Versatile Domino Cyclizations

One-Pot Synthesis of Polyheterocycles by a Palladium-Catalyzed Intramolecular N-Arylation/C–H Activation/Aryl–Aryl Bond-Forming Domino Process**

*Guylaine Cuny, Michèle Bois-Choussy, and Jieping Zhu**

There has been considerable interest in developing novel cyclization methodologies for organic synthesis.[1] Indeed, many complex natural products and drugs are cyclic in nature, and a ring closure reaction is very often the crucial step in a multistep synthesis. In connection with our ongoing project on the synthesis of macrocycles with an *endo* aryl–aryl bond,[2] we examined the cyclization of diamide **1** under modified Miyaura–Suzuki conditions.[3] However, heating a solution of **1** in DMSO in the presence of [$PdCl_2$(dppf)] (5.0 mol%; dppf = 1,1′-bis(diphenylphosphanyl)ferrocene), KOAc (3.0 equiv), and bis(pinacolato)diboron (**2**, 1.2 equiv) did not provide macrocycle **4**. Instead, polyheterocycle **3** was produced in about 50% yield (Scheme 1). Formally, one C_{aryl}–N and one C_{aryl}–C_{aryl} bond were created with concurrent formation of a nine-membered and a six-membered ring. While intramolecular N-arylation leading to five- and six-membered rings is well-established, attempts to access medium-sized and macrocyclic ring systems by the same reaction were, to the best of our knowledge, unsuccessful.[4,5] Intrigued by the potential synthetic power of this novel catalytic domino process,[6] we set out to examine in detail this unprecedented transformation and report herein our preliminary results.

A survey of reaction conditions with variation of the palladium source, the ligand, the temperature, the base, and the solvent is summarized in Table 1. Mechanistically, a domino process involving a sequence of intramolecular Buchwald–Hartwig amination,[4,5] C–H activation, and aryl–aryl bond formation[7] could account for the production of polyheterocycle **3** from linear diamide **1**. This speculative analysis suggested that the diboron reagent **2** is redundant, and a similar yield of **3** was indeed obtained in its absence under otherwise identical conditions (entry 1). The reaction temperature was found to have dramatic effect on the reaction, and higher yields were obtained when the reaction was performed at higher temperature (entries 1 and 2). In contrast to previous studies on the intramolecular N-arylation of amides,[8,9] the present domino process is much less sensitive to the ligands used. Both bidendate phosphanes such as dppf (entries 2, 6) and binap (entries 7, 10, 11) and the monodentate ligand Ph_3P (entry 15) were suitable, although tBu$_3$P (entries 12, 13) seemed to be less efficient.[8i,10] Potassium acetate (entry 2) was more effective than cesium carbonate (entry 5) as base, while DMSO was a better solvent than DMF (entry 3) and toluene (entry 4). The highest yield was obtained with a catalyst prepared in situ from $Pd(OAc)_2$ and binap in a molar ratio of 1:2, but we chose [$PdCl_2$(dppf)] as the catalyst for the subsequent studies for simplicity of manipulation and product purification ([$PdCl_2$(dppf)], KOAc, DMSO, 120 °C, concentration of substrate = 0.02 M).

Table 1: Palladium-catalyzed cyclization of **1**: survey of reaction conditions.[a]

Entry	Catalyst[b]	Solvent	Base	T [°C]	Yield of **3** [%][c]
1	[$PdCl_2$(dppf)]	DMSO	KOAc	80	48
2	[$PdCl_2$(dppf)]	DMSO	KOAc	120	65
3	[$PdCl_2$(dppf)]	DMF	KOAc	120	32
4	[$PdCl_2$(dppf)]	Toluene	KOAc	reflux	0
5	[$PdCl_2$(dppf)]	DMSO	Cs_2CO_3	120	25
6	[$Pd(dba)_2$]/dppf (1:1)	DMSO	KOAc	120	51
7	[$Pd(dba)_2$]/binap (1:1)	DMSO	KOAc	120	60
8	[$Pd(dba)_2$]/tBu$_3$P (1:1)	DMSO	KOAc	120	50
9	[$Pd(dba)_2$]/tBu$_3$P (1:2)	DMSO	KOAc	120	40
10	$Pd(OAc)_2$/binap (1:1)	DMSO	KOAc	120	62[d]
11	$Pd(OAc)_2$/binap (1:2)	DMSO	KOAc	120	77[d]
12	$Pd(OAc)_2$/tBu$_3$P (1:1)	DMSO	KOAc	120	44
13	$Pd(OAc)_2$/tBu$_3$P (1:2)	DMSO	KOAc	120	44
14	[$PdCl_2$(dppf)]/dppf (1:1)	DMSO	KOAc	120	46
15	$[Pd(PPh)_3]_4$	DMSO	KOAc	120	60

[a] Concentration: 0.02 M, reaction time: 16 h, in the absence of bis(pinacolato)diboron. [b] 5 mol% of catalyst was used; binap = [1,1′-binaphthalene]-2,2′-diylbis(diphenylphosphane), dba = dibenzylideneacetone, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene. [c] Yields refer to the average of two runs. [d] Contains a small amount of binap derivatives.

As shown in Figure 1, this novel catalytic domino process can be applied to the construction of azaphenanthrenes fused with an 8-membered (**5**), 10-membered (**6**), 11-membered (**7**), and 13-membered lactam motif (**8**), in addition to the 9-

[*] Dr. J. Zhu, G. Cuny, Dr. M. Bois-Choussy
Institut de Chimie des Substances Naturelles
CNRS
91198 Gif-sur-Yvette Cedex (France)
Fax: (+33) 1-6907-7247
E-mail: zhu@icsn.cnrs-gif.fr

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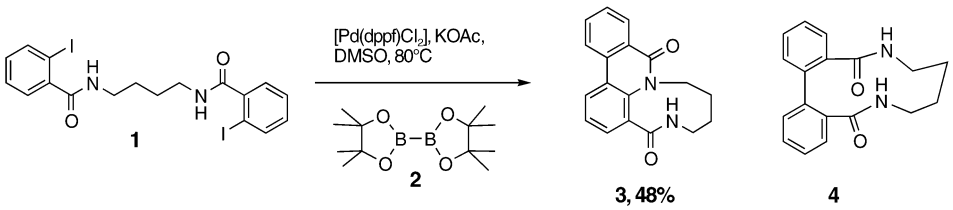


Scheme 1. Catalytic domino process leading to polyheterocycles.

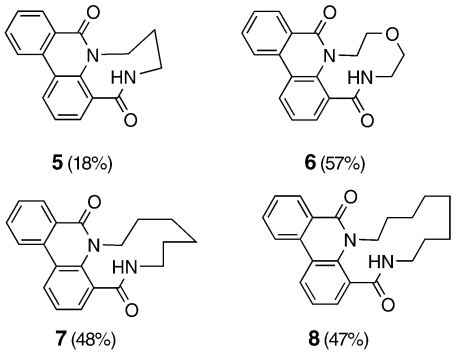
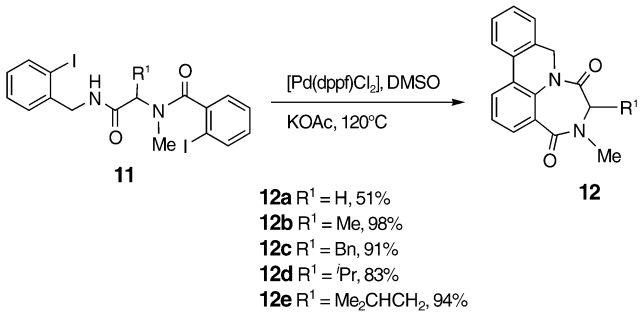


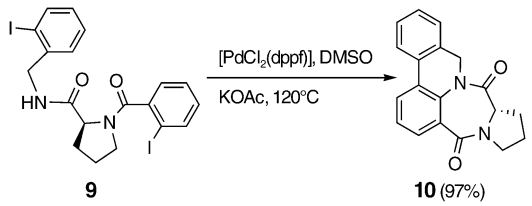
Figure 1. Structure of dihydroazaphenanthrenes fused with a macrocyclic ring.



Scheme 3. Synthesis of substituted 5,6-dihydro-8*H*-[5,7-*a*]diazacycloheptа[*jk*]phenanthrene-4,7-diones.

membered polyheterocycle **3**. To the best of our knowledge, these are the first examples where an intramolecular Buchwald–Hartwig amidation has been successfully applied to the synthesis of medium-sized ring systems and macrocycles.

To further exploit the generality of this catalytic domino process, we synthesized proline derivative **9** by standard procedures and subjected it to the cyclization conditions. The catalytic domino cyclization occurred smoothly to give the desired pentacyclic compound **10** in 97% yield of isolated product (Scheme 2). Double cyclization of *ent*-**9**, prepared

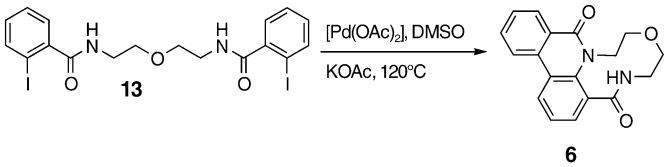


Scheme 2. One-pot synthesis of a pentacyclic compound.

from D-proline, provided *ent*-**10** (structure not shown) in a similar yield. Its optical rotation was opposite in sign and nearly equal in magnitude to that of **10**. Chiral HPLC analysis shown that the enantiomeric excesses of **10** and *ent*-**10** are both greater than 98%.

The scope of this reaction was further examined by applying the optimized conditions to differently substituted amides **11** (Scheme 3). The 1,4-benzodiazepine-2,5-dione derivatives incorporating sarcosine (**12a**), *N*-methylalanine (**12b**), *N*-methylphenylalanine (**12c**), *N*-methylvaline (**12d**), and *N*-methyl leucine (**12e**) can be prepared in good-to-excellent yields. The ready accessibility of the starting material and the generality of this process clearly indicated its potential in the diversity-oriented synthesis of this family of compounds.[11,12]

Synthesis of simple seven-membered rings by palladium-catalyzed intramolecular N-arylation of aryl halides with xantphos and 2-methoxy-2′-diphenylphosphanyl-1,1′binaphthyl (MOP) as ligands has been reported,[8c] but application of this reaction to the synthesis of medium-sized and larger rings was unsuccessful.[8] The efficiency of the present domino process is thus intriguing. A template effect due to the chelation of the metal by two amido groups leading to conformational preorganization could be a reasonable explanation. Such a template effect would require at least one open coordination site of the putative Pd^{II} oxidative adduct. This consideration prompted us to examine the "ligand-free" palladium acetate as a catalyst for this transformation.[13] To our delight, treatment of a solution of **13** in DMSO in the presence of $Pd(OAc)_2$ and KOAc provided the tetracyclic compound **6** (Scheme 4) in a yield (55%) comparable to that obtained with [$PdCl_2$(dppf)]. Similarly, **10** was obtained in 90% yield from **9** with $Pd(OAc)_2$ as catalyst. To the best of our knowledge, these are the first examples in which a ligand-free palladium catalyst was employed for the amidation



Scheme 4. "Ligand-free" palladium-catalyzed domino cyclization.

process. It has been established that low-coordinate Pd^{II}–amido complexes should favor the competitive β-hydrogen elimination process and thus reduce the yield of the desired amidation product.[14] This trend is apparently not observed in the present catalytic domino process, probably due to the internal ligation.[15]

To probe the structural requirement for this interesting domino cyclization, we synthesized an amide (structure not shown) in which a simple benzyl group replaced the *ortho*-iodobenzyl group of **11b**. To our surprise, subjecting this monoiodide derivative to the cyclization conditions ([$PdCl_2$(dppf)], DMSO, KOAc, 120 °C) did not provide the corresponding 1,4-benzodiazepine-2,5-dione. The surprising result of this control experiment was indicative of the crucial rule of the bisiodido functionality. Since two chemical bonds are formed in the present process by way of a formal Buchwald–Hartwig amidation and C–H activation/aryl–aryl bond-forming processes, we surmised that there is some kind of cooperative effect in these two distinct palladium catalyzed bond-forming processes.[16] Further studies will be necessary to determine the mechanistic features of the reaction.

In conclusion, we have established a novel catalytic domino process.[17] The reaction generates significant molecular complexity from simple and readily accessible starting materials. We are exploring the scope, mechanism, and synthetic utility of this reaction.

Experimental Section

Typical procedure: Freshly distilled DMSO was added to a flask containing molten KOAc (3 equiv), [$PdCl_2$(dppf)] (0.05 equiv), and diamide (concentration of the substrate: 0.02 M). The mixture was degassed and stirred at 120 °C under argon for 12–36 h. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated on a rotary evaporator. The crude material was purified by flash chromatography to afford the desired polyheterocycle. **10**: $R_f = 0.26$ (toluene/methanol 10:1); m.p. 95 °C; $[\alpha]_D = +589.1$ ($c = 1.1$ in $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3004$, 1679, 1633, 1474, 1434, 1392, 1228, 1167, 983 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 293 K, TMS): $\delta = 1.95$–2.17 (m, 4H), 2.70–2.75 (m, 1H), 3.56–3.65 (m, 1H), 3.83–3.90 (m, 1H), 4.04 (d, 1H, $^1J = 15.0$ Hz), 5.81 (d, 1H, $^1J = 15.0$ Hz), 7.35–7.43 (m, 3H), 7.40 (t, 1H, $^1J = 7.4$ Hz), 7.77 (d, 1H, $^1J = 7.4$ Hz), 7.95 ppm (d, 2H, $^1J = 7.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 23.6$, 26.6, 43.9, 46.8, 56.4, 123.6, 125.9, 126.1, 127.5, 128.4, 128.7, 129.2, 129.8, 131.1, 133.8, 134.7, 164.9, 168.5 ppm; MS (ESI): $m/z = 327$ [M+Na], 305 [M+H]. HRMS calcd for $C_{19}H_{16}N_2O_2$+H: 305.1290; found: 305.1304. *ent*-**10**: $\alpha_D = -589.8$ ($c = 0.8$ in $CHCl_3$). HPLC (chiral AD column, hexane/2-propanol 9:1): retention times of **10** and *ent*-**10**: 46.69 and 22.69 min, respectively.

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[1] Reviews: a) C. J. Roxburgh, *Tetrahedron* **1995**, *51*, 9767–9822; b) R. H. Grubbs, S. J. Miller, G. C. Fu, *Acc. Chem. Res.* **1995**, *28*, 446–452; c) J. Zhu, *Synlett* **1997**, 133–144; d) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; e) K. E. Krakowiak, R. M. Izatt, J. S. Bradshaw, *J. Heterocycl. Chem.* **2001**, *38*, 1239–1248; Recent examples from this group: f) G. Zhao, X. Sun, H. Bienaymé, J. Zhu, *J. Am. Chem. Soc.* **2001**, *123*, 6700–6701; g) P. Janvier, M. Bois-Choussy, H. Bienaymé, J. Zhu, *Angew. Chem.* **2003**, *115*, 845–847; *Angew. Chem. Int. Ed.* **2003**, *42*, 811–814, and references therein.

[2] A. C. Carbonnelle, J. Zhu, *Org. Lett.* **2000**, *2*, 3477–3480.

[3] N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457–2483.

[4] a) J. P. Wolfe, S. Wagaw, J. F. Marcoux, S. F. Buchwald, *Acc. Chem. Res.* **1998**, *31*, 805–818; b) B. H. Yang, S. L. Buchwald, *J. Organomet. Chem.* **1999**, *576*, 125–146.

[5] a) J. F. Hartwig, *Angew. Chem.* **1998**, *110*, 2154–2177; *Angew. Chem. Int. Ed.* **1998**, *37*, 2046–2067; b) J. F. Hartwig in "*Modern Amination Methods* (Ed. A. Ricci), Wiley-VCH, Weinheim, **2000**, Chap. 7.

[6] a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; b) A. Padwa, M. D. Weingarten, *Chem. Rev.* **1996**, *96*, 223–269.

[7] Reviews: a) G. Dyker, *Angew. Chem.* **1999**, *111*, 1808–1822; *Angew. Chem. Int. Ed.* **1999**, *38*, 1698–1712; b) V. Ritleng, C. Sirlin, M. Pfeffer, *Chem. Rev.* **2002**, *102*, 1731–1769; c) M. Catellani, *Synlett* **2003**, 298–313; Recent examples: d) Harayama, T. K. Shibaike, *Heterocycles* **1998**, *49*, 191–195; e) T. Harayama, T. Akiyama, H. Akamatsu, K. Kawano, H. Abe, Y. Takeuchi, *Synthesis* **2001**, *3*, 444–450; f) T. Harayama, T. Akiyama, Y. Nakano, H. Nishioka, H. Abe, Y. Takeuchi, *Chem. Pharm. Bull.* **2002**, *50*, 519–522; g) F. Kakiuchi, S. Kan, K. Igi, N. Chatani, S. Murai, *J. Am. Chem. Soc.* **2003**, *125*, 1698–1699; h) A. Mori, A. Sekiguchi, K. Masui, T. Shimada, M. Horie, K. Osakada, M. Kawamoto, T. Ikeda, *J. Am. Chem. Soc.* **2003**, *125*, 1700–1701.

[8] a) J. P. Wolfe, R. A. Rennels, S. L. Buchwald, *Tetrahedron* **1996**, *52*, 7525–7546; b) S. Wagaw, R. A. Rennels, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 8451–8458; c) B. H. Yang, S. L. Buchwald, *Org. Lett.* **1999**, *1*, 35–37; d) A. Abouabdellah, R. H. Dodd, *Tetrahedron Lett.* **1998**, *39*, 2119–2122; e) K. Yamada, T. Kubo, H. Tokuyama, T. Fukuyama, *Synlett* **2002**, 231–234; f) M. Qadir, R. E. Priestley, T. W. D. F. Rising, T. Gelbrich, S. J. Coles, M. B. Hursthouse, P. W. Sheldrake, N. Whittall, K. K. Hii, *Tetrahedron Lett.* **2003**, *44*, 3675–3678; g) G. Evindar, R. A. Batey, *Org. Lett.* **2003**, *5*, 133–136; h) B. J. Margolis, J. J. Swidorski, B. N. Rogers, *J. Org. Chem.* **2003**, *68*, 644–647; i) K. Nozaki, K. Takahashi, K. Nakano, T. Hiyama, H. Z. Tang, M. Fujiki, S. Yamaguchi, K. Tamao, *Angew. Chem.* **2003**, *115*, 2097–2099; *Angew. Chem. Int. Ed.* **2003**, *42*, 2051–2053; j) R. Omar-Amrani, A. Thomas, E. Brenner, R. Schneider, Y. Fort, *Org. Lett.* **2003**, *5*, 2311–2314.

[9] For an elegant application in natural product synthesis, see F. He, B. M. Foxman, B. B. Snider, *J. Am. Chem. Soc.* **1998**, *120*, 6417–6418.

[10] Efficient arylamination procedure using tBu$_3$P as ligand: M. K. Hooper, M. Utsunomiya, J. F. Hartwig, *J. Org. Chem.* **2003**, *68*, 2861–2873. For a recent review, see A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350–4386; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176–4211.

[11] S. L. Schreiber, *Science* **2000**, *287*, 1964–1968.

[12] a) S. Bräse, C. Gil, K. Knepper, *Bioorg. Med. Chem.* **2002**, *10*, 2415–2437; b) C. Hulme, V. Gore, *Curr. Med. Chem.* **2003**, *10*, 51–80; c) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893–930.

[13] "Ligand-free" palladium-catalyzed cross-coupling reaction: a) Review: I. P. Beletskaya, *Bull. Acad. Sci. USSR Div. Chem. Sci. (Engl. Transl.)* **1991**, *40*, 2013–2028; Recent examples: b) T. I. Wallow, B. M. Novak, *J. Org. Chem.* **1994**, *59*, 5034–5037; c) M. Moreno-Mañas, F. Pajuelo, R. Pleixats, *J. Org. Chem.* **1995**, *60*, 2396–2397; d) D. Badone, M. Baroni, R. Cardamone, A. Ielmini, U. Guzzi, *J. Org. Chem.* **1997**, *62*, 7170–7173; e) C. G. Blettner, W. A. König, W. Stenzel, T. Schotten, *J. Org. Chem.*

1999, *64*, 3885 – 3890; f) N. E. Leadbeater, M. Marco, *Org. Lett.* **2002**, *4*, 2973 – 2976; g) R. B. Bedford, M. E. Blake, C. P. Butts, D. Holder, *Chem. Commun.* **2003**, 466 – 467.

[14] a) G. M. Whitesides, J. F. Gaasch, E. R. Stedronsky, *J. Am. Chem. Soc.* **1972**, *94*, 5258 – 5270; b) J. F. Hartwig, S. Richards, D. Baranãno, F. Paul, *J. Am. Chem. Soc.* **1996**, *118*, 3626 – 3633; c) J. F. Marcoux, S. Wagaw, S. L. Buchwald, *J. Org. Chem.* **1997**, *62*, 1568 – 1569.

[15] DMF as ligand: a) J. M. Gioria, B. P. Susz, *Helv. Chim. Acta* **1971**, *54*, 2251 – 2256; b) C. Amatore, A. A. Bahsoun, A. Jutand, G. Meyer, A. N. Ntepe, L. Richard, *J. Am. Chem. Soc.* **2003**, *125*, 4212 – 4222.

[16] It is also possible that the formation of an Ar-Pd-Ar′ intermediate proceeded Ar–N bond formation, as proposed by one of the referees. We are further investigating this mechanistic issue.

[17] Intermolecular N-arylation followed by aryl–aryl bond formation leading to five-membered carbazoles was recently reported: R. B. Bedford, S. J. Cazin, *Chem. Commun.* **2002**, 2310 – 2311. Sequential intra- and intermolecular N-arylation leading to functionalized 1-aminoindoles: M. Watanabe, T. Yamamoto, M. Nishiyama, *Angew. Chem.* **2000**, *112*, 2620 – 2623; *Angew. Chem. Int. Ed.* **2000**, *39*, 2501 – 2504.

