidation addition reaction barrier is quite small with a barrier of only 1.3 kcal/mol from **i1B** to **i3B**. The five-membered ring formation reaction occurs from **i4B** to **i6B** with a barrier 27.7 kcal/mol. The barrier of β-H elimination is 10.5 kcal/mol from **i6B** to **i8B**. The rds is 27.7 kcal/mol, which is 4.7 kcal/mol higher than in the case of the pathway involving the π-allyl intermediate.

A plausible mechanism is proposed that is consistent with the experimental results previously mentioned (Scheme 4).

Scheme 4. Proposed Mechanism



The Pd(0) species undergoes oxidative addition of aryl iodide **1b** to produce π-allylpalladium complex **I**. Then, the nucleophilic 2-iodophenolate ion is trapped by electrophilic aziridine **2a**. Next, the newly generated π-allylpalladium species **J** undergoes reductive elimination to yield the desired allylamine product **6ba** and regenerate the Pd(0) catalyst. Finally, cyclization products **4ba** and **5ba** are isolated through the Heck reaction with allylamine **6ba**.[22]

In summary, a palladium-catalyzed chemoselective oxidative addition of allyloxy-tethered aryl iodides with aziridines has been developed. The aryl iodide substrate has two oxidative addition sites, that is, the aromatic C–I bond and the allyl–oxygen bond. By adjusting the reaction conditions, Pd(0) can be made to react first with the allyl–oxygen bond to generate a π-allylpalladium species; then, this forms new C–O and C–N bonds with aziridines to obtain allylamine derivatives. This is followed by the production of nine- and eight-membered benzannulated medium-sized rings via the Heck reaction in one pot. Because the reaction proceeds by way of a favored π-allylpalladium species, it seems that the special electrophilic partner aziridine plays a very important role. Preliminary mechanistic studies and DFT calculations shed light on the reaction pathway. Further applications of this method for syntheses of other heterocycles are underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01238.

Complete experimental procedures and characterization data for the prepared compounds (PDF)

Accession Codes

CCDC 2011199, 2011201, and 2011212 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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