

A New Method for the Generation of Indole-2,3-quinodimethanes from Allenamides

Haruhiko Fuwa,* Tomomi Tako, Makoto Ebine, and Makoto Sasaki*

Laboratory of Biostructural Chemistry, Graduate School of Life Sciences, Tohoku University,
1-1 Tsutsumidori-amamiya, Aoba-ku, Sendai 981-8555

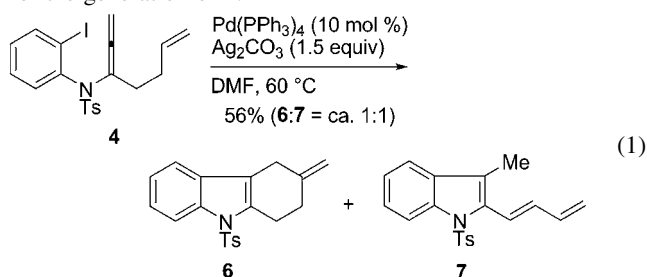
(Received June 12, 2008; CL-080591; E-mail: hfuwa@bios.tohoku.ac.jp)

A new method for the generation of indole-2,3-quinodimethanes based on a palladium-catalyzed cascade process starting from *N*-(*o*-iodophenyl)allenamides has been developed.

Since substituted indole nucleus is widely found in natural products and pharmaceuticals, the development of efficient and versatile methodologies for the synthesis of indole derivatives has long been an intense area of research for organic chemists.¹ We have recently reported a strategy for the synthesis of indole derivatives **3** starting from *N*-(*o*-halophenyl)allenamides **1**, wherein an allenamide functionality acts as a relay unit to generate a π -allylpalladium intermediate **2**, which is subsequently trapped with an appropriate nucleophile^{2,3} (Scheme 1). Although our strategy has successfully provided a series of 3-substituted and 2,3-disubstituted indoles in good yields, its extension to the synthesis of polycyclic nitrogen heterocycles has yet to be realized (e.g., **4** \rightarrow **6**).

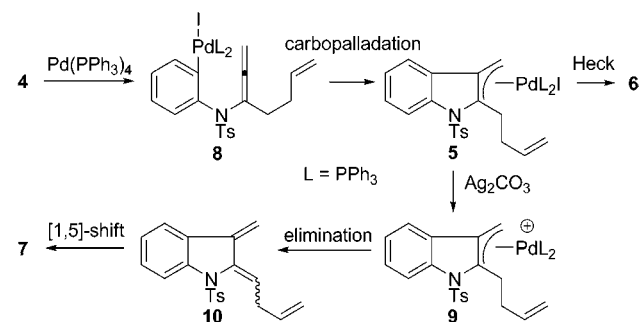
Indole-2,3-quinodimethane is a highly reactive diene that readily undergoes Diels–Alder cycloaddition to deliver tetrahydrocarbazoles and related compounds.^{4,5} Its synthetic utility has been demonstrated by Magnus and co-workers in their total synthesis of *Aspidosperma* alkaloids.^{4a} The majority of the reported methods for the generation of indole-2,3-quinodimethanes requires multistep synthetic manipulations for elaboration of appropriately functionalized 2,3-disubstituted indole derivatives. During the course of our ongoing studies on the synthesis of 3-substituted tetrahydrocarbazoles based on palladium-catalyzed cascade cyclizations starting from allenamides, we found a new and efficient method for the generation of indole-2,3-quinodimethanes. Thus, upon exposure of allenamide **4** to 10 mol % of Pd(PPh₃)₄ and 1.5 equiv of Ag₂CO₃ in DMF at 60 °C, an approximately 1:1 mixture of tetrahydrocarbazole **6** and diene **7** was obtained in 56% combined yield (eq 1). The structure of **7** was deduced based on a careful inspection of the ¹H,

¹³C NMR, COSY, HSQC, and HMBC spectra. A plausible mechanism that accounts for the formation of the by-product **7** is summarized in Scheme 2. Oxidative addition of **4** to the palladium catalyst generates **8**, which upon cyclization onto the allenamide moiety gives a π -allylpalladium intermediate **5**.⁶ The expected tetrahydrocarbazole **6** should arise from the second cyclization (Heck cyclization⁷) onto the alkene tether. On the other hand, by the action of Ag₂CO₃, a cationic palladium species **9** may possibly be generated and could undergo elimination to provide an indole-2,3-quinodimethane intermediate **10**, from which diene **7** would be delivered via a [1,5]-sigmatropic hydrogen shift.⁸ In this reaction, the use of Ag₂CO₃ as a base was found to be critical; the reaction using K₂CO₃ gave **6** as a sole isolatable product in 56% yield.⁹ These results suggested the importance of cationic palladium intermediate **9** for the generation of **7**.



Scheme 1. A strategy for the synthesis of 3-substituted and 2,3-disubstituted indoles **3** based on palladium-catalyzed cascade reactions and its extension to the synthesis of 3-substituted tetrahydrocarbazole **6**.

The formation of **7** suggested the possibility of the generation of indole-2,3-quinodimethane **10** via a novel mechanism. Therefore, we undertook several proof-of-concept experiments to confirm this hypothetical mechanism, and the results are summarized in Table 1. We surmised that a highly reactive indole-2,3-quinodimethane **12** generated from an allenamide **11** would be trapped efficiently by an appropriate dienophile in the reaction mixture, giving a substituted tetrahydrocarbazole derivative **13**. In the event, upon treatment of allenamide **14** with 10 mol % of Pd(PPh₃)₄, 1.5 equiv of Ag₂CO₃, 10 equiv of methyl acrylate in DMF at 60 °C, an approximately 2:1 mixture of 2- and 3-methoxycarbonyl tetrahydrocarbazoles **15a** and **15b** was



Scheme 2. A plausible reaction mechanism for by-product **7**.

Table 1. Synthesis of a variety of substituted tetrahydrocarbazoles

Allenamide	Dienophile	Product
 11	 12	 13
 14	 15a, 15b (53%, 2-CO ₂ Me:3-CO ₂ Me = ca. 2:1) ^a	 16 (81%) ^b
 19		 17 (93%) ^b
 20		 18a, 18b (55%; 18a:18b = ca. 10:1) ^b
 21		 18a, 18b (55%; 18a:18b = ca. 10:1) ^b
 22		 22 (63%) ^b
 23		 23 (77%) ^b
 24		 24 (87%) ^b

^aReactions were performed using Pd(PPh₃)₄ (10 mol %), Ag₂CO₃ (1.5 equiv), dienophile (10 equiv) in DMF at 60 °C.

^bReactions were performed using Pd(PPh₃)₄ (10 mol %), Ag₂CO₃ (1.5 equiv), dimethyl fumarate (1.5 equiv) in CH₃CN at 60–70 °C.

obtained in 53% combined yield.¹⁰ Changing the dienophile to dimethyl fumarate or *N*-methylmaleimide also provided the desired products **16** or **17** in excellent yield, respectively. The use of acetonitrile as a solvent proved to be also effective for the present reaction to provide the products **16–18** and **22–24**. On the other hand, in the absence of a dienophile, an inseparable 10:1 mixture of the dimerized product **18a** and its isomer **18b** was isolated in 55% combined yield. These results clearly indicated the generation of an indole-2,3-quinodimethane intermediate and its subsequent Diels–Alder trapping.

Additional experiments were performed to investigate the scope of the reaction. Thus, α -substituted allenamides **19–21** afforded the corresponding tetrahydrocarbazoles **22–24** in good

yields, respectively, suggesting that a variety of substitution patterns of the benzene ring could be tolerated. Thus, the present reaction should provide an efficient means to synthesize a variety of substituted tetrahydrocarbazoles of biological interest under mild reaction conditions.

In conclusion, an efficient method for the generation of indole-2,3-quinodimethanes from *N*-(*o*-iodophenyl)allenamides based on a novel reaction mechanism has been developed. A variety of substituted tetrahydrocarbazoles were synthesized in good yields from readily available starting materials. Further investigations on the palladium-catalyzed reactions of allenamides are currently underway and will be reported in due course.¹¹

This work was supported in part by a Grant-in-Aid for Scientific Research for Young Scientists (B) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

References and Notes

- For recent reviews of the synthesis of indole derivatives, see: a) G. W. Gribble, *J. Chem. Soc., Perkin Trans 1* **2000**, 1045. b) T. L. Gilchrist, *J. Chem. Soc., Perkin Trans 1* **2001**, 2491. c) G. R. Humphrey, J. T. Kuethe, *Chem. Rev.* **2006**, 106, 2875.
- H. Fuwa, M. Sasaki, *Org. Biomol. Chem.* **2007**, 5, 2214; Additions and corrections: H. Fuwa, M. Sasaki, *Org. Biomol. Chem.* **2007**, 5, 2506.
- For a review of carbopalladation/anion capture cascade, see: R. Grigg, V. Sridharan, *J. Organomet. Chem.* **1999**, 576, 65.
- For reviews of indole-2,3-quinodimethanes, see: a) P. Magnus, T. Gallagher, P. Brown, P. Pappalardo, *Acc. Chem. Res.* **1984**, 17, 35. b) U. Pindur, H. Erfanian-Abdoust, *Chem. Rev.* **1989**, 89, 1681. c) J. L. Segura, N. Martin, *Chem. Rev.* **1999**, 99, 3199.
- Selected recent reports on the generation of indole-2,3-quinodimethanes: a) M. Laronze, J. Sapi, *Tetrahedron Lett.* **2002**, 43, 7925. b) M. Terzidis, C. A. Tsoleridis, J. Stephanidou-Stephanatou, *Tetrahedron Lett.* **2005**, 46, 7239. c) N. Kuroda, Y. Takahashi, K. Yoshinaga, C. Mukai, *Org. Lett.* **2006**, 8, 1843. d) H. Fuwa, M. Sasaki, *Chem. Commun.* **2007**, 2876.
- For a review of carbopalladation, see: E. Negishi, C. Copéret, S. Ma, S.-Y. Liou, F. Liu, *Chem. Rev.* **1996**, 96, 365.
- For selected reviews of Heck reaction, see: a) S. E. Gibson, R. J. Middleton, *Contemp. Org. Synth.* **1996**, 3, 447. b) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, 100, 3009.
- For a discussion on a related [1,5]-sigmatropic hydrogen shift, see: F. Augé, J. Sapi, J.-Y. Laronze, *Tetrahedron* **2004**, 60, 6005.
- M. M. Abelman, T. Oh, L. E. Overman, *J. Org. Chem.* **1987**, 52, 4130.
- Typical experimental procedure: To a solution of allenamide **14** (69.4 mg, 0.163 mmol) in anhydrous CH₃CN (1.7 mL) under argon atmosphere were added Ag₂CO₃ (67.6 mg, 0.245 mmol), dimethyl fumarate (35.3 mg, 0.245 mmol), and Pd(PPh₃)₄ (19.3 mg, 0.0167 mmol). The resultant mixture was heated at 60 °C for 2.6 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (10 to 25% EtOAc/hexanes) gave substituted tetrahydrocarbazole **16** (58.2 mg, 81%) as a yellow oil.
- Supporting Information is available electronically on the CSJ-Journal Web site, <http://www.csj.jp/journals/chem-lett/index.html>.