

Suppressed β -Hydride Elimination in Palladium-Catalyzed Cascade Cyclization–Coupling Reactions: An Efficient Synthesis of 3-Arylmethylpyrrolidines

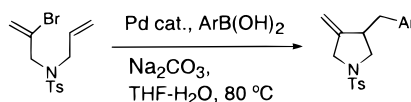
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ABSTRACT



A novel type of palladium-catalyzed cascade cyclization–coupling reaction that proceeds with suppressed β -hydride elimination has been found. One of the *N*-sulfonyl oxygens is suggested to coordinatively stabilize an alkylpalladium intermediate, thus preventing the intermediate from the usual β -elimination. This is the first sequential palladium-catalyzed coupling reaction where the Suzuki and Heck reactions can compete. The reaction provides an efficient synthetic route to 4-methylene-3-arylmethylpyrrolidines, which are not readily available by other routes.

Transition metal catalyzed cross-coupling reactions have emerged as powerful and versatile coupling methods available to us.¹ Thanks to the recent developments of the coupling reactions, traditionally difficult C–C bond-forming reactions now become possible in many cases. The transition metal catalyzed reactions, mostly palladium- or nickel-catalyzed reactions, usually proceed under mild reaction conditions and are tolerant of most functional groups. A general mechanism of the metal catalyzed cross-coupling reactions involves three stages: oxidative addition, transmetalation, and reductive elimination. One severe limitation of the process is that the oxidative addition intermediate from an alkyl halide that has β -hydrogen(s) is prone to undergo β -hydride elimination. Therefore, the corresponding couplings are limited to those substrates in which the elimination is unfavorable owing to stereoelectronic reasons. Several exceptions to this category have been recently overviewed.²

Negishi³ reported a palladium-catalyzed carbonylative cyclization in which the β -elimination is suppressed. It was suggested that an adjacent carbonyl oxygen atom coordinatively stabilizes an alkylpalladium intermediate. Fast CO insertion is also considered to be a contributing factor to the success of the process, which proceeds prior to the decomposition of the alkylpalladium intermediate. Oh⁴ and Meijere⁵ reported palladium-catalyzed cyclization reactions in which cyclizations are preferred over the β -hydride elimination routes. In both cases, explanations for the exceptions are left

(3) (a) Negishi, E.; Ma, S.; Amanfu, J.; Copéret, C.; Miller, J. A.; Tour, J. M. *J. Am. Chem. Soc.* **1996**, *118*, 5919–5931. (b) Tour, J. M.; Negishi, E. *J. Am. Chem. Soc.* **1985**, *107*, 8289–8291. (c) Copéret, C.; Negishi, E.-i. *Org. Lett.* **1999**, *1*, 165–167.

(4) Oh, C. H.; Rhim, C. Y.; Kang, J. H.; Kim, A.; Park, B. S.; Seo, Y. *Tetrahedron Lett.* **1996**, *37*, 8875–8878.

(5) Schweizer, S.; Song, Z.-Z.; Meyer, F. E.; Parsons, P. J.; de Meijere, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1452–1454.

(6) Ishiyama, T.; Abe, S.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1992**, 691–694.

(7) (a) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133–12134. (b) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895–5904.

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(1) *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds; Wiley-VCH: Weinheim, 1998.

(2) Cárdenas, D. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3018–3020.

open. Suzuki reported palladium-catalyzed coupling reactions between alkyl iodides and alkylboranes, although yields were moderate.⁶ Delgado⁷ reported an interesting nickel-promoted cascade cyclization–capture reaction in which the β -elimination was suppressed. They suggested that an *N*-benzyl nitrogen atom coordinatively stabilizes an alkylnickel intermediate. Recently, Knochel⁸ reported a more general nickel-catalyzed cross-coupling reaction between alkyl halides and diorganozincs. In this case, all the alkyl halides contain a carbonyl, sulfide, or ethylene group that facilitates the reductive elimination. In addition, a cocatalyst such as *m*-(trifluoromethyl)styrene is suggested to promote the reductive elimination. Also, nickel complexes generally react faster with alkyl iodides than palladium species do. It would be beneficial in utilizing the powerful coupling methods in organic synthesis if we understood those factors that suppress the undesired β -hydride elimination. Herein, we wish to report a novel palladium-catalyzed cascade cyclization–coupling reaction in which a possible β -hydride elimination is suppressed. This finding has led to an efficient synthesis of 3-arylmethylpyrrolidines.

In the course of our study to synthesize pyrrolidine analogues that might have serotonin 1A ligand activity,⁹ we had a chance to treat *N*-allyl-*N*-(2-bromoallyl)-4-methylbenzenesulfonate (**1a**)¹⁰ with 4-fluorophenylboronic acid in the presence of a catalytic amount of Pd(PPh₃)₄ and aqueous Na₂CO₃ in THF at 80 °C. The reaction mixture provided a major compound, which was isolated and characterized to be 3-(4-fluorobenzyl)-4-methylene-1-(*p*-toluenesulfonyl)pyrrolidine (**2**, R = Ts). Apparently, the β -hydride elimination is suppressed during the reaction. To confirm the generality of this reaction, we used other phenylboronic acid derivatives and could obtain the same type of reaction products, though the yields were varied. Side products were diaryl compounds of the arylboronic acids and a trace amount of an unknown compound in all cases, except for 3-nitrophenylboronic acid which showed a complex pattern on TLC.¹¹ Notably, possible intramolecular Heck reaction products were not observed.

When *n*-butylboronic acid or a heteroarylboronic acid such as 2-furanboronic acid was used, however, the cascade cyclization–coupling product was not observed. Instead, a mixture of cyclization products was obtained, along with starting material **1a**. A careful analysis of the cyclization mixture by NMR spectroscopy indicated that it was composed of two compounds that have no aryl moieties. The

two compounds were barely separable on TLC. One of the compounds was identified as six-membered cyclic compound **3**, which was confirmed later by an authentic sample. The other was assigned to be pyrrole derivative **4**, which was an expected Heck product resulting from double bond migration.¹² When the *N*-tosyl group in **1** was changed to the *N*-benzyl (**1b**) or *N*-acetyl group (**1c**), poor results were obtained. The results are summarized in Table 1.

Table 1. Pd-Catalyzed Cascade Cyclization–Coupling Reactions

substrate	ArB(OH) ₂	product	yield (%) ^b
1a R = Ts	4-fluorophenylboronic acid	2	92
	phenylboronic acid	2	75
	1-naphthylboronic acid	2	88
	4-methoxyphenylboronic acid	2	69
	3-nitrophenylboronic acid	2	49
	2-furanboronic acid	3+4	26 ^c (58)
	ferroceneboronic acid	3+4	61 ^d (19)
	<i>n</i> -butylboronic acid	-	(69)
1b R = Bn	4-fluorophenylboronic acid	2	30
1c R = Ac	phenylboronic acid	2 ^a	18
1d R = Boc	phenylboronic acid	-	-

^aContaminated with an isomeric compound of double bond migration. ^bYield in parenthesis indicates that of the recovered starting material. ^c**3/4** = 3.3/1. ^d**3/4** = 3.2/1.

A plausible reaction mechanism for the formation of compounds **2–4** is depicted in Scheme 1. The first step should involve an oxidative addition of Pd(0) to vinyl bromide **1**, giving Pd(II) intermediate **5**. From vinylpalladium **5**, two reaction pathways are expected: (1) a carbopalladation route to give alkylpalladium intermediate **6**; (2) a direct Suzuki coupling process with an added arylboronic acid (**5** → **7**). The former route is apparently preferred over the latter one in the case of substrate **1a** because the direct Suzuki coupling product **7** was not observed. For the success of the cascade reaction, alkylpalladium intermediate **6** should favorably undergo transmetalation with an arylboronic acid, rather than undergo β -elimination, to produce intermediate **8**, from which a fast reductive elimination ensures the cascade reaction. We found that the cascade cyclization–coupling reaction is slow below 80 °C by VT ¹H NMR studies at temperature ranging from 20 to 80 °C. When we carried out the same reaction with substrate **1a** (R' = H) in the absence of an arylboronic acid at 90 °C under otherwise

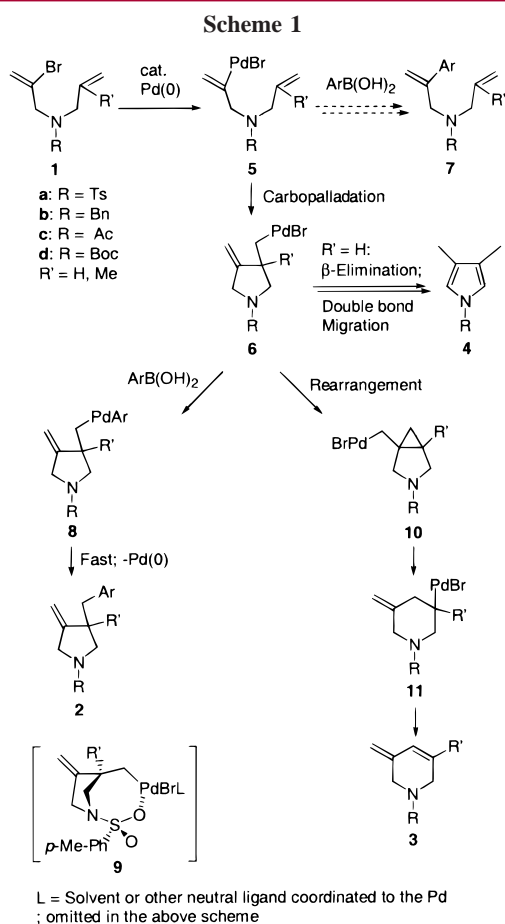
(12) Notably, the combined yield of the two compounds is significantly different depending on the boronic acid used.

(8) (a) Giovannini, R.; Stüdemann, T.; Dussin, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 2387–2390. (b) Giovannini, R.; Knochel, P. *J. Am. Chem. Soc.* **1998**, *120*, 11186–11187.

(9) Ahn, K. H.; Lee, S. J.; Lee, C.-H.; Hong, C. Y.; Park, T. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1379–1384.

(10) Prepared from allylamine in two steps: (1) TsCl, Et₃N, CH₂Cl₂, 25 °C, 100%; (2) 2,3-dibromo-1-propene, K₂CO₃, toluene, reflux, 91%.

(11) **General procedure:** To a stirred solution of vinyl bromide **1a** (165 mg, 0.5 mmol) and Pd(PPh₃)₄ (29 mg, 0.025 mmol) in dry THF (6 mL) was added 4-fluorophenylboronic acid (140 mg, 1.0 mmol) under N₂, followed by aqueous Na₂CO₃ (2 M, 1 mL), and the resulting mixture was heated at 80 °C overnight. The mixture was cooled and poured into water (30 mL); then it was extracted with CH₂Cl₂. The organic layer was dried over MgSO₄ and concentrated. Purification of the crude product by chromatography on SiO₂ (ethyl acetate–hexane as eluant) gave 3-(4-fluorophenylmethyl)-4-methylene-*N*-(*p*-toluenesulfonyl)pyrrolidine in 92% yield (159 mg).



identical reaction conditions, the rearrangement product **3** (R = Ts, R' = H) was produced in 20% yield, along with 36% of the starting material, and the expected Heck product **4** (R = Ts) was only observable as a minor contaminant (about 10%) of product **3** (R = Ts, R' = H). Therefore, under the reaction conditions, the rearrangement route is preferred over the β -elimination route.

As noted previously, we could not observe the direct Suzuki coupling product **7** in the case of vinyl bromide **1a**. When we extended the *N*-allyl group in **1a** to an *N*-homoallyl group as in *N*-(2-bromoallyl)-*N*-(but-3-enyl)-4-methylbenzenesulfonate, however, the direct Suzuki coupling process was observable. Thus, with 4-fluorophenylboronic acid under the same reaction conditions, we could isolate the corresponding Suzuki coupling product in 34% yield and a mixture of intramolecular Heck reaction products in 58% yield.¹³ In this case, the carbopalladation route is supposed to be slower than the case of substrate **1a**, probably because it involves the formation of a six-membered ring rather than a five-membered ring. These results indicate that the cascade

(13) Because of the double bond isomerization, an isomeric mixture of Heck products was observed, which were inseparable on TLC.

(14) The cascade cyclization–coupling reaction is different from the first example of the tandem Heck–Suzuki reaction reported by Shibasaki and co-workers (Kojuma, A.; Honzawa, S.; Boden, C. D. J.; Shibasaki, M. *Tetrahedron Lett.* **1997**, *38*, 3455–3458). In our case, the first step is not a complete Heck reaction but it involves a “Heck-type” carbopalladation intermediate.

reaction results from a subtle balance between several competing pathways.¹⁴ As in the above case, where the intramolecular carbopalladation is slow, direct Suzuki coupling can compete with it.

As a possible origin of the suppressed β -elimination, we propose a neighboring group coordination to the alkylpalladium intermediate such as in **9**, which is reminiscent of Delgado’s nickel-catalyzed reaction.⁷ However, in our case, *N*-sulfonyl oxygen(s), not the nitrogen, is believed to stabilize the alkylpalladium intermediate. The nitrogen may coordinate to the palladium in the case of *N*-benzyl analogue **1b**, though it seems less effective. A theoretical calculation on the relative stability of the *N*- vs *O*-coordination in the case of **1a** indicated that the latter mode leads to a more stable system by 3.1 kcal/mol.¹⁵ When we changed the *N*-sulfonyl group in **1** to the *N*-acetyl or *N*-Boc group, the cascade reaction route became less favorable, as noted previously. Treatment of vinyl bromide **1c** with phenylboronic acid under the same reaction conditions provided a rather complex reaction mixture compared with the case of **1a**.¹⁶ In the case of **1d**, an even more complex reaction pattern was observed. These results suggest that, in both cases, the coordinative stabilization is less favorable than that of the *N*-sulfonyl case, possibly due to the strain that develops on the metal coordination. We believe that this is one of the reasons why a similar cascade reaction has not been observed in other related cases.¹⁷

Apparently, ease of the transmetalation of an aryl group from the boron to the palladium is also an important factor that determines the product distribution. With arylboronic acids that are comparatively reluctant to transmetalation, alkylpalladium **6** can go back to the starting material, follow the β -elimination route, or undergo the rearrangement route.

When the β -elimination route was blocked in substrate **1a** (R' = Me), the cascade cyclization–coupling reaction with phenylboronic acid proceeded but with competition by the rearrangement route in this case producing a mixture of **2** (R = Ts, R' = Me) and **3** (R = Ts, R' = Me) in a ratio of 7:3.¹⁸ Thus, the rearrangement route becomes favorable if we introduce a substituent such as R' that facilitates the

(15) The calculations were carried out at the HF/3-21G level using Gaussian 94 (Frisch et al. *Gaussian 94*; Gaussian Inc.: Pittsburgh, PA, 1995).

(16) From the mixture, two major compounds were isolated and characterized by NMR and mass analysis. One of the products was assigned as the corresponding cascade reaction product (18% yield) and the other was tentatively assigned as the direct Suzuki coupling product (9% yield). In both products, an extensive double bond migration occurred probably due to the acetyl group, which resulted in a mixture of isomeric products.

(17) For example, see: (a) de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88–110. (b) Bräse, S.; de Meijere, A. *Palladium-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; pp 99–164. (c) Grotjahn, D. B.; Zhang, X. *J. Mol. Catal. A: Chem.* **1997**, *116*, 99–107.

(18) Both products were barely separable on TLC; hence, the ratio was determined by ¹H NMR analysis of the mixture. The isolated yield of the mixture was 60% on the basis of the product ratio.

(19) For related rearrangements, see: (a) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091–10092. (b) Grigg, R.; Sridharan, V. *Tetrahedron Lett.* **1992**, *33*, 7965–7968. (c) Grigg, R.; Rasul, R.; Redpath, J.; Wilson, D. *Tetrahedron Lett.* **1996**, *37*, 4609–4612. (d) Steinig, A. G.; de Meijere, A. *Eur. J. Org. Chem.* **1999**, 1333–1344.

elimination step from **11** to **3**. In the absence of an arylboronic acid, only product **3** (R = Ts, R' = Me) was obtained in 90% yield, starting from **1a** (R' = Me) under the same reaction conditions, as expected. Six-membered ring compound **3** is presumably produced via cyclopropane-methylpalladium **10**.¹⁹

In conclusion, we have presented a novel type of palladium-catalyzed cascade cyclization–coupling reaction that proceeds with suppressed β -hydride elimination. The cascade reaction has been found to be the result of a subtle balance between various competing reaction pathways. The cascade process provides 3-arylmethylpyrrolidines which are not

readily available by other routes in moderate to high yields. Application to other substrates is under investigation.

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Supporting Information Available: Synthesis and characterization of the vinyl substrates and the reaction products mentioned including **2** and **3**. This material is available free of charge via the Internet at <http://pubs.acs.org>. OL0056426