J|A|C|S
ARTICLES
Published on Web 10/13/2004

Palladium- and Copper-Catalyzed Synthesis of Medium- and Large-Sized Ring-Fused Dihydroazaphenanthrenes and 1,4-Benzodiazepine-2,5-diones. Control of Reaction Pathway by Metal-Switching

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

Contribution from the Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette Cedex, France

Received April 30, 2004; E-mail: zhu@icsn.cnrs-gif.fr

Abstract: Methods for the synthesis of dihydroazaphenanthrene fused to macrocycles (**2**) and medium-ring heterocycles (**4**), as well as 1,4-benzodiazepine-2,5-diones (**5**), are developed. A distinctly different catalytic property of palladium and copper catalysts was uncovered that leads to the development of a divergent synthesis of two different heterocyclic scaffolds from the same starting materials, simply by metal-switching. Thus, starting from linear amide **3**, palladium acetate triggers a domino intramolecular *N*-arylation/C−H activation/aryl−aryl bond-forming process to provide **4**, while copper iodide promotes only the intramolecular *N*-arylation reaction leading to **5**. In combination with the Ugi multicomponent reaction (Ugi-4CR) for the preparation of the linear amides, a two-step synthesis of either the 5,6-dihydro-8*H*-5,7a-diazacyclohepta[*jk*]phenanthrene-4,7-dione (**4**) or 1,4-benzodiazepine-2,5-diones (**5**), by appropriate choice of metal catalyst, is subsequently developed from very simple starting materials.

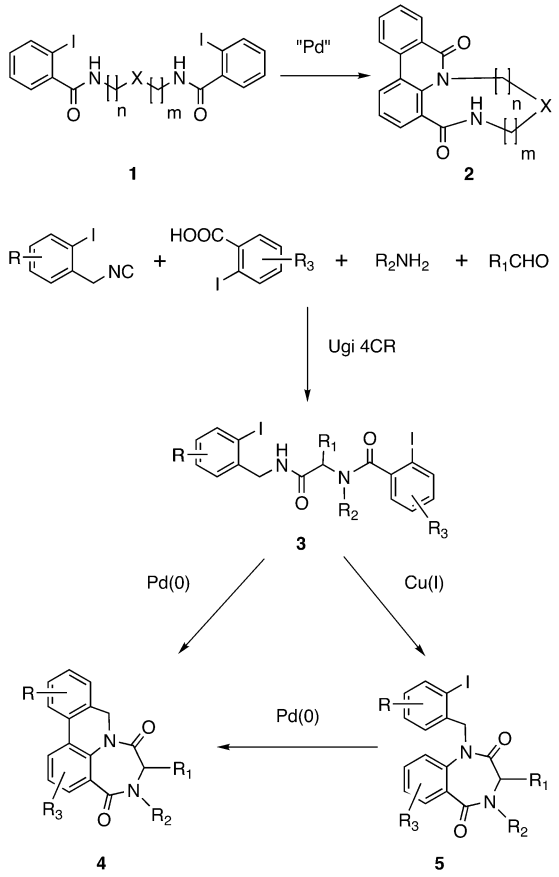
Introduction

Following the pioneering contributions by the groups of Buchwald[1] and Hartwig,[2] there has been a surge of interest in the palladium-catalyzed amination/amidation of aryl halides and pseudo-halides during the past 10 years. By appropriate combination of palladium source, ligand, base, and solvent, this coupling reaction can now be realized under mild conditions for a variety of unactivated aromatic halides/pseudo-halides and a range of nucleophiles.[3] In comparison to the palladium-catalyzed amination/amidation reactions, the copper-mediated version, best known as the Ullmann reaction (*N*-arylation of amine) and the Goldberg reaction (*N*-arylation of amides), has been known for a century.[4] The harsh reaction conditions, in particular high temperatures, and the necessity to use stoichiometric amounts of the copper limited, nevertheless, the application scope of these two otherwise powerful reactions. However, a number of catalytic systems have now been developed since Ma's seminal contribution dealing with the CuI-catalyzed *N*-arylation of amino acids with aryl halides.[5] An array of nitrogen substrates, including amines, amides, nitrogen heterocycles, and α- and β-amino acids can now be arylated under mild catalytic conditions.[6]

Both palladium- and copper-catalyzed intramolecular *N*-arylations leading to five-, six-, and to a lesser extent, seven-membered rings have been investigated, and various efficient catalytic systems have been developed.[7−10] On the other hand, attempts to access medium-sized and macrocyclic ring systems by direct *N*-arylation were, to the best of our knowledge, unsuccessful. This is unfortunate since these medium-sized rings and macrocycles have found numerous applications in drug development, materials science, and supramolecular chemistry

(1) (a) Wolfe, J. P.; Wagaw, S.; Marcoux, J. F.; Buchwald, S. F. *Acc. Chem. Res*. **1998**, *31*, 805−818. (b) Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125−146.
(2) (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046−2067. (b) Hartwig, J. F. In *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 7.
(3) (a) Prim, D.; Campagne, J. M.; Joseph, D.; Andrioletti, B. *Tetrahedron* **2002**, *58*, 2041−2075. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176−4211. (c) Belfield, A. J.; Brown, G. R.; Foubister, A. J. *Tetrahedron* **1999**, 55, 11399−11428.
(4) Lindley, J. *Tetrahedron* **1984**, *40*, 1433−1456.
(5) Ma, D.; Zhang, Y.; Yao, J.; Wu, S.; Tao, F. *J. Am. Chem. Soc*. **1998**, *120*, 12459−12467.
(6) For reviews: (a) Ley, S.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400−5449. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428−2439.
(7) Palladium-catalyzed: (a) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525−7546. (b) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 8451−8458. (c) Yang, B. H.; Buchwald, S. L. *Org. Lett*. **1999**, *1*, 35−37. (d) Abouabdellah, A.; Dodd, R. H. *Tetrahedron Lett*. **1998**, *39*, 2119−2122. (e) Song, J. J.; Yee, N. K. *Org. Lett*. **2000**, *2*, 519−521. (f) Brown, J. A. *Tetrahedron Lett*. **2000**, *41*, 1623−1626. (g) Qadir, M.; Priestley, R. E.; Rising, T. W. D. F.; Gelbrich, T.; Coles, S. J.; Hursthouse, M. B.; Sheldrake, P. W.; Whittall, N.; Hii, K. K. *Tetrahedron Lett*. **2003**, *44*, 3675−3678. (h) Evindar, G.; Batey, R. A. *Org. Lett*. **2003**, *5*, 133−136. (i) Margolis, B. J.; Swidorski, J. J.; Rogers, B. N. *J. Org. Chem.* **2003**, *68*, 644−647. (j) Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H.-Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2051−2053. (k) Brain, C. T.; Steer, J. T. *J. Org. Chem*. **2003**, *68*, 6814−6816.
(8) Copper-catalyzed: (a) Ma, D.; Xia, C. *Org. Lett*. **2001**, *2*, 2583−2586. (b) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231−234.
(9) Nickel catalyzed: Omar-Amrani, R.; Thomas, A.; Brenner, E.; Schneider, R.; Fort, Y. *Org. Lett*. **2003**, *5*, 2311−2314. Iridium-catalyzed oxidative cyclization of amino alcohols: Fujita, K.-I.; Yamamoto, K.; Yamaguchi, R. *Org. Lett*. **2002**, *4*, 2691−2694.
(10) For an elegant application in natural product synthesis, see: He, F.; Foxman, B. M.; Snider, B. B. *J. Am. Chem. Soc*. **1998**, *120*, 6417−6418.

Scheme 1. Palladium- and Copper-Catalyzed Synthesis of Polyheterocycles and Macrocycles



by virtue of their intrinsic three-dimensional structure.[11,12] Our long-term interests in the development of novel macrocyclization reactions[13] brought us to investigate the cyclization of bis-aryldiiodide **1**, and we have uncovered a palladium-catalyzed domino process that efficiently transforms the simple amide **1** into the dihydroazaphenanthrene-fused macrocycle **2** (Scheme 1).[14] In this paper, we report in detail the development and application of this one-pot palladium-catalyzed domino intramolecular *N*-arylation/C−H activation/aryl−aryl bond-forming process. We also document that copper catalyst can interrupt this domino process that leads to the development of a novel synthesis of highly functionalized 1,4-benzodiazepine-2,5-diones (**5**) from the α-acetamido amide (**3**). Since the linear precursor **3** can be easily prepared in one step from readily available aldehyde, amine, carboxylic acid, and isocyanide by the Ugi four-component reaction (Ugi-4CR),[15] either dihydroazaphenanthrene-fused benzodiazepinedione (**4**) or 1,4-benzodiazepine-2,5-diones (**5**) can now be synthesized in two steps from very simple starting materials, by appropriate choice of the metal catalyst. Furthermore, it is demonstrated that compound **5**, obtained by the copper-catalyzed intramolecular *N*-arylation process, can be converted to tetracycle **4** in the presence of palladium catalyst, providing thus the mechanistic insight regarding the domino transformation of **3** to **4**.

Table 1. Palladium-Catalyzed Cyclization of **1**: Survey of Reaction Conditions[a]

entry	catalyst[b]	solvent	base	temp (°C)	yield (%)[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	$Pd(dba)_2$/^{t}Bu$_3$P = 1/1	DMSO	KOAc	120	50
9	$Pd(dba)_2$/^{t}Bu$_3$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	$Pd(OAc)_2$/^{t}Bu$_3$P = 1/1	DMSO	KOAc	120	44
13	$Pd(OAc)_2$/^{t}Bu$_3$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 of substrate **1** in DMSO, 0.02 M; reaction time, 16 h. [b] 5 mol % of catalyst was used. [c] Yields refer to the average of two runs, isolated yields. [d] Contaminated by a small amount of BINAP derivatives.

Results and Discussion

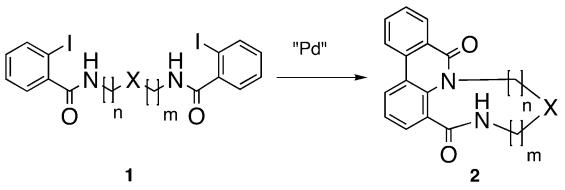
Synthesis of Dihydroazaphenanthrene-Fused Medium-Sized and Macrocyclic Rings. The diamide **1** is synthesized by a double condensation of 2-iodobenzoyl chloride with the corresponding diamine under standard conditions (CH_2Cl_2, triethylamine, room temperature).[16] When a DMSO solution of diamide **1a** ($n = 1$, $m = 2$, X = CH_2, 0.02 M) was treated with $PdCl_2$(dppf)[17] in the presence of KOAc at 80 °C, a polycycle **2a** was isolated in 48% yield (entry 1, Table 1). The formation of a 12-membered macrocycle with an endo aryl−aryl bond via Ullmann biaryl synthesis was not observed, even in the presence of bis(pinacolato)diboron.[13b,18] From a very simplified mechanistic point of view, the reaction proceeded presumably by way of a domino intramolecular Buchwald−Hartwig amidation reaction, C−H activation,[19] and aryl−aryl bond-forming process. In this transformation, one nine-membered ring and one six-membered ring were produced, with the concomitant formation of a carbon−nitrogen bond and a carbon−carbon bond. It is worth noting that a significant molecular complexity was created under these experimentally simple catalytic conditions.

(11) For a recent review on metal-mediated synthesis of medium-sized ring systems, see: Yet, L. *Chem. Rev.* **2000**, *100*, 2963−3008.
(12) General reviews on the synthesis of macrocycles: (a) Roxburgh, C. J. *Tetrahedron* **1995**, *51*, 9767−9822. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446−452. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (d) Krakowiak, K. E.; Izatt, R. M.; Bradshaw, J. S. *J. Heterocycl. Chem.* **2001**, *38*, 1239−1248.
(13) (a) Zhu, J. *Synlett* **1997**, 133−144. (b) Carbonnelle, A. C.; Zhu, J. *Org. Lett.* **2000**, *2*, 3477−3480. (c) Zhao, G.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2001**, *123*, 6700−6701. (d) Janvier, P.; Bois-Choussy, M.; Bienaymé, H.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 811−814.
(14) Preliminary communication: Cuny, G.; Bois-Choussy, M.; Zhu, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4774−4777.
(15) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210.
(16) Stahl, G. L.; Walter, R.; Smith, C. W. *J. Am. Chem. Soc.* **1979**, *101*, 5383−5394.
(17) Abbreviations: dppf, 1,1′-bis(diphenylphosphino)ferrocene; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; dba, dibenzylideneacetone; MOP, 2-(diphenylphosphino)-2′-methoxy-1,1′-binaphthyl; Xantphos, 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.
(18) (a) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508−7510. (b) Yoburn, J. C.; Van Vranken, D. L. *Org. Lett.* **2003**, *5*, 2817−2820. (c) Hutton, C. A.; Skaff, O. *Tetrahedron Lett.* **2003**, *44*, 4895−4898. (d) Zhu, L.; Duquette, J.; Zhang, M. *J. Org. Chem.* **2003**, *68*, 3729−3732. For a review on the Miyaura−Suzuki reaction, see Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457−2483.
(19) For recent reviews on C−H activation, see: (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879−2932. (b) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698−1712. (c) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633−639. (d) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731−1769. (e) Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* **2002**, *35*, 826−834. (f) Catellani, M. *Synlett* **2003**, 298−313.

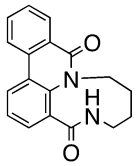
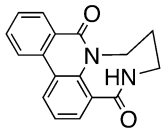
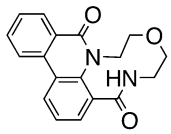
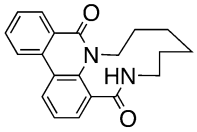
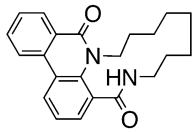
Realizing the potential of this domino transformation in the synthesis of medicinally relevant polycycles, we set out to further optimize this process. A survey of reaction conditions using diamide **1a** as model compound was performed, varying the palladium sources, the ligands, the temperatures, the bases, and the solvents. The results are summarized in Table 1. As can be seen, the reaction temperature has a dramatic effect on the reaction outcome, and higher yield was obtained when the reaction was performed at higher temperature (entry 1 vs 2). Although higher reaction temperature is known to favor the macrocyclization, this technique has not been frequently used in the survey of macrocyclization conditions.[20] In contrast to previous studies on the intramolecular *N*-arylation of amide, the present domino process is much less sensitive to the ligand structure. Both bidentate phosphines, such as dppf (entries 2, 6)[21] and BINAP (entries 7, 10, 11),[22] and monodentate ligand Ph_3P (entry 15) were suitable, although $^tBu_3P$[23] (entries 8, 9, 12, 13) seemed to be less efficient. Potassium acetate (entry 2) was more efficient than cesium carbonate (entry 5) as a base. While DMSO turned out to be a better solvent than DMF (entry 3), toluene is not a solvent of choice, as it gives no product (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; nevertheless, we selected $PdCl_2$(dppf) as the catalyst for the subsequent studies for the simplicity of manipulation and product purification [$PdCl_2$(dppf), KOAc, DMSO, 120 °C, concentration of substrate 0.02 M].

To evaluate the scope of this domino process, various substrates were examined. As shown in Table 2, this novel catalytic domino process can be applied to the construction of azaphenanthrenes fused to 8-membered (**2b**), 10-membered (**2c**), 11-membered (**2d**), and 13-membered (**2e**) lactam motifs, in addition to the 9-membered ring (**2a**). To the best of our knowledge, this represents the first examples wherein an intramolecular Buchwald−Hartwig amidation has been successfully applied to the synthesis of medium-ring and macrocycles. Furthermore, this cyclization was followed by a C−H activation and aryl−aryl bond formation, producing a unique domino process.[24] Parallel to our work, an elegant intermolecular *N*-arylation followed by aryl−aryl bond formation, leading to five-membered carbazoles, has been reported from the group of Bedford,[25] and processes involving sequential intra- and intermolecular *N*-arylation leading to functionalized 1-aminoindole were developed by Watanabe and co-workers.[26] More recently, a palladium-catalyzed cyclodimerization between *N*,*N*′-dimethyl-*m*-phenylenediamine and *N*,*N*′-dimethyl-*N*,*N*′-bis(6′-bromopyrid-2′-yl)-*m*-phenylenediamine has been developed by Wang et al. for the synthesis of azacalix[4]pyridine.[27]

Table 2. From Linear Diamide **1** to Polyheterocycles **2**



1 **2**

entry	substrate	product	yield
1	**1a** n =1, m = 2, X = CH_2		**2a** (65%[a])
2	**1b** n = 1, m = 1, X = CH_2		**2b** (18%[a]) (23%[b])
3	**1c** n =2, m = 2, X = O		**2c** (57%[a]) (85%[b])
4	**1d** n =1, m = 4, X = CH_2		**2d** (48%[a]) (65%[b])
5	**1e** n =1, m = 6, X = CH_2		**2e** (47%[a,b])

[a] $PdCl_2$(dppf) (5 mol %), DMSO (0.02 M), KOAc (3 equiv), 120 °C, isolated yield (average of two runs). [b] $PdCl_2$(dppf) (5 mol %), DMSO (0.001 M), KOAc (3 equiv), 120 °C, isolated yield (average of two runs).

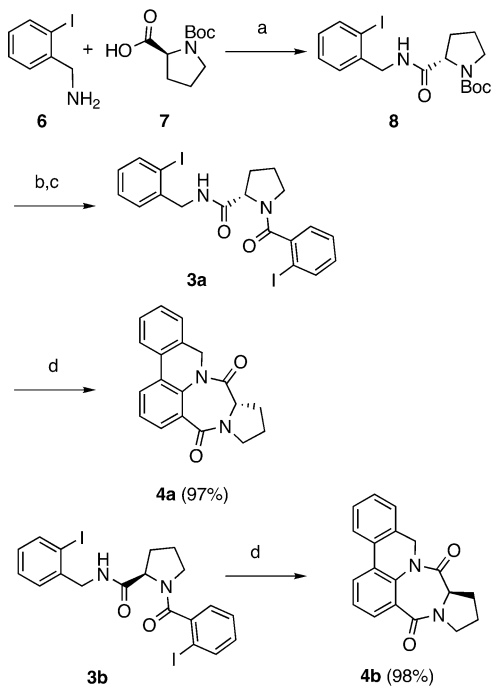
It was interesting to note that cyclization of **1a**−**e** to **2a**−**e** was carried out at 0.02 M, which is not considered to be high-dilution conditions. Higher yields of **2c** and **2d** were obtained when the reaction was performed at 0.001 M under the otherwise identical conditions (conditions b, Table 2).

The ^1H NMR spectra of compounds **2a** and **2c** displays slow interconversion of two conformers on the NMR time scale in both $CDCl_3$ and DMSO-d_6 at room temperature. On the other hand, only one single set of peaks was observed in the ^1H NMR spectra of **2b**, **2d**, and **2e** at room temperature.[28]

Synthesis of Dihydroazaphenanthrene-Fused Benzodiazepinedione. 1,4-Benzodiazepine-2,5-diones (BZDs) and their

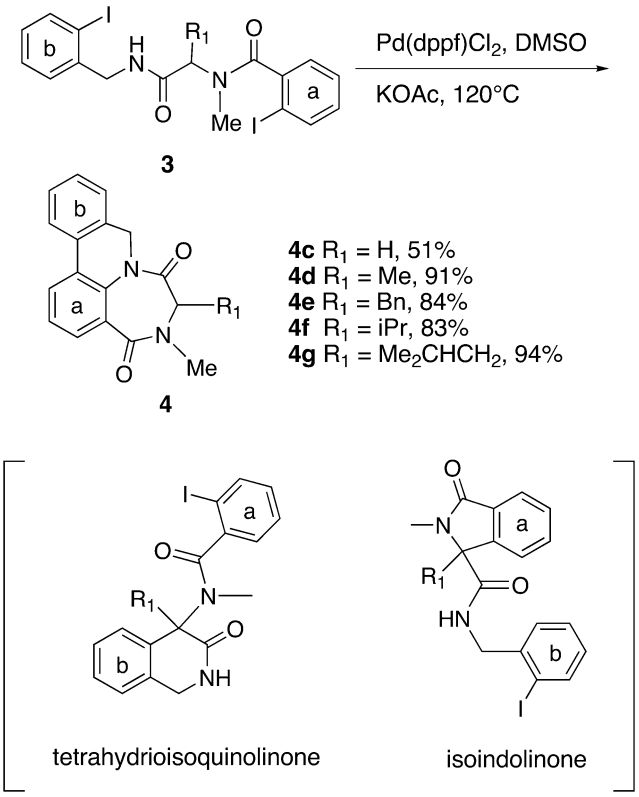
(20) Evans, D. A.; Black, W. C. *J. Am. Chem. Soc.* **1993**, *115*, 4497−4513.
(21) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215−7216.
(22) (a) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217−7218. (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 3694−3703.
(23) Efficient arylamination procedure using $^tBu_3P$ as ligand, see: Hooper, M. W.; Utsunomiya, M.; Hartwig, J. F. *J. Org. Chem.* **2003**, *68*, 2861−2873.
(24) For reviews on domino process, see: (a) Wender, P. A.; Miller, B. L. *Organic Synthesis: Theory and Applications*; JAI Press: Greenwich, CT, 1993; Vol. 2, pp 27−66. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (d) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223−270. (e) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137−165. (f) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167−176. (g) Filippini, M.-H.; Rodriguez, J. *Chem. Rev.* **1999**, *99*, 27−76. (h) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959−5989. (i) Tietze L. F.; Haunert, F. In *Stimulating Concepts in Chemistry*; Shibasaki, M., Stoddart, J. F., Vögtle, F., Eds.; Wiley-VCH: Weinheim, 2000; pp 39−64. (j) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285−2310.
(25) Bedford, R. B.; Cazin, S. J. *J. Chem. Soc., Chem. Commun.* **2002**, 2310−2311.
(26) Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2501−2504.
(27) Wang, M.-X.; Zhang, X.-H.; Zheng, Q.-Y.*Angew. Chem., Int. Ed.* **2004**, *43*, 838−842.
(28) Recent papers on conformational analysis of medium rings, see: (a) Glaser, R.; Novoselsky, A.; Shiftan, D. *J. Org. Chem.* **2000**, *65*, 6345−6353. (b) Glaser, R.; Shiftan, D.; Levi-Roso, G.; Ergaz, I.; Geresh, S. *J. Org. Chem.* **2002**, *67*, 5486−5496 and references therein.

Scheme 2 [a]



[a] Reagents and conditions: (a) EDC, CH_2Cl_2, room temperature, 90%; (b) TFA, CH_2Cl_2, room temperature, 90%; (c) 2-iodobenzoyl chloride, triethylamine, CH_2Cl_2, −30 °C then room temperature, 80%; (d) $Pd(dppf)Cl_2$, KOAc, DMSO, 120 °C.

Scheme 3. Further Examples of Palladium-Catalyzed Synthesis of Polyheterocycle **4**



derivatives, whether natural or synthetic, constitute one of the most important classes of bioactive compounds.[29] The BZDs have been identified as anxiolytic, antitumor, anticonvulsant agents and as non-peptidal inhibitors of platelet aggregation, etc. It follows that many syntheses, including library construction, have been reported in recent years with the hope to further enlarge its bioactivity spectrum and to find new active analogues.[30] Indeed, research on heterocycle-fused BZDs such as pyrrolo[2,1-*c*][1,4]benzodiazepines and imidazo[1,5-*a*][1,4]benzodiazepines has a long history and has led to the discovery of potent bioactive compounds.[31] It occurred to us that the previously unknown dihydroazaphenanthrene-fused BZD (**4**) would be easily accessible by applying the catalytic domino process that we just developed. Since both dihydroazaphenanthrene[32] and BZD[33] were considered to be privileged structures in medicinal chemistry, it would be interesting to develop a facile access to such a new structure that can be considered as a chimeric scaffold of 1,4-benzodiazepine-2,5-dione and dihydroazaphenanthrene.

The cyclization precursor **3a** was synthesized in a stepwise manner as shown in Scheme 2. Thus, coupling of 2-iodobenzylamine (**6**) with (*S*)-*N*-Boc-proline (**7**) provided amide **8** in 90% yield. Removal of *N*-*tert*-butyloxycarbamate under mild acidic conditions, followed by coupling with 2-iodobenzoyl chloride, provided **3a** in 72% overall yield. To our delight, treatment of a DMSO solution of **3a** (0.02 M) in the presence of $PdCl_2$(dppf) and KOAc at 120 °C furnished the polycycle **4a** in 97% isolated yield. To verify whether the chiral integrity was maintained in the course of this double cyclization, the amide **3b**, an enantiomer of **3a**, was synthesized following the same sequence of reactions. Submitting **3b** to the palladium-catalyzed domino process under identical conditions provided compound **4b** in 98% yield. Compound **4b** has the optical rotation nearly identical in magnitude but opposite in sign to that of **4a**. Furthermore, chiral HPLC analysis indicated that the enantiomeric excesses of both **4a** and **4b** are greater than 95%. The results clearly indicated that the present palladium-catalyzed domino process is racemization-free.

The scope of this reaction was further examined by applying the optimized conditions to differentially substituted amides (**3**) (Scheme 3). As can be seen, the 1,4-benzodiazepine-2,5-dione derivatives incorporating sarcosine (**4c**), *N*-methyl alanine (**4d**), *N*-methyl phenylalanine (**4e**), *N*-methyl valine (**4f**), and *N*-methyl leucine (**4g**) 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. Palldiaum-catalyzed intramolecular α-arylation of amide has been reported recently;[34] however, under our experimental conditions, this

(29) Ross, W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press Inc.: San Diego, 1990; Vol. 39, pp 63−97.

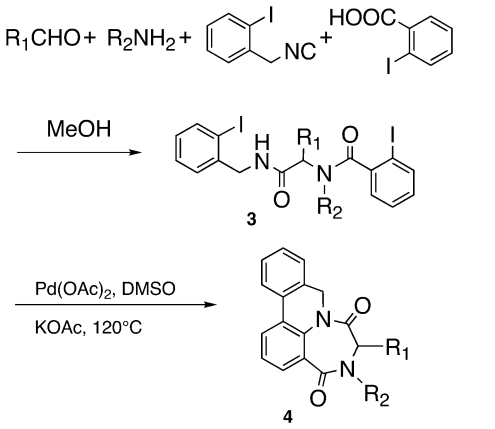
(30) Recent reviews: (a) Ellman, J. A. *Acc. Chem. Res*. **1996**, *29*, 132−143. (b) Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem*. **2002**, *10*, 2415−2437. (c) Hulme, C.; Gore, V. *Curr. Med. Chem*. **2003**, *10*, 51−80. (d) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev*. **2003**, *103*, 893−930.

(31) (a) Rogers-Evans, M.; Spurr, P.; Hennig, M. *Tetrahedron Lett*. **2003**, *44*, 2425−2428. (b) Li, X.; Cao, H.; Zhang, C.; Furtmueller, R.; Fuchs, K.; Huck, S.; Sieghart, W.; Deschamps, J.; Cook, J. M. *J. Med. Chem*. **2003**, *46*, 5567−5570. For a review, see: Thurston, D. E.; Bose, D. S. *Chem. Rev*. **1994**, *94*, 433−465.

(32) (a) Whittaker, J.; McFadyen, W. D.; Baguley, B. C.; Murray, V. *Anti-Cancer Drug Des*. **2001**, *16*, 81−89. (b) Cory, M.; McKee, D. D.; Kagan, J.; Henry, D. W.; Miller, J. A. *J. Am. Chem. Soc*. **1985**, *107*, 2528−2536. (c) Hajduk, P. J.; Bures, M.; Praestgaard, J.; Fesik, S. W. *J. Med. Chem*. **2000**, *43*, 3443−3447.

(33) Evans, B. E.; Rittle, K. E.; Bock, M. G.; Dipardo, R. M.; Freidinger, R. M.; Whitter, W. L.; Lundell, G. F.; Veber, D. F.; Anderson, P. S.; Chang, R. S. L.; Lotti, V. J.; Cerino, D. J.; Chen, T. B.; Kling, P. J.; Kunkel, K. A.; Springer, J. P.; Hirshfield, J. *J. Med. Chem*. **1988**, *31*, 2235−2246.

Scheme 4. Two-Step Synthesis of Polyheterocycle **4**



entry	Ugi-adduct (yield)	tetracycle (yield)
$R_1 = {}^{i}Pr$, $R_2 = {}^{n}Bu$	**3h** (70%)	**4h** (91%)
$R_1 = {}^{n}C_6H_{13}$, $R_2 = {}^{n}Bu$	**3i** (45%)	**4i** (70%)
$R_1 = {}^{i}Pr$, $R_2 = Bn$	**3j** (85%)	**4j** (76%)

potentially competitive reaction, leading to the formation of tetrahydroisoquinolinone or isoindolinone, was not observed.

The benzodiazepinediones are known to exist as a mixture of two slowly interconverting conformers.[35] Depending on the bulk of the R_1 substituent, some of these tetracycles, like compounds **4e** and **4f**, exist also as a mixture of two interconverting conformers on the NMR time scale in $CDCl_3$.

Mechanistic Studies and Further Improvement of Reaction Conditions. Synthesis of simple seven-membered rings by a palladium-catalyzed intramolecular *N*-arylation of amine/amide has been developed using tailored ligands, palladium sources, and bases. In fact, in their pioneering studies, Buchwald and co-workers demonstrated that ligands such as Xantphos[17] and MOP[17] in combination with cesium carbonate are required in order to promote the formation of seven-membered rings.[7c] On the other hand, application of this reaction to the synthesis of medium to larger rings was unsuccessful. The efficiency of the present domino process for the synthesis of medium- and large-sized ring systems via intramolecular *N*-arylation of amide is thus intriguing. The template effect due to the chelation of the metal with amide backbone 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 "ligandless" palladium acetate as catalyst for this transformation. To our delight, treatment of a DMSO solution of **1c** (0.001 M) in the presence of $Pd(OAc)_2$ and KOAc provided the tetracyclic compound **2c** in comparable yield (95%) as with $PdCl_2$(dppf). Similarly, compound **4a** was obtained in 90% yield from **3a** using $Pd(OAc)_2$ as catalyst. To the best of our knowledge, these are the first examples wherein a "ligand-free" palladium catalyst was employed successfully for the amidation process.[36] It has been established that a low-coordinated Pd(II)−amido complex should favor competitive β-hydrogen elimination to give the acyl imine, thus reducing the yield of the desired amidation product.[37] This trend is apparently not observed in the present catalytic domino process, due probably to internal ligation.[38,39]

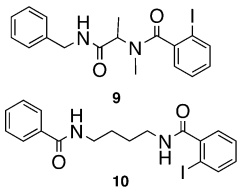


Figure 1.

Additional examples using "ligandless" palladium-catalyzed domino cyclization are summarized in Scheme 4. In these examples, the cyclization precursors were prepared by the Ugi four-component (Ugi-4CR) reaction. Thus, reaction of an *o*-iodobenzyl isonitrile, an *o*-iodobenzoic acid, an amine, and an aldehyde in methanol provided the cyclization precursor **3** under Ugi's conditions. Treatment of a DMSO solution of **3h**−**j** with $Pd(OAc)_2$ in the presence of potassium acetate provided the corresponding polyheterocycles in good to excellent yields, illustrating the generality of these ligandless conditions. Overall, by a combination of Ugi-4CR and the palladium-catalyzed domino process, the complex heterocycles 5,6-dihydro-8*H*-5,7*a*-diazacyclohepta[*jk*]phenanthrene-4,7-dione (**4**) can be synthesized in only two steps from readily available starting materials. Inherent to multicomponent reactions, substituents of this heterocycle can easily be varied by systematically changing the input of the Ugi-4CR, introducing thus the molecular diversity.

To gather further mechanistic insight on this intriguing domino process, amides **9** and **10**, having only one *o*-iodophenyl group, were synthesized (Figure 1). To our surprise, submitting these monoaryl iodide derivatives to the cyclization conditions ($PdCl_2$(dppf), DMSO, KOAc, 120 °C) led only to the recovery of starting material together with a small amount of dehalogenated compound. No expected cyclization product was isolable from the reaction mixture. The surprising result of these control experiments indicated the crucial role of the bis-iodide function in the cyclization of amides **1** and **3**. This observation led us to postulate the following simplified mechanistic hypothesis for the formation of **4** from **3**. The first step would be a double oxidative addition of zerovalent palladium species,

(34) (a) Lee, S.; Hartwig, J. F. *J. Org. Chem.* **2001**, *66*, 3402−3415. (b) Gaertzen, O.; Buchwald, S. L. *J. Org. Chem.* **2002**, *67*, 465−475.

(35) (a) Blackburn, B. K.; Lee, A.; Baier, M.; Kohl, B.; Olivero, A. G.; Matamoros, R.; Robarge, K. D.; McDowell, R. S. *J. Med. Chem.* **1997**, *40*, 717−729. (b) Keating, T. A.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 8935−8939. (c) Gilman, N. W.; Rosen, P.; Earley, J. V.; Cook, C.; Todaro, L. J. *J. Am. Chem. Soc.* **1990**, *112*, 3969−3978. (d) Sunjic, J.; Lisini, A.; Sega, A.; Kovac, T.; Kajfez, F. *J. Heterocycl. Chem.* **1979**, *16*, 757−761. (e) Linscheid, P.; Lehn, J.-M. *Bull. Chem. Soc. Fr.* **1967**, 992−997.

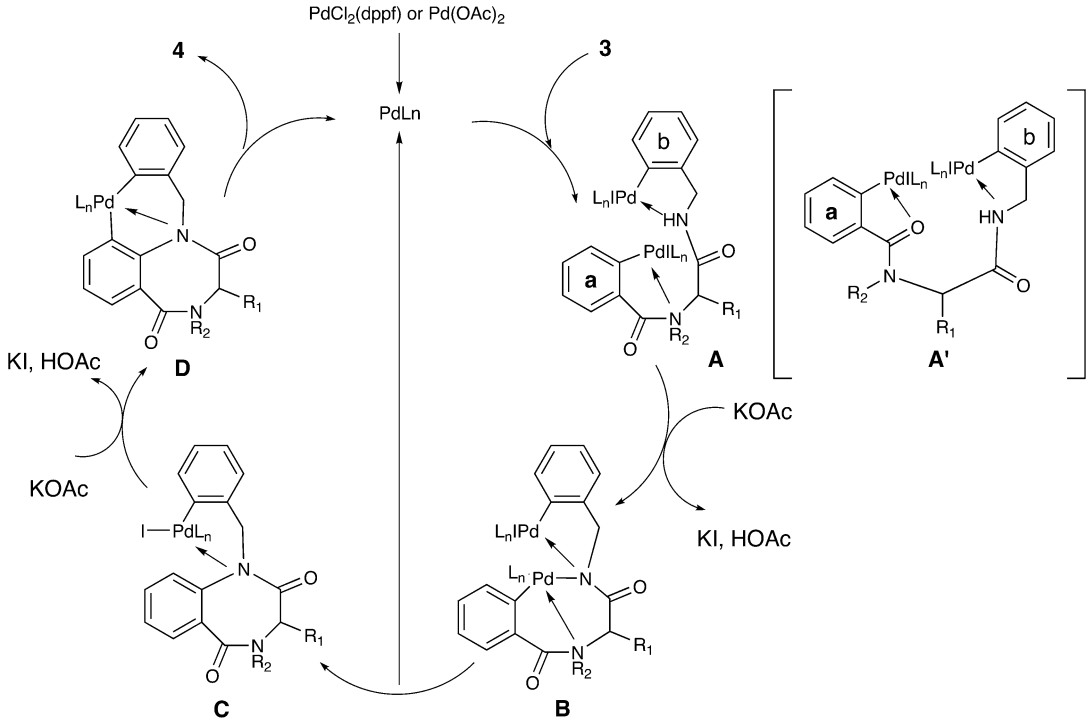
(36) "Ligand-free" palladium-catalyzed cross-coupling reaction, see: (a) (Review) Beletskaya, I. P. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1991**, 2013−2028. Recent examples: (b) Wallow, T. I.; Novak, B. M. *J. Org. Chem.* **1994**, *59*, 5034−5037. (c) Moreno-Mañas, M.; Pajuelo, F.; Pleixats, R. *J. Org. Chem.* **1995**, *60*, 2396−2397. (d) Badone, D.; Baroni, M.; Cardamone, R.; Ielmini, A.; Guzzi, U. *J. Org. Chem.* **1997**, *62*, 7170−7173. (e) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885−3890. (f) Blettner, C. G.; König, W. A.; Stenzel, W.; Schotten, T. *J. Org. Chem.* **1999**, *64*, 3885−3890. (g) Leadbeater, N. E.; Marco, M. *Org. Lett.* **2002**, *4*, 2973−2976. (h) Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *J. Chem. Soc., Chem. Commun.* **2003**, 466−467.

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

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

(39) For a recent review on azapalladacycles, see: Dupont, J.; Pfeffer, M.; Spencer, J. *Eur. J. Inorg. Chem.* **2001**, 1917−1927.

Scheme 5. Palladium-Catalyzed Domino Process: A Mechanistic Proposal



generated in situ, to the bisaryl diiodide, leading to the intermediate **A** or **A′**, depending on the chelating site of the amide function (Scheme 5). This step would probably be assisted by the pre-coordination of Pd(0) to the amide function, and the resulting Pd(II) species should in turn be stabilized by the same effect via the formation of five-membered azapalladacycles (**A** or **A′**).[40,41] For the ring **b** palladium atom, coordination to nitrogen or oxygen of the amide function would produce a five- or seven-membered chelate, respectively. In this case, one would expect that coordination to the nitrogen atom, rather than the carbonyl oxygen, should be favored. On the other hand, the ring **a** palladium may coordinate to either nitrogen or oxygen since in both cases a five-membered chelate would be produced. The internal chelation of amide to palladium adduct should further entropically facilitate the formation of arylpalladium−amido complex **B** from **A** since it involves now formation of a five-membered ring instead of an eight-membered cycle. Reductive elimination of arylpalladium−amido complex **B** would provide **C**, with the concurrent formation of a C_{sp^2}−N bond. Intermediate **C** is nicely functionalized for the subsequent C−H activation process. Although both oxidative insertion of Pd^{II} into the aryl C−H bond to give a hydridopalladacycle (Pd^{IV}) and electrophilic aromatic substitution followed by loss of HI are possible, we would favor the latter mechanism in the present case to account for the formation of the seven-membered palladacycle **D**.[42,43] Once again, this step could be accelerated entropically by the pre-coordination of the nitrogen atom to the pendant palladium(II) species. A second reductive elimination from **D** would then give the observed product with the regeneration of Pd(0) species.[19,44]

From control experiments, it is clear that the formation of the bis-palladium−aryl iodide adduct of type **A** may play an important role in the present reaction.[45] Consequently, we attempted to isolate this putative σ-aryl palladium complex and to study its chemical behavior. Much to our delight, reaction of **3c** with 2 equiv of palladium tetrakis(triphenylphosphine) in toluene at room temperature for 72 h afforded, after flash column chromatography, a single isolable compound. Unfortunately, we failed to obtain a single crystal suitable for X-ray studies. However, the structure of this compound was assigned as

(40) (a) Vicente, J.; Abad, J.-A.; Frankland, A. D.; Ramírez de Arellano, M. C. *Chem. Eur. J.* **1999**, *5*, 3066−3075. (b) Ohff, M.; Ohff, A.; Milstein, D. *J. Chem. Soc., Chem. Commun*. **1999**, 357−358. (c) Gai, X.; Grigg, R.; Ramzan, M. I.; Sridharan, V.; Collard, S.; Muir, J. E. *J. Chem. Soc., Chem. Commun*. **2000**, 2053−2054. (d) Bedford, R. B.; Cazin, C. S. *J. Chem. Soc., Chem. Commun*. **2001**, 1540−1541. (e) Alonso, D. A.; Nájera, C.; Pacheco, M. C. *Org. Lett*. **2000**, *2*, 1823−1826. (f) Viciu, M. S.; Kelly, R. A., III; Stevens, E. D.; Naud, F.; Studer, M.; Nolan, S. P. *Org. Lett*. **2003**, *5*, 1479−1482. (g) Solé, D.; Vallverdú, L.; Solans, X.; Font-Bardiá. M.; Bonjoch, J. *J. Am. Chem. Soc*. **2003**, *125*, 1587−1594.

(41) Palladacycle involving an amide function was relative uncommon; see, however: Oestreich, M.; Dennison, R. P.; Kodanko, J. J.; Overman, L. E. *Angew. Chem., Int. Ed*. **2001**, *40*, 1439−1442.

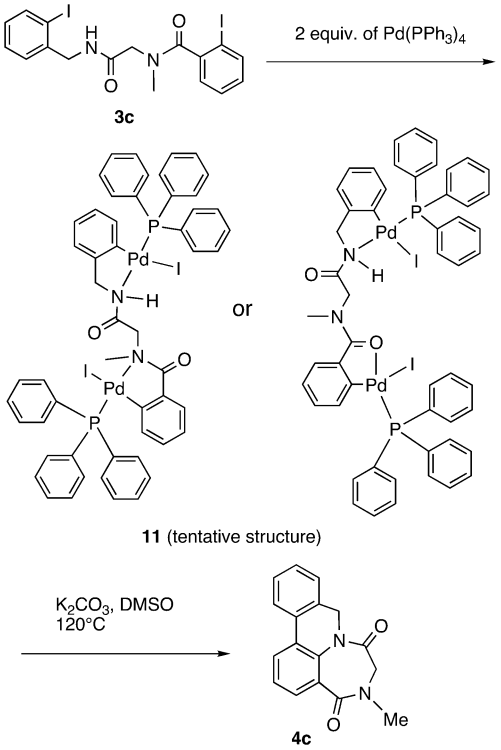
(42) (a) Martín-Matute B.; Mateo, C.; Cárdenas D. J.; Echavarren, A. M. *Chem. Eur. J.* **2001**, *7*, 2341−2348. (b) Cámpora, J.; López, J. A.; Palma, P.; Valerga, P.; Spillner, E.; Carmona, E. *Angew. Chem., Int. Ed.* **1999**, *38*, 147−151. (c) Catellani, M.; Chiusoli, G. P. *J. Organomet. Chem*. **1992**, *425*, 151−154.

(43) Other mechanistic proposals, see: (a) Pfeffer, M.; Sutter, J.-P.; Rotteveel, M. A.; De Cian, A.; Fischer, J. *Tetrahedron* **1992**, *48*, 2427−2440. For a review, see: Dyker, G. *Chem. Ber./Recueil* **1997**, *130*, 1567−1578.

(44) C−H activation, recent examples: (a) Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem*. **1997**, *62*, 2−3. (b) Harayama, T.; Shibaike, K. *Heterocycles* **1998**, *49*, 191−195. (c) Harayama, T.; Akiyama, T.; Akamatsu, H.; Kawano, K.; Abe, H.; Takeuchi, Y. *Synthesis* **2001**, 444−450. (d) Harayama, T.; Akiyama, T.; Nakano, Y.; Nishioka, H.; Abe, H.; Takeuchi, Y. *Chem. Pharm. Bull*. **2002**, *50*, 519−522. (e) Kakiuchi, F.; Kan, S.; Igi, K.; Chatani, N.; Murai, S. *J. Am. Chem. Soc*. **2003**, *125*, 1698−1699. (f) Mori, A.; Sekiguchi, A.; Masui, K.; Shimada, T.; Horie, M.; Osakada, K.; Kawamoto, M.; Ikeda, T. *J. Am. Chem. Soc*. **2003**, *125*, 1700−1701. (g) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc*. **2003**, *125*, 11506−11507. (h) Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem., Int. Ed*. **2003**, *42*, 5736−5740. (i) Sezen, B.; Sames, D. *J. Am. Chem. Soc*. **2003**, *125*, 10580−10585. (j) DeBoef, B.; Pastine, S. J.; Sames, D. *J. Am. Chem. Soc*. **2004**, *126*, 6556−6557. (k) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc*. **2004**, *126*, 7460−7461 and references therein.

(45) Coordination of nitrogen with palladium controls and modifies the course of transition metal-promoted processes; see ref 40 and the following: (a) Mauleón, P.; Alonso, I.; Carretero, J. C. *Angew. Chem., Int. Ed*. **2001**, *40*, 1291−1293. (b) Olofsson, K.; Sahlin, H.; Larhed, M.; Hallberg, A. *J. Org. Chem*. **2001**, *66*, 544−549.

Scheme 6. Synthesis of Bis-σ-arylpalladium Complex **11** (Tentative Structure) and Its Conversion to **4c**



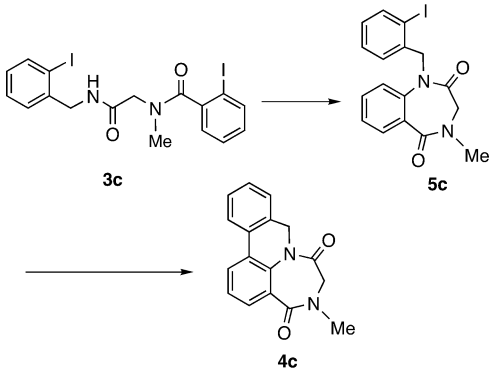
azapalladacycle **11** from the following spectroscopic data (Scheme 6). In the ^{1}H NMR spectrum of this compound, both methylene protons appear as AB systems, indicating a relatively rigid structure. The ^{31}P NMR spectrum shows two peaks at δ 28.0 and 29.3 ppm,[46] and the molecular weight (ESI *m*/*z* 1294.7) corresponds to the molecular formula $C_{53}H_{46}N_2I_2O_2Pd_2P_2$ + Na. The stability of compound **11** is indicative of the presence of internal chelation. Unfortunately, the coordination sites as well as the exact three-dimensional structure of **11** cannot be deduced from the NMR studies. However, we speculated that such coordination might pre-organize the linear substrate to a folded conformer conducive to the cyclization.

The intermediacy of **11** in the palladium-catalyzed transformation of the linear amide **3c** to tetracycle **4c** was proved by the following control experiment. Thus, simply heating a DMSO solution of azapalladacyclcle **11** in the presence of KOAc at 120 °C triggered the domino process, leading to the formation of **4c** in 60% yield. Evidently, complex **11** cannot be the immediate precursor of **4c** since the N-atom and the aryl carbon atom to be coupled are not on the same palladium atom in this complex. Rather, it has to be first transformed into the type **B** complex (cf. Scheme 5), and this step would be facilitated by further coordination of palladium to a heteroatom or hydrogen bond as well as entropic factors (transient five- vs eight-membered ring), as discussed earlier.

Two chemical bonds were created in the present process by way of a formal Buchwald−Hartwig amidation and C−H activation/aryl−aryl bond-forming processes. Although it is reasonable to assume that two bonds were formed sequentially and that the aryl amidation preceded the C−C bond formation, a more convincing support was sought. Attempts to stop the reaction after intramolecular *N*-arylation failed with the present

(46) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 8232−8245.

Scheme 7 [a]



[a] Reagents and conditions: (a) CuI, K_2CO_3, DMSO, 110 °C, 43%; (b) Pd(dppf)Cl_2, DMSO, KOAc, 120 °C, 24 h, 96%.

catalytic conditions at various reaction temperatures. In fact, treatment of **3c** under a range of catalytic conditions led to either the recovery of the starting material under mild conditions or the final tetracyclic compound **4c** at higher temperature. In no case was the benzodiazepinedione **5c** detected (Scheme 7). These experimental results indicated that, if the reaction went through the sequence shown in the Scheme 5, then the second cyclization via C−H activation and C−C bond formation from intermediate **C** might be a very facile process. To access an authentic sample of **5c**, many well-developed synthetic pathways exist; nevertheless, we decided to adopt a more challenging way: to find a metal other than palladium to realize the transformation of **3c** to **5c**. We were interested in this approach not only for the purpose of the present mechanistic studies, but also for the development of a general approach to this class of heterocycles.

Inspection of the structure of **3c** led to the assumption that one of the iodides (the desired one) should be more prone to oxidative addition with copper due to the electronic as well as the coordinating effect of the amide group. If this chemoselective oxidative addition as well as the subsequent steps could occur, then one may expect to stop the reaction at the benzodiazepinedione level, i.e., compound **5c** (Scheme 7). Indeed, treatment of a DMSO solution of **3c** with CuI in the presence of potassium carbonate led to the formation of **5c** in 43% yield. The formation of tetracycle **4c** was not observed under these conditions. However, when **5c** was submitted to the palladium-catalyzed conditions [$PdCl_2$(dppf), DMSO, KOAc, 120 °C], a sequence of C−H activation/aryl−aryl bond-forming processes took place smoothly to provide compound **4c** in 96% yield. From the results of this control experiment, it seems reasonable to suggest that the intramolecular *N*-arylation might precede the C−C bond-forming event in the palladium-catalyzed transformation of **3c** to **4c**.

Copper-Catalyzed Intramolecular *N*-Arylation: New Access to 1,4-Benzodiazepine-2,5-dione. While palladium-catalyzed *N*-arylation has attracted considerable attention for the past 10 years, the search for a milder and more efficient catalyst system for performing the classic copper-catalyzed *N*-arylation of amines (Ullmann reaction) and *N*-arylation of amides (Goldberg reaction) has been the subject of recent focus.[47] Copper-catalyzed intramolecular *N*-arylation of amine

(47) (a) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581−584. (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793−796 and references therein.

Table 3. Copper-Catalyzed Intramolecular *N*-Arylation of **3c** Using Various Reaction Conditions[a]

entry	catalyst	base	ligand	solvent	temp (°C)	yield (%)[b]
1	CuI	K_2CO_3	none	DMSO	110	43
2	CuI	K_2CO_3	**I**[d]	DMSO	110	44 (57)[c]
3	CuCl	K_2CO_3	**I**	DMSO	110	22 (33)[c]
4	$CuCl_2$	K_2CO_3	**I**	DMSO	110	18
5	$Cu(OAc)_2$	K_2CO_3	**I**	DMSO	110	37
6	$CuSO_4 \cdot 5H_2O$	K_2CO_3	**I**	DMSO	110	5 (7)[c]
7	Cu_2O	K_2CO_3	**I**	DMSO	110	15
8	Cu powder	K_2CO_3	**I**	DMSO	110	14 (18)[c]
9	$Cu(OAc)_2$	K_2CO_3	**II**[d]	DMSO	110	21
10	CuI	K_3PO_4	**I**	DMSO	110	38 (45)[c]
11	CuI	Cs_2CO_3	**I**	DMSO	110	0
12	CuI	$CsOH.H_2O$	**I**	DMSO	110	0
13	CuI	CsOAc	**I**	DMSO	110	33 (62)[c]
14	CuI	K_2CO_3	**I**	1,4-dioxane	100	0[f]
15	CuI	K_2CO_3	**I**	DMF	110	38 (71)[c]
16	CuI	K_2CO_3	**I**	DMSO	80−100	16
17	CuI (2 equiv)	K_2CO_3	**I** (4 equiv)	DMSO	110	20 (46)[c]
18	CuI	K_2CO_3	**I**	DMSO	120	36
19	CuI	K_2CO_3	**II**[d]	DMSO	110	27 (32)[c]
20	CuI	K_2CO_3	**III**[d]	DMSO	110	4 (6)[c]
21	CuI	K_2CO_3	**IV**[d]	DMSO	110	41 (85)[c]
22	CuI	K_2CO_3	**V**[d]	DMSO	110	52 (73)[c]
23	CuTc	K_2CO_3	none	DMSO	110	50 (71)[c]
24	CuI[e]	K_2CO_3	**VI**[d]	DMSO	110	22
25	CuI.^{n}Bu$_3$P	K_2CO_3	none	DMSO	110	36 (47)[c]
26	CuI·LiCl	K_2CO_3	**V**	DMSO	110	31 (55)[c]

[a] Normalized reaction conditions: substrate concentration, 0.02 M; catalyst loading, 10%; ligand loading, 20%; reaction stopped after 15 h. [b] Isolated yield. [c] Yield based on the conversion. [d] Ligand **I**, *N*,*N*′-dimethylethylenediamine; ligand **II**, 1,10-phenanthroline; ligand **III**, *trans*-1,2-cyclohexanediamine; ligand **IV**, sarcosine; ligand **V**, thiophene-2-carboxylic acid; ligand **VI**, 2,4-pentanedione. [e] CuTc stands for copper(I) thiophene-2-carboxylate, synthesized according to Liebeskind. [f] Starting material was recovered.

leading to a seven-membered ring has been reported from the groups of Ma[8a] and Fukuyama,[8b] respectively. Both group employed "ligandless" conditions, and only one example was given in each of these two papers. More recently, domino copper-catalyzed intermolecular *N*-arylation of β-lactam followed by ring expansion has been developed for the synthesis of medium-ring nitrogen-containing heterocycles by Buchwald and co-workers.[48]

The promising result obtained for the cyclization of **3c** with a catalytic amount of CuI under ligandless conditions[49] prompted us to carry out a detailed survey of reaction conditions, varying the copper sources, the ligand structures, the solvents, the bases, and the temperatures (Table 3). As is seen, addition of *N*,*N*′-dimethylethylenediamine (**I**) into the reaction mixture (ligand/CuI = 2/1) led to a cleaner reaction with an increased yield based on the substrate conversion (entry 1 vs 2).[50] Several readily available copper compounds, including CuCl, $CuCl_2$, $Cu(OAc)_2$, $CuSO_4 \cdot 5H_2O$, Cu_2O, and copper powders (bronze), were studied as alternative catalyst precursors. Although all these copper compounds having different oxidation states are catalytically active, none of them is as effective as CuI (entries 2−10). Soluble copper sources such as CuI·*n*PBu$_3$ and CuI·LiCl have also been examined[51] and were found to be less effective than CuI under otherwise identical conditions (entry 1 vs 25, entry 22 vs 26, Table 3).

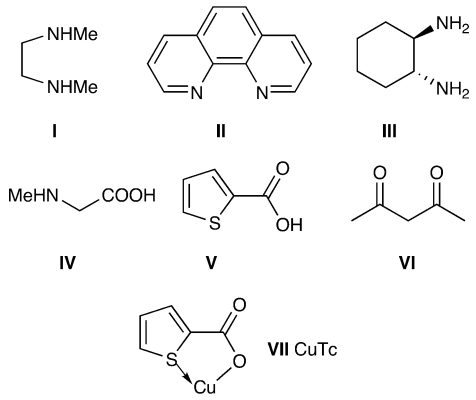
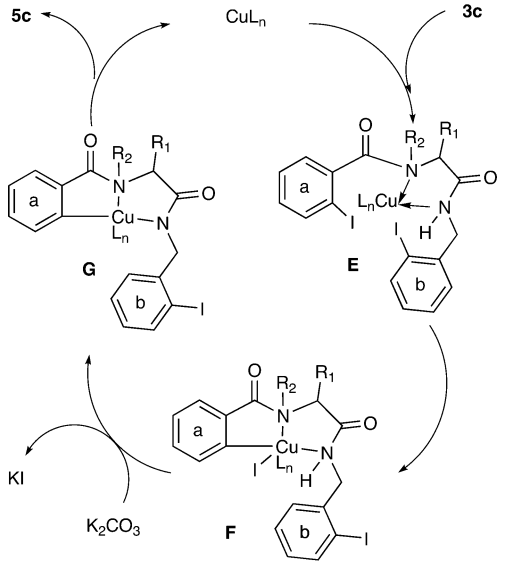


Figure 2. Ligand structure for CuI-catalyzed intramolecular *N*-arylation of **3c**.

Scheme 8. Copper-Catalyzed Synthesis of Benzodiazepinedinone: A Mechanistic Proposal



Bases were found to have a dramatic influence on the reaction outcome. While the presence of cesium carbonate (entry 11) and cesium hydroxide (entry 12) inhibited completely the transformation, both potassium phosphate (entry 10) and cesium acetate (entry 13) were able to promote the reaction, albeit slightly less effectively than potassium carbonate. The choice of the solvent also played an important role. While the cyclization occurred smoothly in polar aprotic solvents such as DMSO and DMF (entry 15),[52] no reaction took place in less polar solvents like dioxane (entry 14). When the reaction was performed at lower temperature (80−100 °C), the reaction became less clean due to the competitive degradation process (entry 16 vs 2).

Finally, other ligands, including 1,10-phenanthroline (**II**),[53] (±)-*trans*-1,2-cyclohexanediamine (**III**),[54] sarcosine (**IV**),[55]

(48) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529−3533.

(49) Recent examples of copper-catalyzed "ligandless" conditions: (a) Kalinin, A. V.; Bower, J. F.; Riebel, P.; Snieckus, V. *J. Org. Chem.* **1999**, *64*, 2986−2987. (b) Gujadhur, R.; Venkataraman, D.; Kintigh, J. T. *Tetrahedron Lett.* **2001**, *42*, 4791−4793. (c) Lange, J. H. M.; Hofmeyer, L. J. F.; Hout, F. A. S.; Osnarbrug, S. J. M.; Verveer, P. C.; Kruse, C. G.; Feenstra, R. W. *Tetrahedron Lett.* **2002**, *43*, 1101−1104. (d) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987−4990.

(50) (b) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421−7428. (b) Kang, S.-K.; Kim, D.-W.; Park, J.-N. *Synlett* **2002**, 427−430.

(51) We thank one of the reviewers for suggesting these experiments.

(52) Polar coordinating solvent such as *N*-methylpyrrolidinone was proposed to be able to generate reactive Cu(I) monomer from the insoluble Cu(I) carboxylatre polymer: Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312−2313.

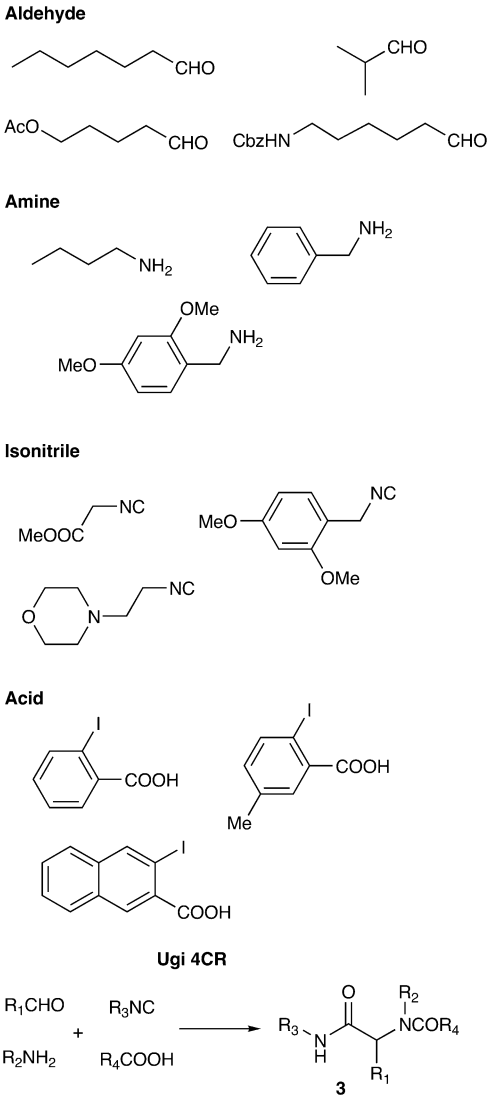
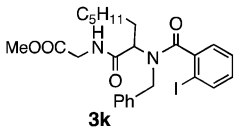
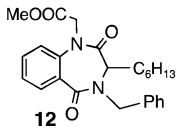
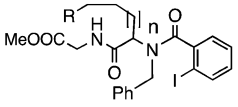
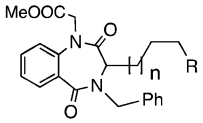
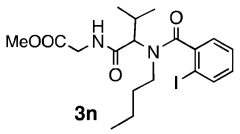
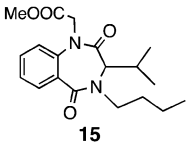
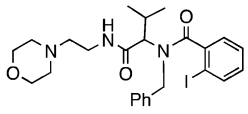
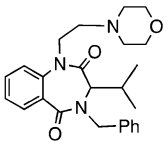
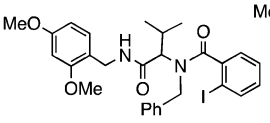
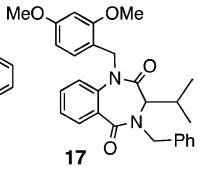
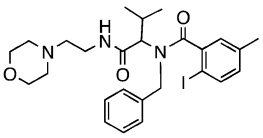
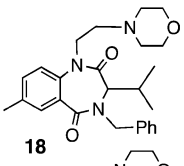
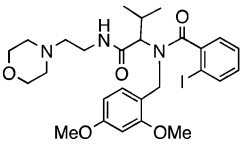
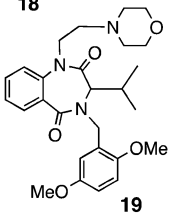
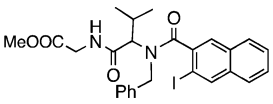
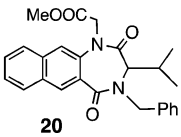


Figure 3. Ugi-4CR for the synthesis of amides; structure of inputs.

thiophene-2-carboxylic acid (**V**),[56,57] and 2,4-pentanedione[58] (**VI**, Figure 2), were examined. While **II**, **III**, and **VI** were less efficient than **I**, **IV** and **V** turned out to be more effective than **I**. Similar results were obtained when presynthesized catalyst CuTc was used. Balancing the yield and the conversion, the thiophene-2-carboxylic acid (**V**) was selected as the ligand for the subsequent studies. Overall, under optimum conditions [CuI (10%), **V** (20%), K_2CO_3, DMSO (0.02 M), 110 °C, 15 h], we found that cyclization of the amide **3c** provided the benzodiazepinedione **5c** in 52% yield (73% based on the substrate conversion). Although the yield remained moderate, we deemed it respectable in light of the number of potential competitive processes due to the presence of the second aryl iodide function.

Table 4. Copper-Catalyzed Synthesis of 1,4-Benzodiazepine-2,5-diones by Intramolecular *N*-Arylation of Amide

entry	starting material	product	yield
1	 **3k**	 **12**	86%
2	 **3l** R = OAc, n = 2	 **13** R = OAc, n = 2	74%
3	**3m** R = NHCbz, n = 3	**14** R = NHCbz, n = 3	88%
4	 **3n**	 **15**	88%
5	 **3o**	 **16**	99%
6	 **3p**	 **17**	95%
7	 **3q**	 **18**	95%
8	 **3r**	 **19**	97%
9	 **3s**	 **20**	50%

Scheme 8 may first coordinate to the two amide nitrogens, leading to a five-membered chelate (**E**).[59] The formation of this chelate would entropically favor the subsequent oxidative addition to the aryl halide. The presence of an amide substituent at the ring **a** would make it more susceptible to the nucleophilic addition

(53) (a) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803−3805. (b) Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133−136. (c) Nordman, G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 4978−4979. (d) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27−30.
(54) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729.
(55) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453−2455.
(56) Original development of this ligand, see: (a) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749. (b) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2001**, *3*, 91−93.
(57) CuTc-catalyzed *N*-vinylation of vinyl iodide, see: (a) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333−1336. (b) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889−7901.
(58) Buck, E.; Song, Z. J.; Tschaen, D.; Dormer, P. G.; Volante, R. P.; Reider, P. J. *Org. Lett.* **2002**, *4*, 1623−1626.
(59) Sigel, H.; Martin, R. B. *Chem. Rev.* **1982**, *82*, 385−426.

A simplified mechanistic view for the formation of benzodiazepine **5c** from **3c** is summarized in Scheme 8. The copper catalyst may first coordinate to the two amide nitrogens, leading to a five-membered chelate (**E**).[59] The formation of this chelate would entropically favor the subsequent oxidative addition to the aryl halide. The presence of an amide substituent at the ring **a** would make it more susceptible to the nucleophilic addition

of Cu(I) for electronic reasons, leading to intermediate **F**. Removal of HI by the action of potassium carbonate would give the copper(III)−amido complex **G**. Reductive elimination would then produce the observed heterocycle, with the concomitant regeneration of the copper catalyst. It is worth noting that CuTc is capable of mediating the reductive coupling of aryl iodide, leading to the biaryl compound.[52] However, under these conditions, neither dimeric nor the 10-membered macrocycle from **3c** via intramolecular aryl−aryl bond formation was isolated.[60]

The ability of copper catalyst to promote the macrocyclization was investigated.[51] When bisamide **1c** or **10** was submitted to the copper catalyst, formation of macrocycle was not observed, and only degradation occurred, leading to untractable materials. The results of these experiments provided indirect evidence that copper and palladium might have different coordination patterns with the amide substrate. Such differences in coordination might lead to different conformational preferences of the intermediate adduct, and hence the outcome of the cyclization reaction.

The scope of this copper-catalyzed intramolecular *N*-arylation of amide for the synthesis of diversely substituted 1,4-benzodiazepine-2,5-diones was next examined. Ugi-4CR was used for the synthesis of cyclization substrates, and the inputs used are listed in Figure 3. From four aldehydes, three amines, three isonitriles, and three carboxylic acids, amides **3k**−**s** (Figure 3) were synthesized in a single operation with good to excellent yields under standard Ugi-4CR conditions (MeOH, 0.2 M, room temperature). The results of the cyclization are summarized in Table 4. As can be seen, the cyclization conditions are applicable to a variety of substrates having different substituents and tolerate a range of functional groups, such as ester, carbamate, tertiary amine, and aryl iodide, etc. The presence of chelating functions such as amino ester (entries 1−4) and vicinal diamine (entries 5, 7, 8) is well tolerated, although these functions can potentially form the complex with the copper catalyst, consuming consequently the active catalytic species. In most cases, the 1,4-benzodiazepine-2,5-diones were obtained in excellent yields.

Ugi-4CR followed by postfunctionalization has been elegantly developed previously by a number of groups.[61] In all these approaches, the seven-membered ring was formed by lactamization. The present two-step synthesis of 1,4-benzodiazepine-2,5-dione represents thus a new synthetic strategy.

(60) For a recent comprehensive review on aryl−aryl bond formation, see: Hassan, J.; Sévignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359−1470.

(61) For reviews, see: (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131. (b) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2002**, *9*, 1241−1253.

Conclusion

In summary, a novel palladium-catalyzed domino process involving intramolecular *N*-arylation of amide/C−H activation/aryl−aryl bond formation has been developed. Although both individual steps are documented in the literature, the combination is without precedent. Moreover, the sequence involves the formation of a medium-sized or a macrocyclic ring by a palladium-catalyzed intramolecular *N*-arylation process, which to the best of our knowledge was unknown at the outset of this work. The effect of ligand structure was found to be minimal for the present domino process, presumably due to the chelating ability of the cyclization substrate. The azapalladacycle **11** resulting from the double oxidative addition of palladium to the bis-aryl iodide **3c** is isolated and is characterized by spectroscopic studies. Its intermediacy in the transformation of **3c** to **4c** is proved by a control experiment. A distinctly different catalytic property of copper and palladium catalysts was observed. While it is impossible to stop the reaction after the completion of intramolecular *N*-arylation with palladium catalyst, it is discovered that copper iodide is capable of interrupting the domino process, leading to the intramolecular *N*-arylation product without inducing the C−H activation process. Indeed, to the best of our knowledge, direct arylation via copper-catalyzed C−H activation has not been developed for the biaryl synthesis. Thus, from the same linear precursor, two different heterocyclic scaffolds can be easily prepared simply by changing the metal (catalyst) engaged. Taking advantage of the powerful Ugi-4CR for the synthesis of linear precursor (**3**), two different heterocycles—the 1,4-benzodiazepine-2,5-dione (**5**) and the 5,6-dihydro-8*H*-5,7*a*-diazacyclohepta[*jk*]phenanthrene-4,7-dione (**4**)—can be prepared in two steps from readily accessible starting materials: amine, aldehyde, acid, and isonitrile. The chemistry developed herein is thus particularly useful in the diversity-oriented synthesis program.

Acknowledgment. We thank CNRS for financial support. A doctoral fellowship from this institute to G.C. is gratefully acknowledged. We thank Professor Lallemand for his interest in this work.

Supporting Information Available: Experimental details and analytical data for compounds **1a**−**e**, **2a**−**e**, **3a**−**s**, **4a**−**j**, **5**, **11**−**20**; copies of ^{1}H NMR spectra of cyclic compounds and the azapalladacycle **5**; and chiral HPLC analyses of compounds **4a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA047472O