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Synthesis of Substituted Carbazoles by a Vinylic to Aryl Palladium Migration Involving Domino C–H Activation Processes

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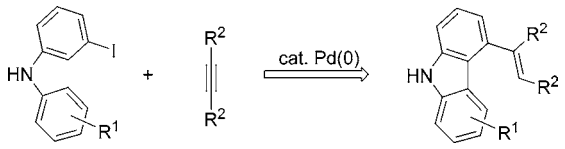
ABSTRACT



Substituted carbazoles are readily prepared in good yields by the palladium-catalyzed cross-coupling of alkynes and *N*-(3-iodophenyl)anilines. This process proceeds by carbopalladation of the alkyne, heteroatom-directed vinylic to aryl palladium migration, and ring closure involving two consecutive C–H activation processes. The process has also been expanded to the synthesis of an indole.

Palladium-catalyzed C−H activation has attracted great interest because this metal possesses an impressive ability to insert into unactivated C−H bonds and subsequently affords a wide variety of useful synthetic processes.[1] Recently, several through-space palladium rearrangements, proceeding by vinylic to aryl,[2] aryl to aryl,[3] and alkyl to aryl[4] palladium migration involving simultaneous C−H activation, have been disclosed. This shift of palladium appears to be quite general, and it provides a novel way to introduce palladium into a specific location within an organic molecule, thus providing unique opportunities for organic synthesis.

Described herein are the successful demonstration of a vinylic to aryl palladium migration and an efficient synthesis of substituted carbazole derivatives. Carbazoles are crucial building blocks in organic synthesis and the core structures of numerous biologically active compounds.[5,6] A wide range of biologically interesting carbazole derivatives have been prepared by metal-catalyzed processes, particularly those employing palladium. For example, the palladium-catalyzed cyclization of *N*,*N*-diarylamines[7] and the heteroannulation of 1,3-dienes[8] have been extensively investigated and provide efficient approaches to the synthesis of carbazoles.

In earlier work, the reaction of iodobenzene, diphenylacetylene, 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, 2 equiv of NaOAc, and 1 equiv of *n*-Bu_4NCl (TBAC) in *N*,*N*-dimethylformamide (DMF) at 100 °C afforded a 62% yield of 9-benzylidene-9*H*-fluorene after 24 h through a vinylic to aryl palladium migration process.[2] However, when we treated

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(4) Huang, Q.; Fazio, A.; Dai, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460.

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(6) For a recent review, see: (a) Knolker, H.-J.; Kethiri, R. R. *Chem. Rev.* **2002**, *102*, 4303 and references therein.

(7) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113 and references therein.

(8) (a) O'Connor, J. M.; Stallman, B. J.; Clark, W. G.; Shu, A. Y. L.; Spada, R. E.; Stevenson, T. M.; Dieck, H. A. *J. Org. Chem.* **1983**, *48*, 807. (b) Larock, R. C.; Berrios-Peña, N.; Narayanan, K. *J. Org. Chem.* **1990**, *55*, 3447.

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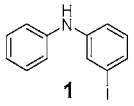
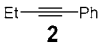
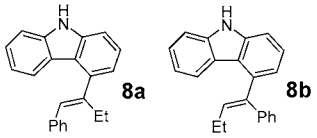
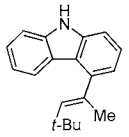
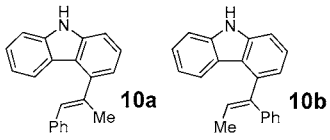
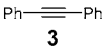
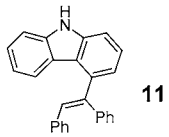
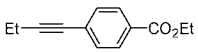
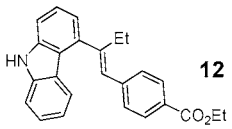
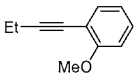
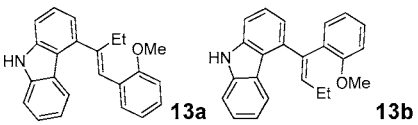
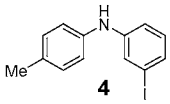
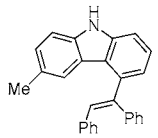
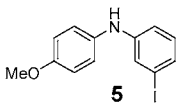
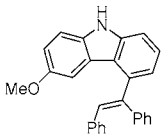
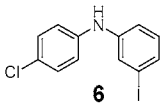
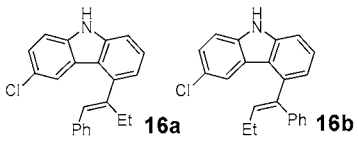
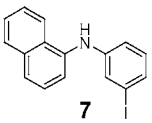
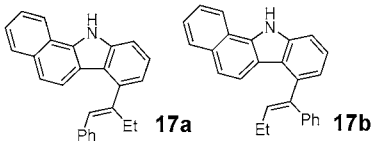
Table 1. Synthesis of Substituted Carbazoles[a]

entry	aryl iodide	alkyne	product(s)	% yield[b]
1	 **1**	 **2**	 **8a** **8b**	73 (10:1)
2	**1**		 **9**	44
3	**1**		 **10a** **10b**	65 (12:1)
4	**1**	 **3**	 **11**	69
5	**1**		 **12**	71
6	**1**		 **13a** **13b**	68 (10:1)
7	 **4**	**3**	 **14**	61
8	 **5**	**3**	 **15**	75
10	 **6**	**2**	 **16a** **16b**	65 (10:1)
11	 **7**	**2**	 **17a** **17b**	64 (10:1)

[a] All reactions were conducted on a 0.25 mmol scale at 100 °C for 6 h, using 5 mol % $Pd(OAc)_2$, 5 mol % bis(diphenylphosphino)methane (dppm), and 2 equiv of CsO_2CCMe_3 (CsPiv) in DMF (4 mL), and the ratio of aryl iodide to alkyne was 1:1 (sealed vial, under Ar). [b] The ratio of **a** to **b** as determined by ^{1}H NMR spectroscopy is reported in parentheses.

N-phenyl-3-iodoaniline and 1-phenyl-1-butyne in the same fashion, after 24 h, only 20% of the desired carbazole product was isolated. The starting materials were completely consumed, and several byproducts were observed by GC-MS analysis. We subsequently found that our recently reported "optimal" reaction conditions for aryl to aryl palladium migration [5 mol % $Pd(OAc)_2$, 5 mol % bis(diphenylphosphino)-methane (dppm), and 2 equiv of CsO_2CCMe_3 (CsPiv) in DMF at 100 °C][3a,b] afforded a much better yield. Under these reaction conditions, the reaction was complete in 6 h and we were able to obtain a 73% yield of a mixture of isomeric carbazoles (see entry 1, Table 1). Surprisingly, this

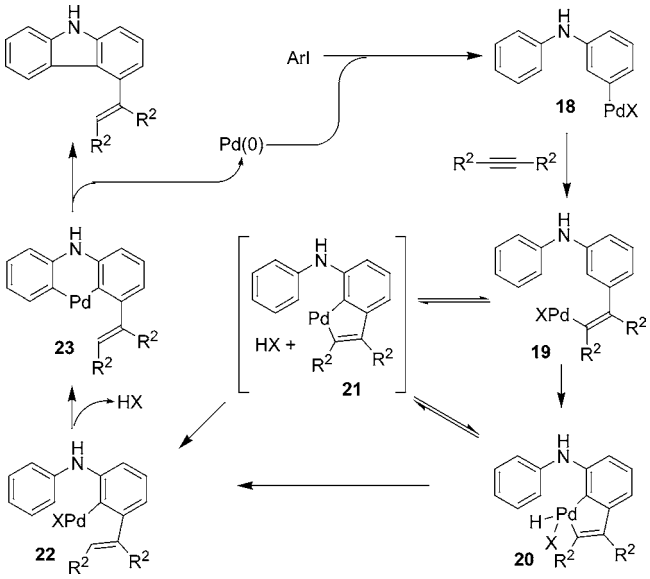
process is quite regioselective for this specific unsymmetrical alkyne, affording the two regioisomers **8a**/**8b** in a 10:1 ratio.

We next examined the reaction using various internal alkynes in order to determine the scope and limitations of this process, as shown in Table 1. 4,4-Dimethyl-2-pentyne afforded only one regioisomer **9** as expected, but the overall yield was only 44%, probably due to the fact that the boiling point of this alkyne is lower than the reaction temperature (entry 2). 1-Phenyl-1-propyne afforded a 65% yield of two regioisomers **10a**/**10b** in a 12:1 ratio (entry 3), and diphenylacetylene afforded a 69% yield of one isomer **11** (entry 4). We also examined the reaction of several aryl acetylenes bearing electron-donating and electron-withdrawing groups. When 1-(*p*-nitrophenyl)-1-butyne was employed as the starting material, a very messy reaction was observed and none of the desired product was evident by GC-MS analysis. However, when a relatively moderate electron-withdrawing group (CO_2Et) was present on the phenyl ring of the alkyne, a 71% yield of carbazole **12** was isolated by flash chromatography (entry 5). An analogous alkyne bearing an *o*-methoxy group afforded a 68% yield of the anticipated 10:1 mixture of carbazoles **13a** and **13b**, respectively (entry 6).

We have also examined the reaction of a number of anilines bearing a substituent on the aromatic ring undergoing substitution by the arylpalladium intermediate (see the later mechanistic discussion). The preparation of the desired starting materials was accomplished by the palladium-catalyzed amination of 1,3-diiodobenzene with the corresponding anilines (see the Supporting Information).[9] Anilines with both electron-rich and electron-poor functional groups on the arene undergoing eventual substitution afforded fairly good yields of carbazoles (entries 7−10). It appears that this approach to carbazoles can tolerate a variety of functional groups. We have also examined the regioselectivity of ring closure by employing *N*-(3-iodophenyl)naphthalen-2-amine (entry 11). Here, cyclization might occur at either the 2 position or the 8 position of the naphthalene. The only products observed are those formed by closure at the 2 position by the presumed intermediacy of a six-membered ring palladacycle as opposed to the analogous seven-membered ring palladacycle required to generate the product of attack at the 8 position.

A plausible mechanism for this process is proposed in Scheme 1. Intermediate **18** is first generated by oxidative addition of the aryl iodide to Pd(0). Subsequent intermolecular carbopalladation[10] would be expected to afford intermediate **19**. The resulting vinylic palladium intermediate undergoes simultaneous C−H activation and palladium migration from the vinylic position to the aryl position generating intermediate **22**. During the palladium migration, an equilibrium between palladacycles **20** and **21** probably is involved,[11] or the rearrangement may proceed through an

Scheme 1. Proposed Mechanism



organopalladium(II) palladacycle and then a palladium π-arene intermediate.[12] Although intermediate **22** is relatively hindered, it may be stabilized by coordination of Pd to the neighboring nitrogen. In addition, the electron-rich nature of the arene undergoing substitution probably also contributes to the shift of palladium.[3b] When R^2 is a phenyl group, the Pd moiety can migrate to either of two different *ortho* positions of the arene and then generate either a carbazole or a fluorene, but only the carbazole product is observed, which suggests that the Pd only migrates to the position that is *ortho* to the nitrogen. This selective migration is probably due to coordination between the *ortho* nitrogen and the palladium moeity, which is not available if Pd migrates to the position *para* to the nitrogen. The six-membered ring intermediate **23** is then presumably generated by a second C−H activation, and the desired products **8**−**17** are formed after reductive elimination.

Intramolecular Heck reactions have been successfully used to prepare indole derivatives.[13] By vinylic to aryl Pd migration, an arylpalladium intermediate can be readily generated, which might then undergo intramolecular Heck reaction to afford indole derivatives. As shown in eq 1, *N*-allyl-3-iodoaniline (**24**) and 1-phenyl-1-butyne were allowed to react with 5 mol % $Pd(OAc)_2$, 5 mol % dppm, and 2 equiv of CsO_2CCMe_3 in DMF at 100 °C. After 3 h, aryl iodide **24** was completely consumed and a 45% yield of two isomeric indoles **25a** and **25b** was observed in a 10:1 ratio,

(9) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.

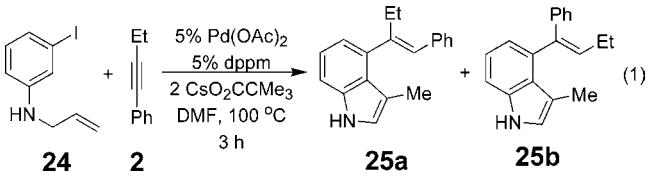
(10) For typical examples of intermolecular carbopalladation, see: (a) Sugihara, T.; Copéret, C.; Owczarczyk, Z.; Harring, L.; Negishi, E. *J. Am. Chem. Soc*. **1994**, *116*, 7923. (b) Gevorgyan, V.; Quan, L.; Yamamoto, Y. *Tetrahedron Lett*. **1999**, *40*, 4089. (c) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 173. (d) Larock, R. C.; Reddy, C. *J. Org. Chem.* **2002**, *67*, 2027.

(11) (a) Catellani, M.; Motti, E.; Ghelli, S. *Chem. Commun*. **2000**, 2003. (b) For a review, see: Catellani, M. *Synlett.* **2003**, *3*, 298. (c) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 1699. (d) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1023. (e) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 103.

(12) Campora, J.; Lopez, J. A.; Palma, P.; Pedro, V.; Edzard, S.; Ernesto, C. *Angew. Chem., Int. Ed.* **1999**, *38*, 147 and references therein.

(13) (a) Odle, R.; Blevins, B.; Ratcliff, M.; Hegedus, L. S. *J. Org. Chem.* **1980**, *45*, 2709. (b) Larock, R. C.; Babu, S. *Tetrahedron. Lett.* **1987**, *28*, 5291. (c) Caddick, S.; Kofie, W. *Tetrahedron Lett.* **2002**, *43*, 9347 and references therein.

respectively. This preliminary work demonstrates that Pd migration intermediates can also be trapped by an intramolecular Heck reaction, affording an efficient way to prepare substituted indole derivatives.



24 **2** **25a** **25b**

In conclusion, a novel heteroatom-directed vinylic to aryl palladium migration process affords an efficient and general way to prepare biologically interesting carbazole and indole derivatives. Work is currently underway to better understand the mechanism of this interesting process and to extend it to additional heterocyclic systems.

Acknowledgment. We deeply appreciate the financial support of the National Science Foundation and thank Johnson Matthey, Inc., and Kawaken Fine Chemical Co. for donations of $Pd(OAc)_2$.

Supporting Information Available: Preparation and characterization of the aryl iodides and characterization of the carbazole and indole products in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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