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Cationic Pd(II)-Catalyzed Cyclization of *N*-Tosyl-aniline Tethered Allenyl Aldehydes with Arylboronic Acids: Diastereo- and Enantioselective Synthesis of Tetrahydroquinoline Derivatives

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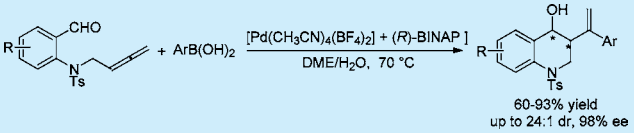
Supporting Information

ABSTRACT: An efficient cyclization of *N*-tosyl-aniline tethered allenyl aldehydes and arylboronic acids catalyzed by cationic palladium complex is developed. This annulation reaction provides a convenient process for the synthesis of 3,4-*cis*-1,2,3,4-tetrahydroquinoline derivatives in high yields with excellent diastereoselectivity and enantioselectivity.



1,2,3,4-Tetrahydroquinoline and its derivatives are of great interest to organic synthesis because of their presence in numerous biologically active natural products and pharmacologically relevant therapeutic agents.[1] As a consequence, there is a continued interest in the development of new methodologies to access this scaffold.[1d,2] Among which, the most used method is Lewis acid or organocatalyzed cyclization of arylamine derivatives. In contrast, there are fewer examples to produce these heterocycles catalyzed by transition metals, especially for their enantioselective synthesis.[3]

Palladium is one of the mostly used metals in transition-metal-catalyzed cascade reactions.[4] An allene functionality has attracted increasing interest during the past two decades for introducing a three-carbon unit in organic synthesis.[5] Recently, there are many palladium-catalyzed cascade reactions by using allenes as the substrates.[6] Among which, a strategy called "umpolung" was used in the reactions of ArX (X = Br or I) with allenes quenched by addition to a carbonyl group. However, this strategy was only applied for Pd(0)-catalyzed reactions because low-valent metals should be added, which can reduce Pd(II) to Pd(0) to accomplish the catalytic cycle (Scheme 1).[7] As for a Pd(II)-catalyzed similar reaction by using $ArB(OH)_2$ to replace ArX, the "umpolung" strategy seems not suitable and some other strategies were then proposed.

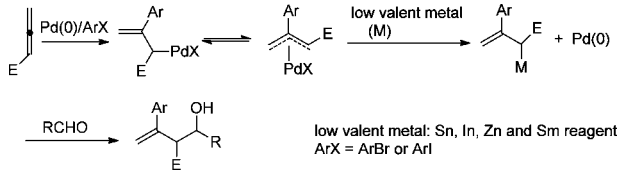
In 2004, Malinakova reported the intermolecular three-component coupling of arylboronic acids with allenes and aldehyde using a β-pinene-derived π-allylpalladium dimer as the catalyst. In the reaction, it was suggested that an in situ assembled bis-π-allylpalladium(II) complex from arylpalladium and allenes may play an important role.[8] In 2008, Tsukamoto and co-workers realized the enantioselective arylative cyclization reactions of allenyl aldehydes with arylboronic acids using Pd(II)-diphosphine as the catalyst in acetonitrile; the plausible mechanism suggests that the use of polar solvents may facilitate the dissociation of an acetate anion from the palladium center generating a cationic arylpalladium species favorable for the cyclization.[9]

Recently, cationic palladium-complex-catalyzed cyclizations of 2-formyl or 2-acylmethoxyarylboronic acids with allenoates, leading to indenol or 1-benzoxepine derivatives, were successfully realized in our group. The use of cationic palladium complexes was the key for the annulations because the η^1-allylpalladium species generated by addition of arylboronic acids to allenes was highly active which added to the carbonyl group before its transfer to η^3-allylpalladium species.[10] Inspired by the above results, we then envisioned a cationic palladium-catalyzed annulation of *N*-tosyl-aniline tethered allenyl aldehydes with arylboronic acids.

After optimization of the reaction conditions using **1a** and phenylboronic acid **2a** as the substrates, it was found that $[Pd(dppe)(H_2O)_2](OTf)_2$ (5 mol %), **1a** (1 equiv) and phenylboronic acid **2a** (1.2 equiv) in DME/H_2O (10/1) at room temperature were optimal, giving the product **3aa** in 99% yield with 20:1 dr (*cis*/*trans*; for details, see Supporting Information (SI)).[11] Then a series of arylboronic acids and *N*-tosyl-aniline tethered allenyl aldehydes bearing different substituents on the benzene ring were screened (Scheme 2).

As shown in Scheme 2, most of the arylboronic acids were appropriate substrates, affording various tetrahydroquinolines in good to excellent yields (**3aa**−**3aq**). In contrast to phenylboronic acid **2a**, electron-rich boronic acids required a

Scheme 1. Umpolung Strategy of the π-Allylpalladium Complex with Aldehydes



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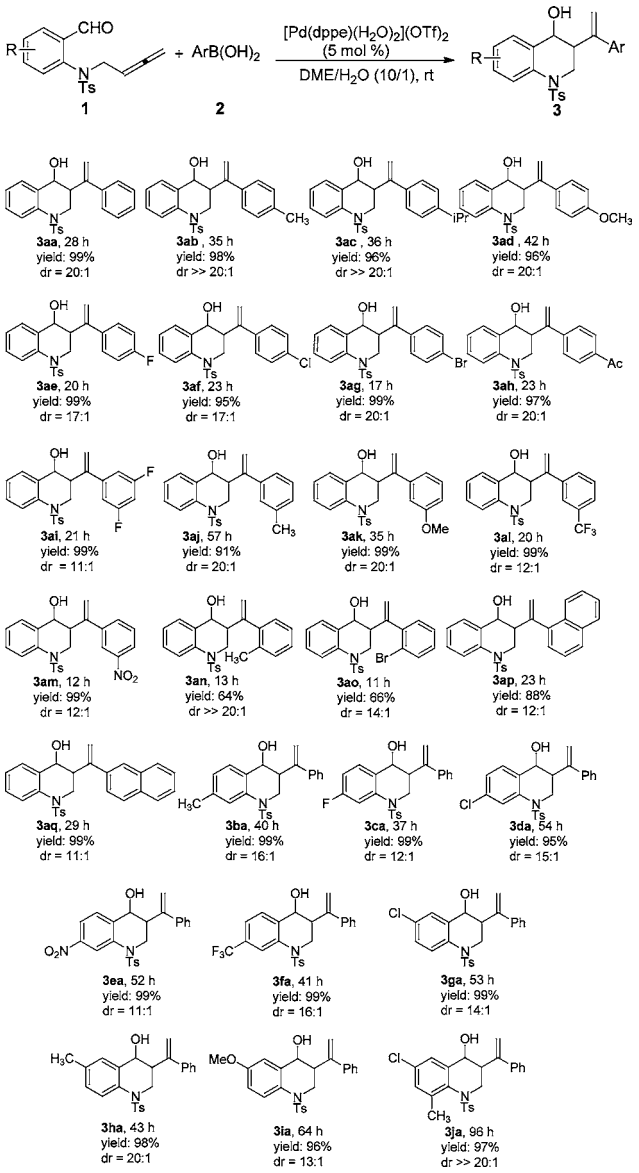
Scheme 2. Cationic Palladium Complex Catalyzed Annulation Reaction of Substrates 1 with Arylboronic Acids 2[a–d]

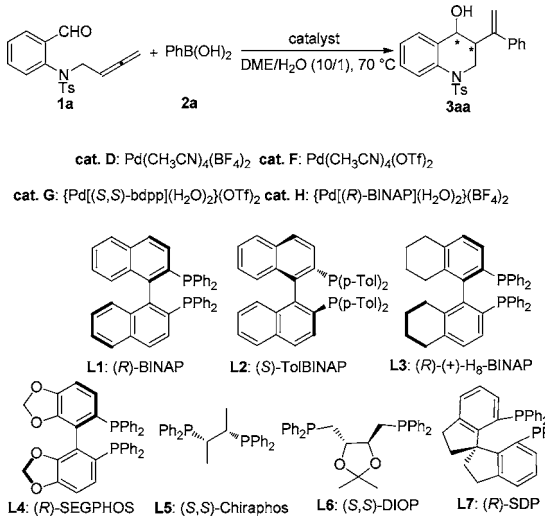


[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), [Pd(dppe)-$(H_2O)_2$]$(OTf)_2$ (0.005 mmol) in DME/H_2O (1 mL/0.1 mL) at room temperature. [b]Yields referred to isolated diastereomeric mixtures. [c]Diastereomeric ratio (cis/trans) was determined by ^1H NMR spectra analysis. [d]The reaction was conducted at 70 °C.

longer reaction time. Diastereoselectivities were generally very high in favor of the *cis* diastereomer. Satisfyingly, naphthylboronic acids were also suitable reaction partners. It is worth noting that the reaction efficiency decreased significantly when substrate **1a** reacted with *ortho*-substituted arylboronic acids, probably due to steric hindrance. For the allenyl aldehydes **1**, all of the tested substrates bearing electron-donating or -withdrawing groups can give the corresponding annulation products **3** in excellent yields with moderate to good diastereoselectivities, indicating that the electronic properties of the aromatic system have little influence on the reactivity (**3ba**–**3ja**).

Subsequently, we turned our attention to the asymmetric version of the annulation reaction to synthesize some chiral tetrahydroquinolines (Table 1). Initially, {Pd[(*S*,*S*)-bdpp]-$(H_2O)_2$}$(OTf)_2$ was used as the chiral catalyst and **3aa** was

Table 1. Screening of the Asymmetric Reaction Conditions of 1a and 2a with Different Ligands[a]



entry	catalyst	time (h)	yield (%)[b]	dr[c]	*ee* (%)[d]
1	**G**	4	99	11:1	7
2	**H**	2	99	16:1	97
3	**D**/**L1**	2	99	12:1	98
4	**F**/**L1**	3.5	94	15:1	97
5[e]	**D**/**L1**	9	84	13:1	97
6	**D**/**L2**	1.5	94	9:1	95
7	**D**/**L3**	2	89	30:1	99
8	**D**/**L4**	1.5	74	11:1	98
9	**D**/**L5**	1	79	6:1	10
10	**D**/**L6**	8	44	4:1	4
11	**D**/**L7**	8	22	6:1	41

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), cationic Pd catalyst (0.005 mmol, for entries 1 and 2) or $Pd(CH_3CN)_4(BF_4)_2$/L* (0.005 mmol/0.005 mmol, for entries 3–11) in DME/H_2O (1 mL/0.1 mL) at 70 °C. [b]Yields referred to isolated diastereomeric mixtures. [c]Diastereomeric ratio (cis/trans) was determined by chiral HPLC analysis. [d]Enantiomeric excess of the major diastereomer (**3aa**) was determined by chiral HPLC analysis. [e]The reaction was conducted at 50 °C.

obtained quantitatively with good diastereoselectivity; however, the enantioselectivity is very poor (entry 1). It is satisfying to see that a high *ee* value was achieved under the catalysis of {Pd[(*R*)-BINAP]$(H_2O)_2$}$(BF_4)_2$ (entry 2). Pd-$(CH_3CN)_4(BF_4)_2$/(*R*)-BINAP can give a similar result as {Pd[(*R*)-BINAP]$(H_2O)_2$}$(BF_4)_2$, indicating that the *in situ* generated chiral cationic catalyst has the same catalytic activity (entry 3). Anion $^-$OTf proved inferior to BF_4^- (entry 4). Meanwhile, the effect of the temperature on the asymmetric version of this annulation reaction was surveyed: by lowering the temperature to 50 °C, a decreased yield was obtained with a prolonged reaction time (entry 5). Then, $Pd(CH_3CN)_4(BF_4)_2$ and some other chiral diphosphine ligands were used to screen the asymmetric version. Tol-BINAP and (*R*)-H_8-BINAP gave similar results as BINAP (entries 6 and 7). The use of (*R*)-SEGPHOS lowered the yield of the product obviously (entry 8). Other diphosphine ligands such as CHIRAPHOS, DIOP, or SDP were tested, and all of them were unfavorable for the cyclization (entries 9–11). Finally, considering the commercial

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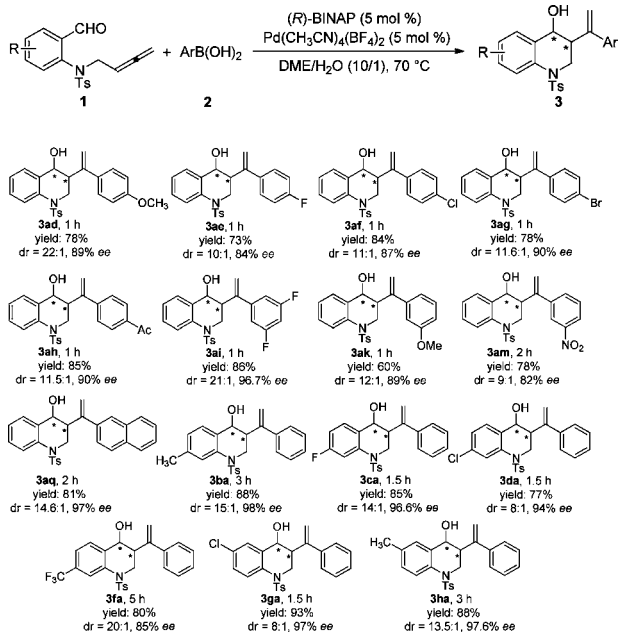
availability, we defined (*R*)-BINAP as the best ligand for the asymmetric reaction.

Under the optimized reaction conditions, a series of chiral 1,2,3,4-tetrahydroquinolines were then synthesized. As shown from Scheme 3, *N*-tosyl-aniline tethered allenyl aldehydes

Scheme 3. Scope of the Asymmetric Reaction[a–d]



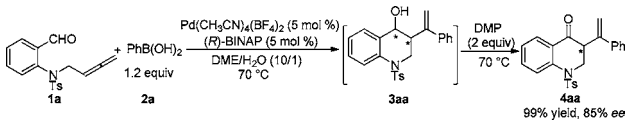
[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), [$Pd(CH_3CN)_4(BF_4)_2$] (0.005 mmol), and (*R*)-BINAP (0.005 mmol) in DME/H_2O (1 mL/0.1 mL) at 70 °C. [b]Yields referred to a chromatographically pure mixture of diastereomers. [c]Diastereomeric ratio was determined by chiral HPLC analysis (see SI). [d]Enantiomeric excess of the major diastereomer was determined by chiral HPLC analysis (see SI).

bearing substituents such as F, Cl, CF_3, or Me on the benzene ring provided the corresponding products in high yields with excellent diastereoselectivity and enantioselectivity (**3ba**–**3ha**). Aryl boronic acids with different groups also gave good results. In the reaction of **1a** with *para* (or *meta*)-methoxyphenyl boronic acid, a considerable amount of **3aa** was isolated together with the formation of target product **3ad** or **3ak**, which may be generated by aryl–aryl exchange[12] of the methoxyphenyl group and the diphosphine ligand during the reaction.

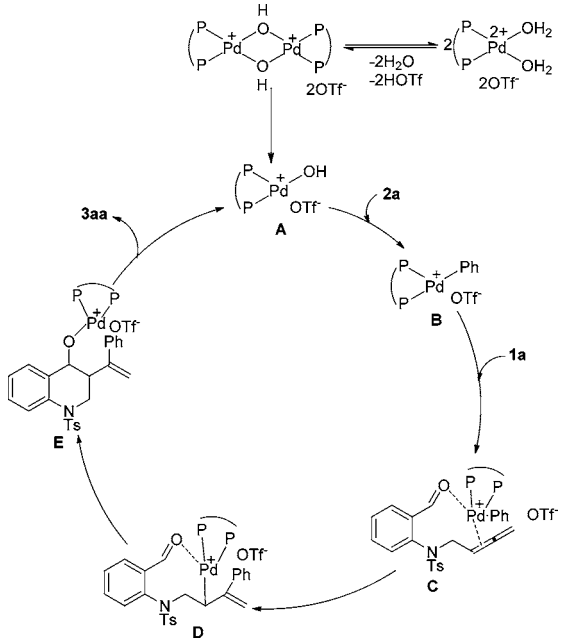
For further potential synthetic utilities of this protocol, the enantioselective oxidation was examined. When chiral tetrahydroquinoline **3aa** was oxidized with DMP, chiral 4-quinolinone **4aa** can be produced efficiently in 99% yield with 85% *ee* (Scheme 4).

Finally, a possible mechanism which is similar to our previous work[10] is proposed for this reaction as shown in Scheme 5. The cationic palladium complex would generate the Pd hydroxo complex **A**, which is supposed to be the active

Scheme 4. Further Synthetic Transformation



Scheme 5. Plausible Mechanism for the Palladium-Catalyzed Annulations



catalytic species[14] and enables transmetalation with the phenylboronic acid **2a** to give intermediate **B**.[14,15] Meanwhile the substrate **1a** will coordinate to the Pd center to give intermediate **C**. Then nucleophilic η^1-allylpalladium complex **D** is formed by insertion of the allene into the carbon–palladium bond. The cationic palladium center in intermediate **D** is highly Lewis acidic and can activate the carbonyl group by coordination, which may result in intramolecular 1,2-addition before its transfer to an η^3-allylpalladium complex to furnish the intermediate **E**. The subsequent protonation of **E** would afford product **3aa** and regenerate the catalytically active species **A** to complete the catalytic cycle.

In conclusion, we have developed a cationic palladium-complex-catalyzed cyclization reaction of *N*-tosyl-aniline tethered allenyl aldehydes with arylboronic acids. This process provided a convenient way for the synthesis of 3,4-*cis*-1,2,3,4-tetrahydroquinoline derivatives in high yields with excellent diastereoselectivity and enantioselectivity. The use of cationic palladium species is crucial for this transformation. Further studies directed toward the synthesis of other heterocycles and a detailed mechanistic investigation are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01894.

Experimental procedures, compounds characterization data, copies of NMR spectra (PDF)

Crystallographic data for compound *cis*-**3aa** (CIF)

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Notes

The authors declare no competing financial interest.

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