Multicomponent Catalysis

DOI: 10.1002/anie.200604407

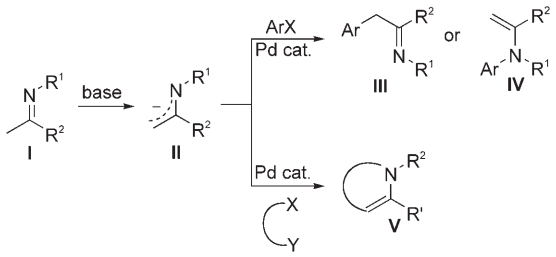
The Azaallylic Anion as a Synthon for Pd-Catalyzed Synthesis of Heterocycles: Domino Two- and Three-Component Synthesis of Indoles**

José Barluenga, Agustín Jiménez-Aquino, Carlos Valdés, and Fernando Aznar*

Pd-catalyzed cross-coupling reactions represent some of the most powerful and versatile tools in modern synthetic organic chemistry.[1] While most of the cross-coupling processes are oriented toward the formation of C–C bonds, during the last decade, the new methodologies developed for the creation of C–N bonds have became extraordinarily popular, as they represent a very efficient entry into different types of important nitrogenated compounds.[2] On the other hand, the efforts of many prominent research groups have provided the synthetic organic chemist with highly active Pd catalytic systems of wide scope and enhanced stability.[3,4] Thus, under the same reaction conditions, several different cross-coupling processes can be carried out consecutively with the same catalytic system. By taking advantage of this versatility of some Pd catalysts, and combining C–C and C–N bond-forming reactions, some new methodologies for the synthesis of heterocycles have been developed.[5,6] For instance, we have recently reported a Pd-catalyzed cascade process which involves an alkenyl amination and a subsequent intramolecular Heck reaction, which together represent a new method for the synthesis of indoles.[7]

In the search for new strategies for the synthesis of heterocycles through Pd-catalyzed cascade processes, we turned our attention to the azaallylic anion **II** (Scheme 1). This species can be easily generated by deprotonation of an imine bearing α-hydrogen atoms. Although azaallylic anions have been extensively employed as three-atom synthons in classic heterocyclic chemistry,[8] to the best of our knowledge, no reaction has been reported of their participation as nucleophiles in Pd-catalyzed intermolecular cross-couplings. In the present paper we describe our preliminary studies on the Pd-catalyzed α-arylation of imines. Moreover, the participation of the azaallylic anions generated from imines in sequential Pd-catalyzed C–C and C–N bond-forming reactions has led to the development of a new and very efficient method for the synthesis of indoles, and has introduced the imine as a new synthon for the synthesis of heterocycles through sequential Pd-catalyzed cross-coupling reactions.

At the outset of this project, we wondered whether under Pd-catalyzed arylation conditions the imines **I** might undergo C-arylation, in a reaction similar to the well-known arylation of enolates of ketones,[9–12] esters,[13] or amides,[14] to give arylated imine **III**, or undergo N-arylation, in a Buchwald–Hartwig amination[2] type of reaction, to provide the enamine **IV** (Scheme 1). Moreover, the bidentate nature of the azaallylic anion led us to believe that it might participate in two consecutive cross-coupling events, and therefore might be an ideal substrate for Pd-catalyzed domino processes oriented toward the synthesis of heterocycles of the general structure **V**.



Scheme 1. Possible pathways for Pd-catalyzed arylation of azaallylic anions.

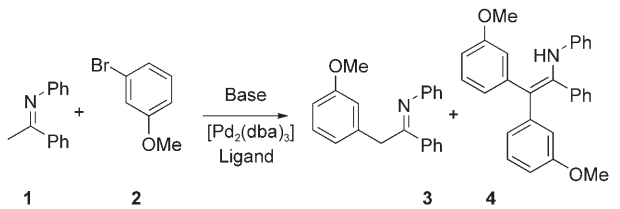
To investigate the reactivity of azaallylic anions under cross-coupling conditions, we chose as a prototype system the reaction of the acetophenone imine **1** with *m*-bromoanisole (**2**). We carried out extensive experimentation with different bases, supporting ligands for the Pd catalyst, solvents, and reaction conditions. Some relevant results are represented in Scheme 2.

The bulky and electron-rich monophosphines Xphos[15] and Davephos[16] were found to be the best ligands to achieve the arylation of **1**. In all cases the reaction occurred exclusively at the C position. No N-arylation was detected even when the reactions were conducted with large excesses of aryl halide and base. The reactions provided a mixture of the monoarylated imine **3** and the diarylated imine **4**. The nature of the base and the supporting ligand influences the ratio of the mono- versus the diarylated products. The diarylated imine **4** can be efficiently obtained by employing two equivalents of aryl bromide, Xphos as the supporting

[*] Prof. J. Barluenga, A. Jiménez-Aquino, Dr. C. Valdés, Prof. F. Aznar
Instituto Universitario de Química Organometálica "Enrique Moles"
Unidad Asociada al CSIC
Universidad de Oviedo
Julián Clavería 8
33071 Oviedo (Spain)
Fax: (+34) 985-103-450
E-mail: barluenga@uniovi.es

[**] Financial support of this work by Fundación Ramón Areces and D.G.I. A predoctoral fellowship by Fundación Ramón Areces to A.J. is gratefully acknowledged.

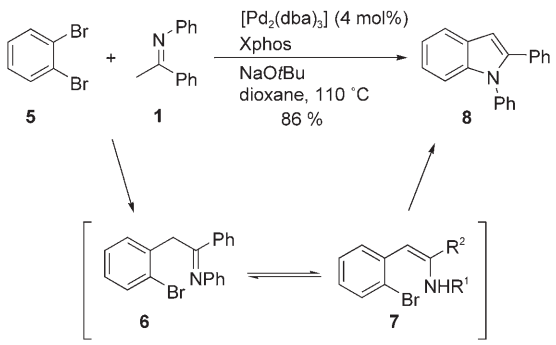
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Scheme 2. Pd-catalyzed α-arylation of imine **1**. Reaction conditions: $[Pd_2(dba)_3]$ (4 mol%), 2:1 Pd/ligand molar ratio, 1.4 equiv base, dioxane, 110°C, 14 h. Xphos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl. Davephos = 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl. [a] Yield of isolated **4** when Cs_2CO_3 was employed as base: 76%.

ligand, and either NaO*t*Bu or Cs_2CO_3 as the base. Selective monoarylation turned out to be more elusive. Moderate selectivity could be attained when Davephos was employed as the ligand and Cs_2CO_3 as the base. Notably, we never detected any N-arylation product under the reaction conditions examined. To the best of our knowledge, this reaction represents the first example of the intermolecular α-arylation of an imine, a transformation of great synthetic potential. We are currently investigating the optimal conditions and scope of this reaction, and a detailed study will soon be reported.

With reaction conditions appropriate for carrying out the intermolecular α-arylation of imines, we decided to explore the possibility of carrying out a cascade sequence involving C- and N-arylations. We chose as a model system the reaction of *o*-dibromobenzene (**5**) with **1**, expecting that after the initial α-arylation that gives imine **6**, the tautomeric enamine **7** might undergo an intramolecular amination to form directly indole **8** (Scheme 3).[17,18] Indeed, when the reaction was conducted with Xphos as the supporting ligand and NaO*t*Bu as the base, indole **8** was cleanly obtained in 86% yield after isolation, an excellent result when one takes into account that the same Pd catalyst is promoting two different cross-coupling reactions: the C-arylation and the intramolecular N-arylation.



Scheme 3. Synthesis of indole **8** through a sequence of C-arylation and intramolecular N-arylation.

The scope of the cascade process was investigated by introducing a set of structurally diverse imines, and turned out to be fairly general. As represented in Table 1, this methodology can be employed for the preparation of 2- and 2,3-disubstituted indoles carrying either aliphatic or aromatic substituents in the 1-, 2-, and 3-positions. Even the bulky *tert*-butyl substituent is tolerated (Table 1, entry 11). Interestingly, the participation of imines derived from cyclic ketones leads to the corresponding tricyclic systems (Table 1, entries 6–8, 13), structures that are not available through metal-catalyzed cyclizations of *o*-alkynyl anilines. Moreover, the reaction is not restricted to dibromoarenes, and can be conducted also with the less reactive *o*-dichlorobenzene without a substantial decrease in the yield of the isolated product (Table 1, entry 1 vs. entry 12).

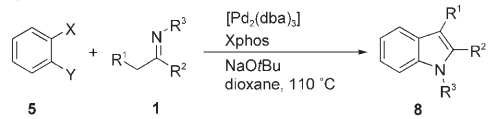
Regarding the regioselectivity of the process, the reaction with the imine derived from 2-heptanone **1i** (Table 1, entry 9) gave a 5:1 mixture of the 2-substituted indole **8i**, which comes from the initial C-arylation of the less substituted position of the imine, and the 2,3-disubstituted indole **8i′**, which is derived from the initial arylation at the more substituted position. Although the selectivity achieved so far is only modest, it is a promising and interesting result, as the Fischer indole synthesis, the most popular method to prepare indoles from ketones, gives precisely the opposite regioisomer under the standard reaction conditions.[19]

On the other hand, particularly important is the example represented in Table 1, entry 14, in which imine **1e** is treated with the unsymmetrical 1-benzyloxymethyl-4-bromo-3-chlorobenzene **5d**. Two different regioisomeric indoles could be formed in this reaction; however, only the isomer **8l** was detected in the crude reaction mixture. The regioselectivity of the process can be explained by taking into account the different reactivity of bromides and chlorides towards oxidative addition to Pd complexes. Thus, the first step is the reaction of the imine with the carbon atom of the arene that carries the bromine atom, and this step determines the regioselectivity of the final product.

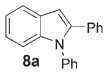
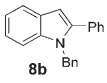
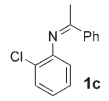
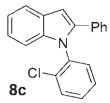
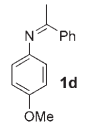
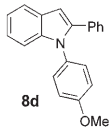
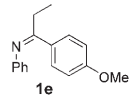
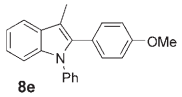
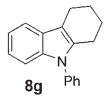
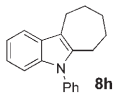
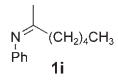
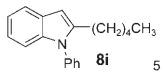
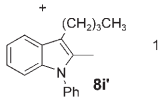
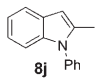
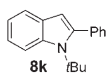
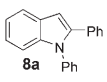
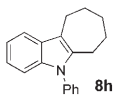
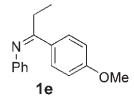
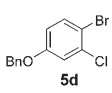
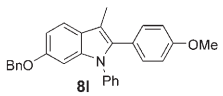
This new methodology represents an original new method for the construction of the important indole heterocycle[20,21] from readily available starting materials, such as *o*-dihaloarenes[22] and imines. In this context, we have recently reported a new method for the synthesis of imines by Pd-catalyzed amination of haloalkenes with primary amines[23] that uses catalytic conditions very similar to those employed in the preparation of the indoles. Therefore, we decided to investigate whether it might be possible to develop a cascade process that would provide indoles from haloalkenes, amines, and *o*-dihaloarenes in a truly three-component reaction promoted by Pd.

In an initial experiment, we treated a mixture of α-bromostyrene, aniline, and *o*-dibromobenzene under the same reaction conditions described above, but with a larger amount of base. To our delight, we obtained cleanly the corresponding indole with an overall yield comparable to that presented in Table 1 (entry 1). It is important to note that the indole is built in a three-component cascade process in which

Table 1: Synthesis of indoles from ketimines and *o*-dihalobenzenes.[a]

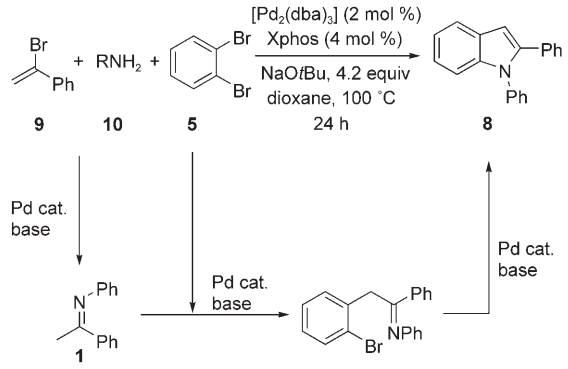


5 1 8

Entry	Imine **1**	Dihalide **5**	Indole **8**	Yield[b] [%]
1	 **1a**	 **5a**	 **8a**	86
2	 **1b**	**5a**	 **8b**	56
3	 **1c**	**5a**	 **8c**	77
4	 **1d**	**5a**	 **8d**	80
5	 **1e**	**5a**	 **8e**	66
6	 **1f**	**5a**	 **8f**	86
7	 **1g**	**5a**	 **8g**	66
8	 **1h**	**5a**	 **8h**	80
9	 **1i**	**5a**	 **8i** 5  **8i'** 1	73
10	 **1j**	**5a**	 **8j**	71
11	 **1k**	**5a**	 **8k**	72
12	 **1a**	 **5b**	 **8a**	80
13	 **1h**	 **5c**	 **8h**	87
14	 **1e**	 **5d**	 **8l**	70

[a] Reaction conditions: **1** (1 mmol), **5** (1 mmol), $[Pd_2(dba)_3]$ (2 mol%), Xphos (4 mol%), NaO*t*Bu (2.8 mmol), dioxane (2 mL), 110°C, 14 h. Reaction times were not optimized. [b] Yield of isolated product after column chromatography.

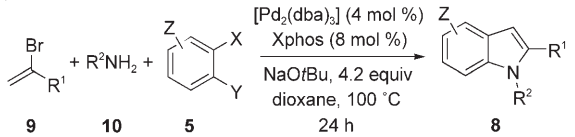
the same Pd catalyst promotes three different and independent reactions: 1) formation of the imine by alkenyl amination, 2) α-arylation of the imine, and 3) intramolecular N-arylation (Scheme 4).

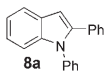


Scheme 4. Cascade three-component synthesis of indole **8a** through a sequence of N-alkenylation, C-arylation, and intramolecular N-arylation.

We have conducted a preliminary study of the scope of the multicomponent process (Table 2). The reactions examined provided the desired indoles with good yields, considering that three independent events take place by action of the

Table 2: Pd-catalyzed three-component synthesis of indoles from primary amines, bromoalkenes, and dihalobenzenes.[a]



Entry	Amine	Bromo-alkene	Dihalide **5**	Indole **8**	Yield[b] [%]
1[c]	$PhNH_2$		 **5a**	 **8a**	76
2[d]	$PhNH_2$		**5b**	**8a**	77
3	$BnNH_2$		**5a**	**8b**	65
4[e]	$PhNH_2$		**5a**	**8j**	68
5	$PhNH_2$		**5d**	**8m**	57

[a] Reaction conditions: bromoalkene (1 mmol), **10** (1 mmol), **5** (1 mmol), $[Pd_2(dba)_3]$ (4 mol%), Xphos (8 mol%), NaO*t*Bu (4.2 mmol), dioxane (3 mL), 110°C, 24 h. Reaction times were not optimized. [b] Yield of isolated product after column chromatography. [c] The reaction was conducted with $[Pd_2(dba)_3]$ (2 mol%) and Xphos (4 mol%). [d] Complete after 72 h. [e] The reaction was kept at 50°C for 3 h until formation of the imine was completed as determined by GC, and then heated up to 90°C for 14 h. Bn = benzyl.

same catalyst. Moreover, the three-component reaction retains the same properties of the tandem synthesis of indoles in terms of the generality of the dihaloarene (both bromo- and chloroarenes are tolerated), the amine (aryl- and benzyl-substituted amines have been employed), the bromoalkene (aryl- and alkyl-substituted systems are tolerated), and the chemoselectivity (Table 2, entry 5).

Notably, a key in the success of this cascade process is the exquisite chemoselectivity of the different cross-coupling events.[7] Thus, the higher reactivity of the bromoalkenes when compared with the haloarenes in the oxidative addition to Pd permits the formation of the imine **1**, instead of the aryl amination reaction. Then, the dihaloarene is incorporated in the second step only when all the alkenyl halide has been consumed.

In summary, we have presented a new efficient method for the synthesis of indoles from readily available starting materials, through Pd-catalyzed domino and three-component/cascade processes. We believe that the present methodology represents a competitive alternative for the preparation of structurally diverse indoles. Finally, this paper introduces for the first time the azaallylic anion—obtained by deprotonation of an imine—as a very promising three-atom synthon for transition-metal-catalyzed syntheses of heterocycles. We are currently investigating further applications of this concept.

Received: October 27, 2006
Published online: January 16, 2007

Keywords: arylation · indoles · multicomponent reactions · palladium · synthetic methods

[1] a) *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley, Hoboken, NJ, **2002**; b) *Metal-Catalyzed Cross-Coupling Reactions* (Eds.: A. de Meijere, F. Diederich), Wiley-VCH, Weinheim, **2004**; c) J. Tsuji, *Palladium Reagents and Catalysts*, Wiley, Chichester, **2004**.

[2] For recent revisions of palladium-catalyzed C–N bond-forming reactions, see: a) L. Jiang, S. L. Buchwald, *Metal-Catalyzed Cross Coupling Reactions*, *Vol. 2*, 2nd ed., Wiley-VCH, Weinheim, **2004**, pp. 699–760; b) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131; c) J. F. Hartwig in *Handbook of Organopalladium Chemistry of Organic Synthesis*, Vol. 1, Wiley-Interscience, New York, **2002**, pp. 1051–1096; d) B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599; e) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127.

[3] a) A. F. Littke, G. C. Fu, *Angew. Chem.* **2002**, *114*, 4350; *Angew. Chem. Int. Ed.* **2002**, *41*, 4176; b) A. Zapf, M. Beller, *Chem. Commun.* **2005**, 431; c) M. Muira, *Angew. Chem.* **2004**, *116*, 2251; *Angew. Chem. Int. Ed.* **2004**, *43*, 2201.

[4] a) K. L. Billingsley, K. W. Anderson, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 3564; *Angew. Chem. Int. Ed.* **2006**, *45*, 3484; b) K. W. Anderson, R. E. Tundel, T. Ikawa, R. A. Altman, S. L. Buchwald, *Angew. Chem.* **2006**, *118*, 6673; *Angew. Chem. Int. Ed.* **2006**, *45*, 6523, and references therein.

[5] a) R. B. Bedford, C. S. J. Cazin, *Chem. Commun.* **2002**, 2310; b) Y.-Q. Fang, M. Lautens, *Org. Lett.* **2005**, *7*, 3549; c) A. Fayol, Y.-Q. Fang, M. Lautens, *Org. Lett.* **2006**, *8*, 4203.

[6] For a recent account, see: J. Barluenga, C. Valdés, *Chem. Commun.* **2005**, 4891.

[7] J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Eur. J.* **2005**, *11*, 2276.

[8] For a review of the application of azaallyl anions in classic heterocyclic synthesis, see: S. Mangelinckx, N. Giubellina, N. De Kimpe, *Chem. Rev.* **2004**, *104*, 2353.

[9] a) M. Palucki, S. L. Buchwald, *J. Am. Chem. Soc.* **1997**, *119*, 11108; b) D. W. Old, J. P. Wolfe, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 9722; c) J. M. Fox, X. Huang, A. Chieffi, S. L. Buchwald, *J. Am. Chem. Soc.* **2000**, *122*, 1360; d) T. Hamada, A. Chieffi, J. Åhman, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 1261.

[10] a) B. C. Hamann, J. F. Hartwig, *J. Am. Chem. Soc.* **1997**, *119*, 12382; b) M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **1999**, *121*, 1473.

[11] a) T. Satoh, Y. Kawamura, M. Miura, M. Nomura, *Angew. Chem.* **1997**, *109*, 1820; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1740; b) T. Satoh, Y. Kametani, Y. Terao, M. Miura, M. Nomura, *Tetrahedron Lett.* **1999**, *40*, 5345; c) Y. Terao, Y. Fukuoka, T. Satoh, M. Miura, M. Nomura, *Tetrahedron Lett.* **2002**, *43*, 101.

[12] a) A. Ehrentraut, A. Zapf, M. Beller, *Adv. Synth. Catal.* **2002**, *344*, 209; b) M. S. Viciu, R. F. Germaneau, S. P. Nolan, *Org. Lett.* **2002**, *4*, 4053; c) G. Adjabeng, T. Brenstrum, C. S. Frampton, A. J. Robertson, J. Hillhouse, J. McNulty, A. Capretta, *J. Org. Chem.* **2004**, *69*, 5082; d) V. Lavallo, Y. Canac, C. Präsang, B. Donnadieu, G. Bertrand, *Angew. Chem.* **2005**, *117*, 5851; *Angew. Chem. Int. Ed.* **2005**, *44*, 5705.

[13] a) M. Jørgensen, S. Lee, X. Liu, J. P. Wolkowski, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 12557; b) X. Liu, J. F. Hartwig, *J. Am. Chem. Soc.* **2004**, *126*, 5182.

[14] T. Hama, D. A. Culkin, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 4976, and references therein.

[15] X. Huang, W. Anderson, D. Zim, L. Jiang, A. Klapars, S. L. Buchwald, *J. Am. Chem. Soc.* **2003**, *125*, 6653.

[16] J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550.

[17] S. D. Edmonson, A. Mastrachio, E. R. Parmee, *Org. Lett.* **2000**, *2*, 1109.

[18] a) H. Siebeneicher, I. Bytschkov, S. Doye, *Angew. Chem.* **2003**, *115*, 3151; *Angew. Chem. Int. Ed.* **2003**, *42*, 3042; b) M. C. Willis, G. N. Brace, I. P. Holmes, *Angew. Chem.* **2005**, *117*, 407; *Angew. Chem. Int. Ed.* **2005**, *44*, 403.

[19] D. Zhao, D. L. Hughes, D. R. Bender, A. M. DeMarco, P. J. Reider, *J. Org. Chem.* **1991**, *56*, 3001.

[20] For general reviews on the synthesis of indoles, see: a) U. Pindur, R. Adam, *J. Heterocycl. Chem.* **1988**, *25*, 1; b) C. J. Moody, *Synlett* **1994**, 681; c) R. J. Sundberg, *Indoles*, Academic Press, San Diego, **1996**; d) G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1* **2000**, 1045.

[21] For reviews on Pd-catalyzed indole syntheses, see: a) J. J. Li, G. W. Gribble, *Palladium in heterocyclic chemistry*, Pergamon, Oxford, **2000**; b) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873.

[22] For some modern methods for the synthesis of *o*-dihaloarenes, see: a) R. Sanz, M. P. Castroviejo, Y. Fernández, F. J. Fañanás, *J. Org. Chem.* **2005**, *70*, 6548; b) K. Menzel, E. L. Fischer, L. DiMichele, D. E. Frantz, T. D. Nelson, M. H. Kress, *J. Org. Chem.* **2006**, *71*, 2188.

[23] a) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Commun.* **2002**, 2362; b) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Commun.* **2004**, 1400; c) J. Barluenga, M. A. Fernández, F. Aznar, C. Valdés, *Chem. Eur. J.* **2004**, *10*, 494.

