Fused Polycycles

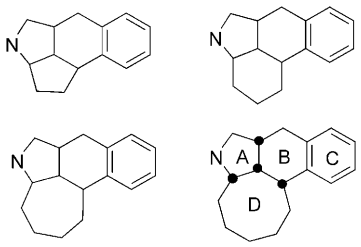
DOI: 10.1002/anie.200901246

# One-Step Synthesis of the Benzocyclo[penta- to octa-]isoindole Core**

*Yimin Hu,* Chenli Yu, Dong Ren, Qiong Hu, Lidong Zhang, and Dong Cheng*

Owing to the prevalence of heterocyclic compounds in medicinal chemistry and natural products, the development of new transition-metal-catalyzed reactions for the formation of fused heterocycles continues to be an active area of research.[1–3] The construction of such ring systems by means of C–H activation[4] and Heck coupling[5] is a complementary approach to remarkably powerful domino reactions.[6] Recently, Yu and co-workers reported a promising C–H activation route for the preparation of indolines and tetrahydroisoquinolines.[7] Fujii and co-workers developed a palladium-catalyzed C($sp^3$)–H activation for the direct preparation of indoline derivatives.[8] In a particularly straightforward approach, Chang and co-workers reported the synthesis of condensed pyrroloindoles through the intramolecular functionalization of a pyrrole C–H bond.[9] These syntheses exhibit good selectivity and high atom economy, and are carried out under mild reaction conditions at low catalyst loadings.[10,11]

Herein, we report a novel domino cyclization method involving carbopalladation and the subsequent regioselective functionalization of an unactivated C–H bond for the preparation the benzocyclo[penta- to octa-]isoindole core (Scheme 1). The fused heterocyclic ring systems contain




***Scheme 1.*** Target benzocyclo[penta- to octa-]isoindole core structures.

tertiary stereocenters at the A–B and B–D ring junctures. Control of the relative and absolute configurations of these stereocenters, and the construction of the tetracyclic framework of the complex heterocyclic system, represent significant synthetic challenges. In a typical procedure, a mixture of *N*-allyl-*N*-(cyclohex-2-enyl)-4-methylbenzenesulfonamide (**1b**), 4-bromobenzonitrile, tributylamine, $Pd(OAc)_2$, and $PPh_3$ was heated in *N*,*N*-dimethylformamide (DMF) under an argon atmosphere overnight. Standard workup procedures afforded the coupled products with excellent regio- and stereoselectivity for most dienes (Table 1). The temperature is crucial for this reaction: No domino reaction occurred below 130 °C; in contrast, higher reaction temperatures (> 145 °C) led to the decomposition of **3bb**, as indicated by TLC. The use of other phosphine compounds, such as $PEt_3$, $P(OEt)_3$, or 1,2-bis(diphenylphosphanyl)ethane, led to very similar results to those obtained with $PPh_3$. Among the catalysts tested ([$Pd(PPh_3)_4$], [$Pd(dba)_2$]/$PPh_3$ (dba = dibenzylideneacetone), $PdCl_2/PPh_3$, $Pd(OAc)_2/PPh_3$, [$AuCl(PPh_3)$]/$AgSbF_6$, [$Rh(cod)_2$]$^+SbF_6^-$ (cod = 1,5-cyclooctadiene)), the combination $Pd(OAc)_2/PPh_3$ was found to be the most effective. *N*,*N*-Dimethylformamide proved to be a better solvent than *N*,*N*-dimethylacetamide, toluene, or 1,4-dioxane for this reaction; $nBu_3N$ was more effective than any inorganic bases tested. Thus, the following standard reaction conditions were selected for this study: The diene (1 equiv) was treated with an aryl halide (1.1 equiv) in the presence of $Pd(OAc)_2$ (2 mol %), $Ph_3P$ (4 mol %), and $nBu_3N$ (2 equiv) in DMF at 140 °C.

A number of dienes and substituted aryl halides are suitable for this palladium-catalyzed cross-coupling reaction (Table 1). A range of dodecahydrobenzo[*f*]cycloocta[*cd*]-isoindoles were isolated readily in good to excellent yields when aryl halides with electron-withdrawing groups were employed (Table 1; entries 4–13, 16, 17, and 19). The electron-withdrawing group could be a methoxycarbonyl, keto, sulfonyl, or cyano group. Electron-donating substituents could be present on the benzene ring, and *ortho*- and *meta*-substituted aryl halides were also suitable substrates (Table 1; entries 10 and 18–20). When 1-bromonaphthalene was used in the reaction with the cyclohexenyl sulfonamide **1b**, the desired isoindole with a fused cyclohexyl ring was obtained in very good yield (Table 1; entry 3).

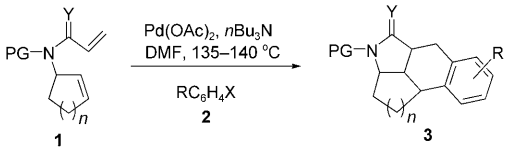
Differences in the diene substrates have much influence on the domino reaction. The output of reactions of substrates **1a** and **1c** with aryl halides were much lower than that of the corresponding reactions of **1b**, **1d**, **1f**, and **1g**, probably because of the high torsional strain of the cycloalkenyl group (cyclopentenyl or cycloheptenyl). The yield of the desired product was reduced when 4-iodobenzonitrile was employed (Table 1, entry 14). Interestingly, it was found that the C–Br bond reacted selectively with the diene when bromine and chlorine substituents were both present on the benzene ring (Table 1; entry 20).

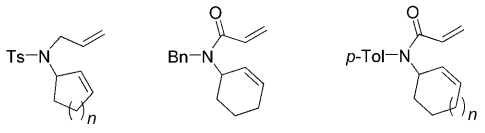
[*] Prof. Dr. Y. Hu, C. Yu, D. Ren, Q. Hu, L. Zhang, D. Cheng
Laboratory of Functional Molecular Solids, Ministry of Education
Anhui Key Laboratory of Functional Molecular-Based Materials
Institute of Organic Chemistry
School of Chemistry and Materials Science
Anhui Normal University, Wuhu, Anhui 241000 (China)
Fax: (+86) 553-388-3517
E-mail: yiminhu@mail.ahnu.edu.cn

[**] Support of this research by grants from the National Science Foundation of China (20872002, 20572001) and the Education Department of Anhui Province (TD200707) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200901246.

***Table 1:*** Palladium-catalyzed one-pot reaction for the formation of fused heterocycles.[a]

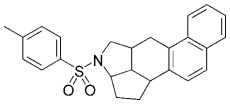
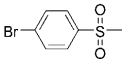
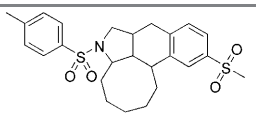
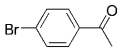
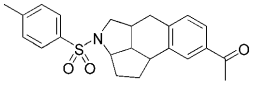
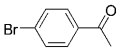
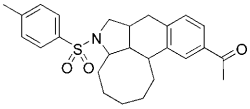
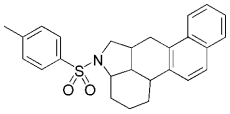
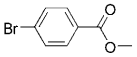
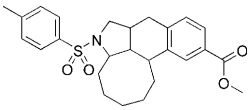
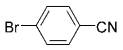
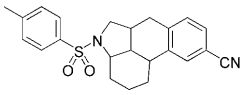
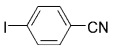
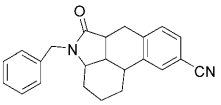
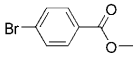
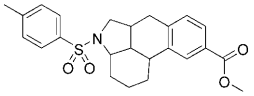
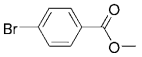
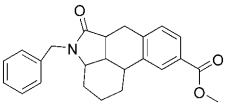
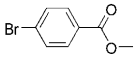
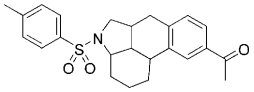
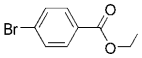
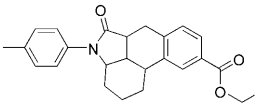
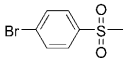
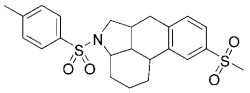
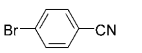
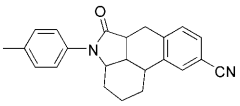
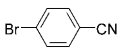
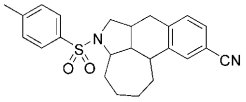
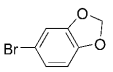
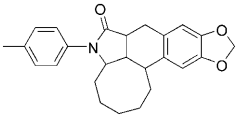
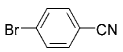
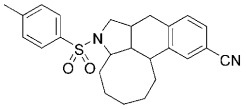
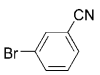
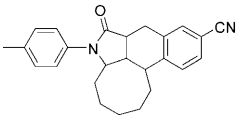
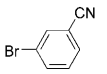
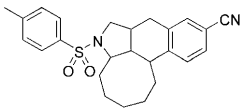



**1a** : $n = 1$
**1b** : $n = 2$
**1c** : $n = 3$
**1d** : $n = 4$

**1e**

**1f** : $n = 1$
**1g** : $n = 3$

| Entry | 1 | ArX | Product (yield [%][b]) | | Entry | 1 | ArX | Product (yield [%][b]) | |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** |  |  | **3aa** (49) | 11 | **1d** |  |  | **3dc** (65) |
| 2 | **1a** |  |  | **3ab** (36) | 12 | **1d** |  |  | **3dd** (70) |
| 3 | **1b** |  |  | **3ba** (80) | 13 | **1d** |  |  | **3de** (75) |
| 4 | **1b** |  |  | **3bb** (85) | 14 | **1e** |  |  | **3ea** (52) |
| 5 | **1b** |  |  | **3bc** (67) | 15 | **1e** |  |  | **3eb** (56) |
| 6 | **1b** |  |  | **3bd** (60) | 16 | **1f** |  |  | **3fa** (78) |
| 7 | **1b** |  |  | **3be** (63) | 17 | **1f** |  |  | **3fb** (75) |
| 8 | **1c** |  |  | **3ca** (62) | 18 | **1g** |  |  | **3ga** (67) |
| 9 | **1d** |  |  | **3da** (64) | 19 | **1g** |  |  | **3gb** (71) |
| 10 | **1d** |  |  | **3db** (68) | 20 | **1g** |  |  | **3gc** (69) |

[a] General conditions: **1a–g** (1.0 equiv), ArX (1.1 equiv), $Pd(OAc)_2$ (2 mol%), $PPh_3$ (4 mol%), $nBu_3N$ (2 equiv), DMF (10 mL), 135–140°C. [b] Yield of the isolated product after flash column chromatography. Bn = benzyl, Ts = *p*-toluenesulfonyl.

All new products were characterized fully by various spectroscopic techniques and high-resolution mass spectrometry. The molecular structures of **3ab** (Figure 1), **3bb**, **3bd**, **3dd**, **3de** (Figure 2), and **3ea** were confirmed by single-crystal X-ray analysis (see the Supporting Information for details).[12]

Scheme 2 shows a plausible mechanism for the formation of the coupled products. The coordination of an aryl palladium(II) halide and insertion into the allyl moiety in **1** produces the intermediate **A**, which then reacts with the remaining carbon–carbon double bond through carbopalladation to afford **B**. σ-Bond metathesis[13] onto the aryl group in **B**, followed by proton abstraction by the base, then generates **3**.

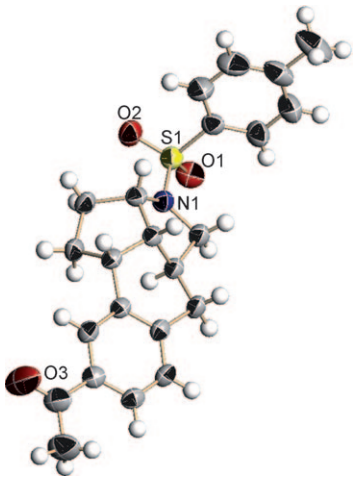



***Figure 1.*** Molecular structure of **3 ab**.

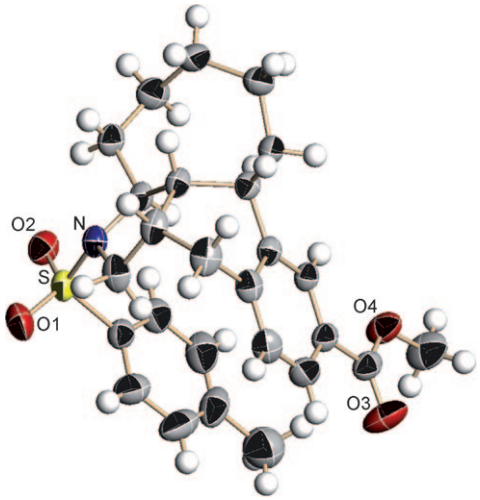
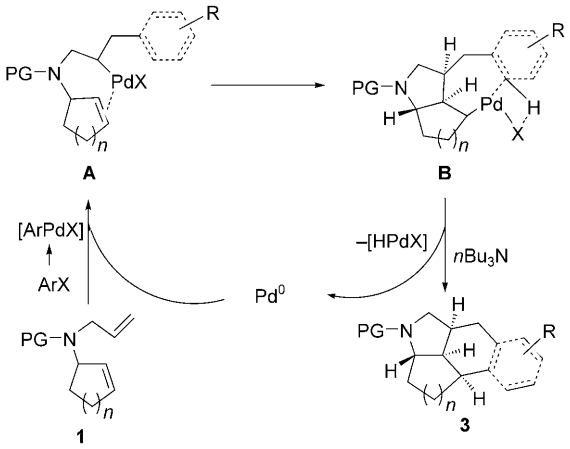



***Figure 2.*** Molecular structure of **3 de**.

In summary, we have developed a palladium-catalyzed domino reaction for the synthesis of fused polycycles. The treatment of cycloalkene-containing dienes with a variety of aryl halides in the presence of a palladium catalyst and an amine base led to the formation of multiple C–C bonds and C–H activation of the benzene ring to give dodecahydrobenzo[f]cyclo[penta- to octa-]isoindole derivatives in moderate to very good yield and with excellent regioselectivity and stereoselectivity. The ready accessibility of the starting materials, the broad compatibility of the cycloalkene and aryl halide substrates, and the generality of this process make the reaction highly valuable in view of the synthetic and medicinal importance of fused heterocycles of this type. Further investigations are in progress in our laboratory to improve our understanding of this catalytic transformation, to evaluate the process with a broader range of substrates, and to synthesize more complex products and test their biological activity.




***Scheme 2.*** Proposed mechanism of the reaction. PG = protecting group.

## *Experimental Section*

Typical procedure: Sulfonamide **1 b** (1.0 equiv), 4-bromobenzonitrile (1.1 equiv), $Pd(OAc)_2$ (2 mol%), and $PPh_3$ (4 mol%) were added to a degassed solution of $(n\text{Bu})_3\text{N}$ (2 equiv) in DMF (10 mL), and the mixture was stirred at room temperature for half an hour and then heated at 140 °C for 30 h. The reaction mixture was then cooled, quenched with water, and extracted with ethyl acetate (30 mL). The combined organic layers were washed with hydrochloric acid (5%), sodium carbonate (5%), and saturated sodium chloride solution, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography to give **3 bb** (85%).

Received: March 5, 2009
Published online: May 19, 2009

**Keywords:** C–H activation · cycloalkenes · domino reactions · palladium · polycyclic compounds

[1] a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861 – 863; b) A. Diéguez-Vázquez, C. C. Tzschucke, W. Y. Lam, S. V. Ley, *Angew. Chem.* **2008**, *120*, 216 – 219; *Angew. Chem. Int. Ed.* **2008**, *47*, 209 – 212; c) Y. Murata, D. Yamashita, K. Kitahara, Y. Minasako, A. Nakazaki, S. Kobayashi, *Angew. Chem.* **2009**, *121*, 1428 – 1431; *Angew. Chem. Int. Ed.* **2009**, *48*, 1400 – 1403.

[2] a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292 – 7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134 – 7186; b) S. Huo, J. C. Shi, E. Negishi, *Angew. Chem.* **2002**, *114*, 2245 – 2247; *Angew. Chem. Int. Ed.* **2002**, *41*, 2141 – 2143; c) K. C. Nicolaou, T. Montagnon, S. A. Snyder, *Chem. Commun.* **2003**, 551 – 564.

[3] a) H. Li, T. P. Loh, *J. Am. Chem. Soc.* **2008**, *130*, 7194 – 7195; b) N. Tsukada, T. Mitsuboshi, H. Setoguchi, Y. Inoue, *J. Am. Chem. Soc.* **2003**, *125*, 12102 – 12103; c) M. R. Axet, J. B. Buchholz, C. Claver, S. Castillón, *Adv. Synth. Catal.* **2007**, *349*, 1983 – 1998; d) R. Felstead, S. E. Gibson, A. Rooney, E. S. Y. Tse, *Eur. J. Org. Chem.* **2008**, 4963 – 4971.

[4] a) J. Zhao, M. Campo, R. C. Larock, *Angew. Chem.* **2005**, *117*, 1907 – 1909; *Angew. Chem. Int. Ed.* **2005**, *44*, 1873 – 1875; b) M. A. Campo, Q. Huang, T. Yao, Q. Tian, R. C. Larock, *J. Am. Chem. Soc.* **2003**, *125*, 11506 – 11507; c) Q. Huang, A. Fazio, G. Dai, M. A. Campo, R. C. Larock, *J. Am. Chem. Soc.* **2004**, *126*, 7460 – 7461.

[5] a) P. Mauleón, I. Alonso, P. Mauleon, I. Alonso, J. C. Carretero, *Angew. Chem.* **2001**, *113*, 1331 – 1333; *Angew. Chem. Int. Ed.* **2001**, *40*, 1291 – 1293; b) P. Mauleón, A. A. Núñez, I. Alonso, J. C. Carretero, *Chem. Eur. J.* **2003**, *9*, 1511 – 1520; c) I. Alonso, M. Alcamí, P. Mauleón, J. C. Carretero, *Chem. Eur. J.* **2006**, *12*, 4576 – 4583; d) T. Doi, Y. Iijima, M. Takasaki, T. Takahashi, *J. Org. Chem.* **2007**, *72*, 3667 – 3671.

[6] a) L. F. Tietze, G. Brasche, K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**; b) L. F. Tietze, T. Kinzel, C. Brazel, *Acc. Chem. Res.* **2009**, *42*, 367 – 378.

[7] a) J.-J. Li, T.-S. Mei, J.-Q. Yu, *Angew. Chem.* **2008**, *120*, 6552 – 6555; *Angew. Chem. Int. Ed.* **2008**, *47*, 6452 – 6455; b) M. Wasa, J.-Q. Yu, *J. Am. Chem. Soc.* **2008**, *130*, 14058 – 14059; c) R. Giri, N. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510 – 3511.

[8] T. Watanabe, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 1759 – 1762.

[9] S. J. Hwang, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2008**, *130*, 16158 – 16159.

[10] a) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174 – 238; b) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651 – 2710; c) M. Catellani, E. Motti, F. Faccini, R. Ferraccioli, *Pure Appl. Chem.* **2005**, *77*, 1243 – 1248.

[11] Y.-M. Hu, F.-F. Song, F.-H. Wu, D. Cheng, S.-W. Wang, *Chem. Eur. J.* **2008**, *14*, 3110 – 3117.

[12] CCDC 695812 (**3ab**), 695813 (**3bb**), 695814 (**3bd**), 695815 (**3dd**), 695816 (**3de**), and 695817 (**3ea**) 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.

[13] a) D. García-Cuadrado, P. D. Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880 – 6886; b) D. García-Cuadrado, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2006**, *128*, 1066 – 1067.