β-Carbon Elimination

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Synthesis of Enantioenriched 5,6-Dihydrophenanthridine Derivatives through retro-Carbopalladation of Chiral *o*-Bromobenzylamines**

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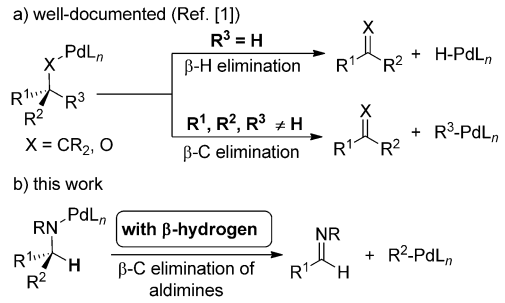
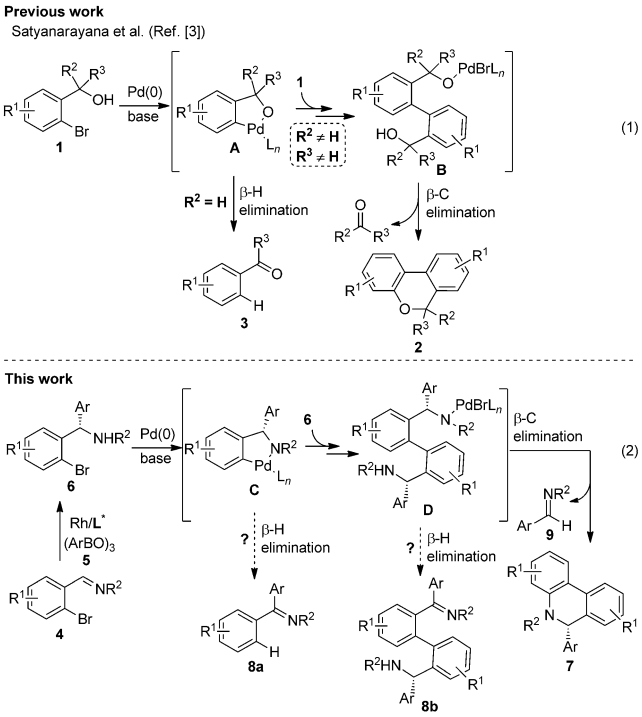
Abstract: *Retro-carbopalladation of aldimines in the presence of a suitable β-hydrogen atom has been observed in the Pd-catalyzed homocoupling reactions of o-bromobenzylamines, providing an expeditious synthetic route to 5,6-dihydrophenanthridine derivatives. Furthermore, a highly enantioselective synthesis of 6-aryl-substituted 5,6-dihydrophenanthridines was achieved in a one-pot manner by taking advantage of Rh and Pd catalysis.*

Palladium-catalyzed C–C bond cleavage through β-carbon elimination, or retro-carbopalladation, has emerged as an effective strategy for the activation of carbon–carbon single bonds as well as for the development of novel synthetic approaches over the last few decades.[1] Being thermodynamically unfavorable, this process usually occurs when there is no *syn*-β-hydrogen atom or in cyclic systems in which a significant release of ring strain is possible. Retro-carbopalladation has rarely been observed in the presence of a suitable β-hydrogen, especially in acyclic systems (Scheme 1).[1,2]

Recently, Satyanarayana and co-workers reported a Pd-catalyzed homocoupling reaction of tertiary *o*-bromobenzyl alcohols **1** for the preparation of chromenes **2** via the intermediacy of palladium species **A** and **B** [Eq. (1), Scheme 2], which delivered the final product through a mechanism involving a Pd^{IV} intermediate and β-carbon elimination.[3] It should be noted that when primary or secondary *o*-bromobenzyl alcohols were employed, β-H elimination of the palladacycle **A** occurred to give the carbonyl products **3** [Eq. (1), Scheme 2].[3a] Based on these interesting observations and our previous work on the Catellani reaction,[4] in which formation of Pd^{IV} intermediate and retro-carbopalladation of norbornene are two of the key steps,[5] we anticipated that 5,6-dihydrophenanthridine derivatives **7**, which are prevalent structural units in natural products and biologically active molecules,[6,7] might be accessible if *o*-bromobenzylamines **6** undergo a similar Pd-catalyzed homocoupling reaction as that of *o*-bromobenzyl alcohols **1** [Eq. (2), Scheme 2]. However, when compared with tertiary alcohols **1**, a major obstacle is that the palladacycle **C** as well as the key intermediate **D** contain a β-hydrogen at the benzylic position, which might form the undesired imine products **8a** and/or **8b** instead of the desired product **7**. Moreover, whereas retro-carbopalladation reactions of ketones and alkenes are well documented,[16] retro-carbopalladation of aldimines, to the best of our knowledge, has not been uncovered to date.



Scheme 1. Pd-catalyzed β-hydride elimination versus β-carbon elimination.



Scheme 2. Previous work and proposal of this work.

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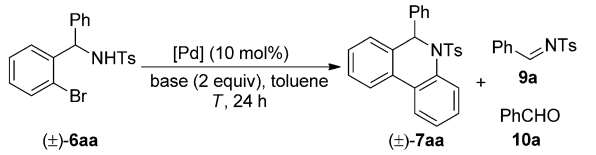
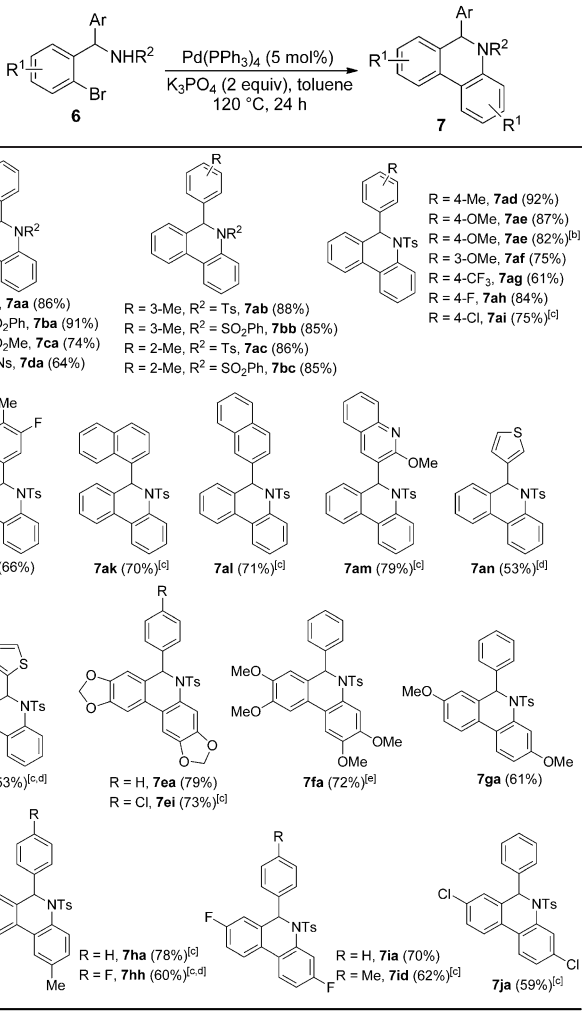
Table 1: Optimization of reaction conditions.[a]



Entry	[Pd]	Base	T [°C]	Yield [%][b]
1[c]	$Pd(OAc)_2/PPh_3$	K_2CO_3	120	64 (62)
2[c]	$Pd(dba)_2/PPh_3$	K_2CO_3	120	72
3	$Pd(PPh_3)_4$	K_2CO_3	120	72
4[d]	–	K_2CO_3	120	n.r.
5	$Pd(PPh_3)_4$	K_2CO_3	110	72[e]
6	$Pd(PPh_3)_4$	K_2CO_3	130	76
7	$Pd(PPh_3)_4$	Na_2CO_3	120	12[f]
8	$Pd(PPh_3)_4$	Cs_2CO_3	120	68
9	$Pd(PPh_3)_4$	K_3PO_4	120	86
10[g]	$Pd(PPh_3)_4$	K_3PO_4	120	60
11[h]	$Pd(PPh_3)_4$	K_3PO_4	120	(86)

[a] The reaction was performed using **6aa** (0.1 mmol), [Pd] (10 mol%), and base (2 equiv) in toluene (1 mL) in a microwave vial at the indicated temperature for 24 h unless otherwise noted. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture. Value in the parentheses is the yield of isolated **7aa**. [c] PPh_3 (10 mol%) was added. [d] No palladium catalyst was used, n.r. = no reaction. [e] 90% conversion. [f] 16% conversion. [g] K_3PO_4 (1 equiv) was used. [h] $Pd(PPh_3)_4$ (5 mol%) was used. Ts = 4-toluenesulfonyl, dba = dibenzylideneacetone.

Table 2: Substrate scope of the Pd-catalyzed homocoupling reaction of *o*-bromobenzylamines.[a]



[a] The reaction was performed using **6** (0.3 mmol), $Pd(PPh_3)_4$ (5 mol%), and K_3PO_4 (2 equiv) in toluene (1.5 mL) at 120°C for 24 h unless otherwise noted. Yields of isolated product **7** were given. [b] $Pd(PPh_3)_4$ (3 mol%) was used. [c] Reaction conducted at 130°C. [d] Reaction time: 48 h. [e] Reaction time: 28 h. 4-Ns = 4-nitrobenzenesulfonyl.

With these challenges in mind, *o*-bromobenzylamine **6aa** was chosen as a model substrate to test the feasibility of our proposal (Table 1). After some screening, we were pleased to find that the desired product **7aa**, whose structure was confirmed by X-ray crystallographic analysis,[8] was isolated in 62% yield using $Pd(OAc)_2$ (10 mol%), PPh_3 (10 mol%), and K_2CO_3 (2 equiv) in toluene at 120°C for 24 h (entry 1, Table 1). The imine **9a** and its decomposition product **10a** were observed as the by-products of this reaction.[9] Encouraged by these results, a range of reaction parameters was examined and representative results are shown in Table 1. Better results were obtained with $Pd(dba)_2$ and PPh_3 or $Pd(PPh_3)_4$ (entries 2 and 3) and $Pd(PPh_3)_4$ was chosen for further optimization. A control experiment was carried out in the absence of the palladium catalyst and no reaction occurred (entry 4). Changing the temperature did not lead to an appreciable improvement (entries 5 and 6). Among the bases surveyed, K_3PO_4 proved to be the best (entries 7–9). Whereas reducing the amount of K_3PO_4 to 1.0 equivalent resulted in a lower yield (entry 10), decreasing the loading of $Pd(PPh_3)_4$ to 5 mol% maintained the yield of **7aa** at 86% upon isolation (entry 11). These conditions were used in the remainder of the study.

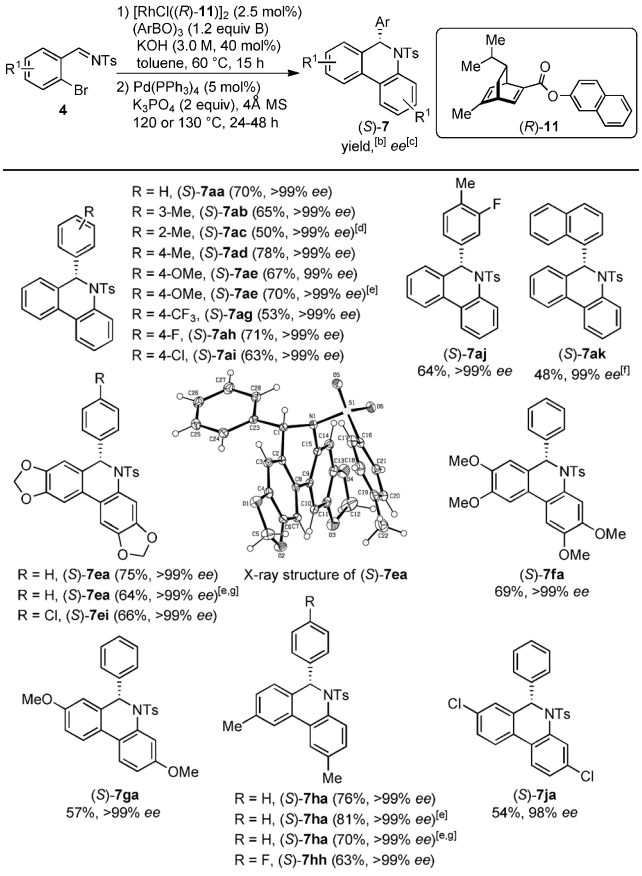
The substrate scope of the Pd-catalyzed homocoupling reaction of *o*-bromobenzylamines **6** was investigated (Table 2). In addition to 4-toluenesulfonyl (Ts), other *N*-sulfonyl protecting groups such as benzenesulfonyl, methanesulfonyl, and 4-nitrobenzenesulfonyl can also be utilized for this transformation. Although the 4-toluenesulfonyl and benzenesulfonyl substituent gave comparable yields of the corresponding products (**7aa** vs. **7ba**, **7ab** vs. **7bb**, **7ac** vs. **7bc**), the 4-toluenesulfonyl group was chosen for further study for its relative ease of purification. The reactivity of *o*-bromobenzylamines **6** with different aromatic substituents at the benzylic position (Ar) was then evaluated. Monosubstituted electron-rich (**7ad**–**7af**) or electron-poor aryl groups (**7ag**–**7ai**), a disubstituted aryl group (**7aj**), and 1- or 2-naphthyl (**7ak** and **7al**) were all tolerated, furnishing the homocoupling products in moderate to excellent yields. *o*-Bromobenzylamines with a heteroaromatic substituent such as 2-methoxyquinolin-3-yl and 2- or 3-thienyl also reacted at elevated temperature and/or with prolonged reaction time (**7am**–**7ao**). Substitution effects on the brominated aromatic moiety of *o*-bromobenzylamines **6** (R^1) were also explored. Both electron-rich and electron-poor substrates underwent the reaction smoothly to give highly substituted 5,6-dihydrophenanthridine derivatives **7ea**–**7ja** in moderate to good yields. It is worth mentioning that the chlorine counterpart of *o*-bromobenzylamine **6aa** also afforded the desired product

7aa in a 75% yield when $Pd(P^tBu_3)_2$ (10 mol%) was used as the catalyst instead of $Pd(PPh_3)_4$.[10]

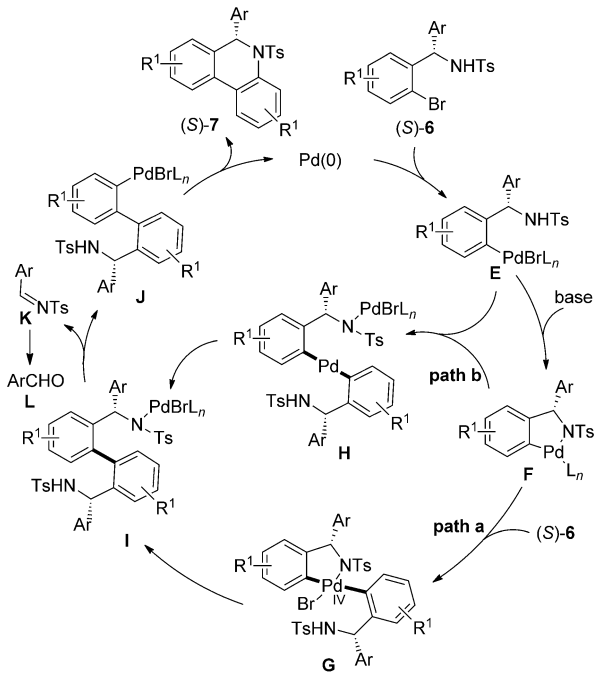
Having realized the Pd-catalyzed synthesis of 6-aryl-5,6-dihydrophenanthridine derivatives **7** from *o*-bromobenzylamines **6**, we turned our attention to the enantioselective synthesis of these compounds. Although optically active 6-substituted 5,6-dihydrophenanthridine derivatives have exhibited interesting biological activities,[6e] no catalytic asymmetric approach has been reported.[11] Based on Hayashi's pioneering work on the asymmetric arylation of imines using Rh/chiral dienes[12,13] and our previous studies on multimetal-catalyzed one-pot/domino reactions,[14] we envisioned that the implementation of Rh and Pd catalysis might enable a one-pot enantioselective synthesis of 5,6-dihydrophenanthridines **7** from *o*-bromobenzaldimines **4** and aryl boronic acids or boroxines. However, compatibility issues and potential racemization of the sensitive benzylic stereocenter were the major concerns. Fortunately, after extensive screening,[15] a 70% overall yield of (*S*)-**7aa** with 99% *ee* was obtained when the first step was conducted with rhodium/diene complex $[RhCl((R)\text{-}\mathbf{11})]_2$[12b,c] as the catalyst, phenyl boroxine (1.2 equiv of B) as the nucleophile, and 40 mol% of KOH solution (3.0 M) as the base followed by the addition of $Pd(PPh_3)_4$ (5 mol%), K_3PO_4 (2 equiv), and 4 Å molecular sieves in the second step. Under these conditions, the generality of this enantioselective one-pot reaction was explored (Table 3). Arylboroxines containing an electron-donating or -withdrawing group all afforded the corresponding products (*S*)-**7ab**–(*S*)-**7ai** in moderate to good overall yields with excellent enantioselectivity (≥99% *ee*). A disubstituted arylboroxine worked as well to give the enantiomerically pure product (*S*)-**7aj** in 64% yield. The reduced yields in the cases of (*S*)-**7ac** and (*S*)-**7ak** may be attributable to the sluggish arylation of imine with sterically bulky 2-methylphenylboroxine and 1-naphthylboroxine in the first step. Highly oxygenated 5,6-dihydrophenanthridine derivatives ((*S*)-**7ea**, (*S*)-**7ei**, and (*S*)-**7fa**), which are common scaffolds in natural products,[6] were also obtained in good overall yield with excellent enantioselectivity. *o*-Bromobenzaldimine substituted with an electron-donating group such as 5-OMe or 4-Me are also suitable substrates for this reaction, furnishing the corresponding products (*S*)-**7ga**, (*S*)-**7ha**, and (*S*)-**7hh** in synthetically useful yields with >99% *ee*. Dichloro-substituted 5,6-dihydrophenanthridine (*S*)-**7ja** was also obtained in moderate yield with high enantiopurity. The absolute configuration of the enantiopure products **7** was unambiguously determined to be *S* by X-ray diffraction analysis of (*S*)-**7ea** and (*S*)-**7ha**.[8]

A possible mechanism for the formation of 5,6-dihydrophenanthridines **7** from *o*-bromobenzylamines **6** under palladium catalysis is shown in Scheme 3.[3,16] Oxidative addition of *o*-bromobenzylamines **6** to Pd^0 would form intermediate **E**,

Table 3: Substrate scope of enantioselective one-pot syntheses of 5,6-dihydrophenanthridines **7** through Rh/Pd catalysis.[a]



[a] The reaction was performed on 0.3 mmol scale of **4** at 60°C for 15 h followed by the addition of $Pd(PPh_3)_4$ (5 mol%), 4 Å molecular sieves (300 mg), and K_3PO_4 (2 equiv) and stirred at 120 or 130°C for 24–48 h unless otherwise noted (see the Supporting Information for details). [b] Yields of isolated product (*S*)-**7**. [c] *ee* was determined by HPLC using a chiral stationary phase. [d] Reaction time of the first step: 48 h. [e] The reaction was carried out on 1.0 mmol scale of **4**. [f] $[RhCl((R)\text{-}\mathbf{11})]_2$ (5 mol%) was used, reaction time of the first step: 24 h. [g] $[RhCl((R)\text{-}\mathbf{11})]_2$ (1.5 mol%) and $Pd(PPh_3)_4$ (3 mol%) were used.



Scheme 3. A possible mechanism.

which was deprotonated to generate palladacycle **F**. At this point, two pathways are possible for the generation of intermediate **I**. In path a, palladacycle **F** undergoes oxidative addition with a second molecule of *o*-bromobenzylamines **6**, affording the Pd^{IV}[16c] species **G**, which delivers the intermediate **I** upon aryl–aryl reductive coupling. Alternatively, dinuclear Pd^{II} complex **H**,[17] which was formed through a transmetalation-type reaction between palladacycle **F** and the palladium species **E**, may also afford the intermediate **I** after reductive elimination (path b). β-Carbon elimination of intermediate **I** then furnishes the aryl palladium species **J** with concomitant formation of the imine byproduct **K** and its decomposition product **L**. Buchwald–Hartwig amination of intermediate **J** produces the final product and regenerates the catalytically active Pd^0 species.

In conclusion, we have developed a novel synthetic approach for the rapid generation of biologically important 5,6-dihydrophenanthridine skeletons,[6] in which an unprecedented retro-carbopalladation of aldimines was observed. By taking advantage of Rh and Pd catalysis, a highly enantioselective synthesis of 6-aryl-substituted 5,6-dihydrophenanthridine derivatives was achieved in a one-pot manner. Further studies on extending this strategy to related processes are being pursued in our laboratory.

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Keywords: dihydrophenanthridines · enantioselective synthesis · palladium · β-carbon elimination

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[8] See the Supporting Information for X-ray structures. CCDC 1021153 (**7aa**), 1026833 (**7ak**), 1021957 ((*S*)-**7ea**), and 1021729 ((*S*)-**7ha**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[9] Due to decomposition of the imine under the reaction conditions and its instability on the silica gel column, only a low yield (< 10%) of **9a** was isolated. The formation of imine **9a** and benzaldehyde **10a** was further confirmed by comparing the ^{1}H NMR spectra of the crude reaction mixture with the authentic samples. See the Supporting Information for details.

[10] A very low yield was obtained under the optimized conditions, see the Supporting Information for details.

[11] Ridgway et al. reported two approaches for the enantioselective synthesis of 6-alkyl-substituted 5,6-dihydrophenanthridine derivatives through asymmetric reduction of phenanthridines or intramolecular Mitsunobu reaction of enantioenriched alcohols with amines, however, a stoichiometric amount of chiral reducing agent and/or multistep syntheses were required. For details, see Ref. [6e].

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[15] When all reagents were added at the outset of the reaction, direct Suzuki coupling reaction of the *o*-bromobenzaldimine **4a** with phenylboroxine occurred to give the corresponding *o*-phenylbenzaldimine. For details on the optimization of reaction conditions, see the Supporting Information.
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