ORGANIC LETTERS

2010
Vol. 12, No. 23
5422−5425

Pd-NHC Catalyzed Cyclopentannulation of Diazabicyclic Alkenes with *ortho*-aryl halides

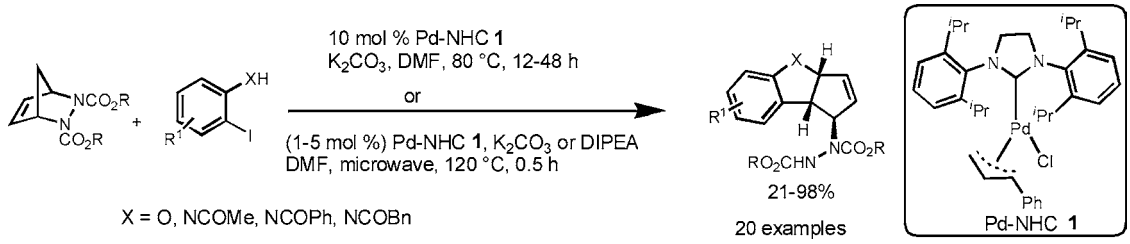
B. A. Bhanu Prasad, Alexander E. Buechele, and Scott R. Gilbertson*

Department of Chemistry, University of Houston, Houston, Texas 77204, United States

srgilbe2@central.uh.edu

Received September 21, 2010

ABSTRACT



Pd-NHC catalyzed cyclopentannulation of diazabicyclic alkenes with *ortho*- functionalized aryl halides is described. In all the reactions, a single diastereomer of the cyclopentannulated product is observed, and this reaction is very efficient under microwave irradiation.

The transition-metal catalyzed ring-opening of diazabicyclic alkenes with various nucleophiles, including organometallic catalysts such as palladium,[1] copper[2] and rhodium,[3] is a useful method. Until recently, the one-pot ring-opening and ring-closing of diazabicycles with *ortho*- functionalized aryl halides to yield cyclopentannulated cyclopenta[*b*]benzofurans was not known.[4] For the past few years, we have been involved in developing new methods for the synthesis of *N*-heterocyclic carbene (NHC) ligands and in the development of NHC−metal complexes for new reactions.[5] Herein reported is the Pd-NHC catalyzed cyclopentannulation of diazabicyclic alkenes with *ortho*-functionalized aryl halides.

The chemsitry reported here provides cyclopenta[*b*]benzofurans and cyclopenta[*b*]indolines, two structures that are contained in a variety of biologically interesting molecules (Figure 1).[6,7] The most common methods for their construction are acid/metal catalyzed or photochemical oxidative cyclization of 2-allylphenols[8,9] and heterocyclization of alkenylarylamines.[10,11] In many of these methods, several

(1) (a) Sajisha, V. S.; Smitha, M.; Anas, S.; Radhakrishnan, K. V. *Tetrahedron* **2006**, *62*, 3997–4002. (b) John, J.; Anas, S.; Sajisha, V. S.; Viji, S.; Radhakrishnan, K. V. *Tetrahedron Lett.* **2007**, *48*, 7225–7227. (c) Luna, A. P.; Cesario, M.; Bonin, M.; Micouin, L. *Org. Lett.* **2003**, *5*, 4771–4774. (d) John, J.; Sajisha, V. S.; Mohanlal, S.; Radhakrishnan, K. V. *Chem. Commun.* **2006**, 3510–3512.

(2) (a) Pineschi, M.; Del Moro, F.; Crotti, P.; Macchia, F. *Org. Lett.* **2005**, *7*, 3605–3607. (b) Bournaud, C.; Falciola, C.; Lecourt, T.; Rosset, S.; Alexakis, A.; Micouin, L. *Org. Lett.* **2006**, *8*, 3581–3584. (c) Palais, L.; Mikhel, I. S.; Bournaud, C.; Micouin, L.; Falciola, C. A.; Vuagnoux-d'Augustin, M.; Rosset, S.; Bernardinelli, G.; Alexakis, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7462–7465.

(3) (a) Menard, F.; Lautens, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2085–2088. (b) Menard, F.; Weise, C. F.; Lautens, M. *Org. Lett.* **2007**, *9*, 5365–5367. (c) Crotti, S.; Bertolini, F.; Macchia, F.; Pineschi, M. *Chem. Commun.* **2008**, 3127–3129. (d) Bertolini, F.; Macchia, F.; Pineschi, M. *Tetrahedron Lett.* **2006**, *47*, 9173–9176.

(4) John, J.; Indu, U.; Suresh, E.; Radhakrishnan, K. V. *J. Am. Chem. Soc.* **2009**, *131*, 5042–5043.

(5) (a) Xu, G.; Gilbertson, S. R. *Org. Lett.* **2005**, *7*, 4605–4608. (b) Prasad, B. A. B.; Gilbertson, S. R. *Org. Lett.* **2009**, *11*, 3710–3713.

(6) (a) Pedram, B.; Van Oeveren, C. A.; Zhi, L.; Shen, Y. International Patent PCT/US2006/023111, 2006. (b) Gao, H.; Stack, G. P.; Sabb, A. L. International Patent PCT/US2003/012691, 2003. (c) Engelmeier, D.; Hadacek, F.; Pacher, T.; Vajrodaya, S.; Greger, H. *J. Agric. Food Chem.* **2000**, *48*, 1400–1404. (d) Yamamura, S.; Hirata, Y. *Tetrahedron* **1969**, *19*, 1485–1496. (e) Irie, T.; Suzuki, M.; Kurosawa, E.; Masamune, T. *Tetrahedron* **1970**, *26*, 3271–3277. (f) Ohta, K.; Takagi, M. *Phytochemistry* **1977**, *16*, 1062–1065. (g) Ojika, M.; Shizuri, Y.; Yamada, K. *Phytochemistry* **1982**, *21*, 2410–2411. (h) Shizuri, Y.; Yamada, A.; Yamada, K. *Phytochemistry* **1984**, *23*, 2672–2411.

(7) (a) Sabb, A. L.; Vogel, R. L.; Nelson, J. A.; Rosenzweig-Lipson, S. J.; Welmaker, G. S.; Sabalski, J. E. U.S. Patent Appl. Publ. No 2002/0107242 A1, Published August 8, 2002 . (b) Welmaker, G. S.; Sabalski, J. E.; Smith, M. D. U.S. Patent Appl. Publ. No 2002/0058689 A1, Published May 16, 2002.

10.1021/ol102270r
Published on Web 11/02/2010

synthetic steps are required to prepare the starting precursors and the final cyclized products are often a mixture of isomers.

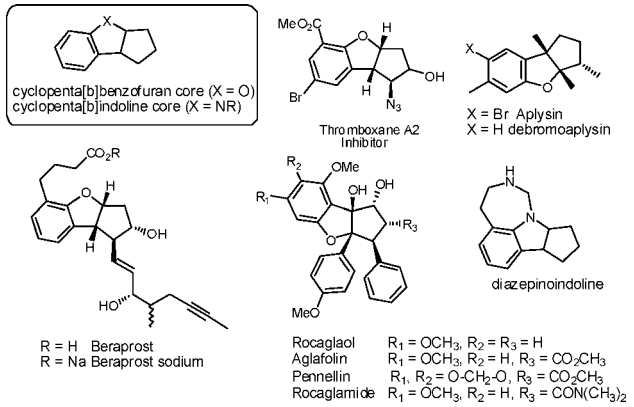
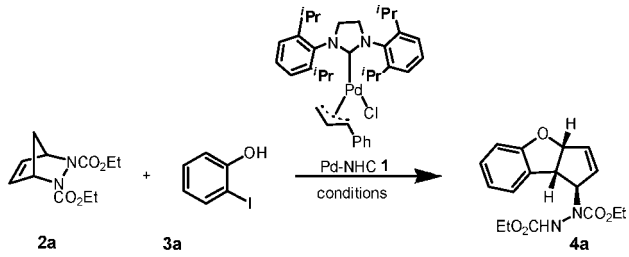


Figure 1. Biologically important cyclopenta[*b*]benzofurans and cyclopenta[*b*]indolines.

Table 1. Optimization Studies for Cyclopentannulation of Diazabicycles in the Presence of Pd-NHC **1**



2a **3a** **4a**

entry	**2a** *(equiv)*	**3a** *(equiv)*	**1** *(mol %)*	K_2CO_3 *(equiv)*	reaction conditions	yield[c] *(%)*
1	1	1.5	10	2	toluene, 80 °C, 24 h[a]	nr
2	1	1.5	10	2	DMF, 80 °C, 24 h[a]	nr
3	1	1.5	10	2	toluene, 80 °C, 24 h	90
4	1	1.5	10	2	CH_3CN, 80 °C, 24 h	78
5	1	1.5	10	2	DMF, 80 °C, 24 h	97
6	2	1	10	2	DMF, 80 °C, 24 h	54
7	***1***	***1.1***	***10***	***1***	***DMF, 80 °C, 12 h***	***98***
8	1	1.1	10	1	DMF, rt, 38 h	< 5
9	1	1.1	5	1	DMF, 80 °C, 36 h	97
10	1	1.1	10	1	MW, 80 °C, 0.5 h[b,d]	nr
11	1	1.1	10	—	MW, 80 °C, 0.5 h	nr
12	1	1.1	10	1	MW, 120 °C, 0.5 h	98
13	***1***	***1.1***	***5***	***1***	***MW, 120 °C, 0.5 h***	***98***
14	1	1.1	2	1	MW, 120 °C, 50 min	97
15	1	1.1	1	1	MW, 120 °C, 1 h	96

[a] Two equivalents of Bu_4NCl or Bu_4NBr were used as additives. [b] One equivalent of Bu_4NCl or Bu_4NBr were used as additives. [c] Isolated yields. [d] All microwave reactions where carried out in DMF solvent. There was no desired product formation in THF, DCE, 1,4-dioxane. Unreacted starting material was recovered.

Initial experiments, based on previous literature precedent, using tetraalkylammonium salts as additives failed to provide the desired product (Table 1, entries 1 and 2). However catalysis with complex **1**, without such additives, led to nearly exclusive formation of the desired cyclopentannulated product as a single diastereomer (Table 1, entries 3−5). This is in contrast to the results observed by Radhakrishnan et al. where the anion of the quaternary ammonium salt (an additive) purportedly plays a key role in regeneration and stabilization of the Pd(0) species, facilitating the catalytic cycle.[4] Given their electron rich complexation and σ-donor character with metals, *N*-heterocyclic carbenes do not appear to require an external ionic source to stabilize the metal, and when such species were added, they inhibited the reaction.

Excess diazabicyclic alkene, resultes in the formation of the cyclic product in poor yield (entry 6). Reducing the amount of iodophenol to 1.1 and base to 1.0 equivalents with respect to **2a** in anhydrous DMF at 80 °C provides the **4a** in 98% yield in 12 h (entry 7). There was no significant change in terms of yield when 5 mol % of the catalyst was used but the reaction required 36 h to reach completion (entry 9).

Since the cyclopentannulation of diazabicyclic alkenes with 2-iodophenol is very efficient with 5 mol % of the Pd-NHC catalyst, it was decided to study the reaction further by reducing the amount of catalyst and using microwave irradiation. Under microwave conditions, the reaction was complete in 30 min with 5 mol % Pd-NHC. With the use of 1 mol % of the catalyst the reaction was complete in one hour with a slight diminution in yield (Table 1, entries 12−15). Although the cyclopentannulation could be achieved with 1 mol % of the catalyst, due to decrease in yield, further studies were carried out with 5 mol % of the Pd-NHC catalyst under microwave irradiation.

With these results in hand, the scope of this reaction was investigated. As shown in Table 2, the reaction is general for a range of iodophenols (**3a**−**3m**) and diazabicyclic alkenes (**2a**−**2c**). In all cases, the cyclopentannulated products were obtained in good to excellent yields, with a number of functional groups on the iodophenol being tolerated under the optimized conditions. Pivaloyl or tosyl protected amino 2-iodophenol gave the cyclopenta[*b*]benzofurans in good to high yields (Table 2, entries 6 and 7). Alkyl and phenyl

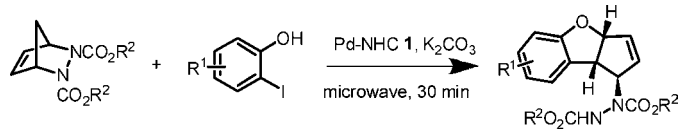
(8) (a) Fráter, V. G.; Schmid, H. *Helv. Chim. Acta* **1967**, *50*, 255–262. (b) Orovecz, O.; Kovács, P.; Kolonits, P.; Kaleta, Z.; Párkányi, L.; Szabó, É.; Novák, L. *Synthesis* **2003**, *104*, 3–1048. (c) Kita, Y.; Futamura, J.; Ohba, Y.; Sawama, Y.; Ganesh, J. K.; Fujioka, H. *Tetrahedron Lett.* **2003**, *44*, 411–413. (d) Hosokawa, T.; M:iyagi, S.; Shun-Ichi, M.; Sonoda, A. *J. Org. Chem.* **1978**, *43*, 2752–2757. (e) Emrich, D. E.; Larock, R. C. *J. Organomet. Chem.* **2004**, *689*, 3756–3766. (f) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett.* **1999**, *40*, 8271–8272.

(9) (a) Yamashita, M.; Okuyama, K.; Kawasaki, I.; Ohta, S. *Tetrahedron Lett.* **1995**, *36*, 5603–5606. (b) Yamashita, M.; Okuyama, K.; Kawajiri, T.; Takada, A.; Inagaki, Y.; Nakano, H.; Tomiyama, M.; Ohnaka, A.; Terayama, I.; Kawasaki, I.; Ohta, S. *Tetrahedron* **2002**, *58*, 1497–1505. (c) Noland, W. E.; Kedrowski, B. L. *J. Org. Chem.* **2002**, *67*, 8366–8373. (d) Srikrishna, A.; Babu, N. C.; Rao, M. S. *Tetrahedron Lett.* **2004**, *60*, 2125–2130. (e) Orovecza, O.; Kovácsc, P.; Kolonitsa, P.; Kaletaa, Z.; Párkányic, L.; Szabód, É.; Novák, L. *Synthesis* **2003**, *104*, 3–1048.

(10) (a) Chapman, O. L.; Eian, G. L. *J. Am. Chem. Soc.* **1968**, *90*, 5329–5330. (b) Gataullin, R. R.; Kazhanova, T. V.; IIyasova, L. T.; Fatykhov, A. A.; Spirikhin, L. V.; Abdrakhmanov, I. B. *Russ. Chem. Bull.* **1999**, *48*, 975–978.

(11) Reductive cyclization, see: (a) Scott, T. L.; Söderberg, B. C. G. *Tetrahedron* **2003**, *59*, 6323–6332. (b) Scott, T. L.; Burke, N.; Carrero-Martínez, G.; Söderberg, B. C. G. *Tetrahedron* **2007**, *63*, 1183–1190. For halocyclization, see: (c) Gataullin, R. R.; Ishberdina, R. R.; Shitikova, O. V.; Minnigulov, F. F.; Spirikhin, L. V.; Abdrakhmanov, I. B. *Chem. Heterocycl. Compd.* **2006**, *42*, 1025–1031. For Fisher indole cyclization, see: (d) Welmaker, G. S.; Sabalski, J. E. *Tetrahedron Lett.* **2004**, *45*, 4851–4854. For aryl radical cyclization, see: (e) Murphy, J. A.; Scott, K. A.; Sinclair, R. S.; Lewis, N. *Tetrahedron Lett.* **1997**, *41*, 7295–7298.

Table 2. Cyclopentannulation of Diazabicyclic Alkenes with 2-Iodophenols



entry	iodophenol	olefin	product[a]	yield (%)[b]
1	**3a**	R^2 = Et **2a**	**4a**	98
2	**3a**	R^2 = ^{i}Pr **2b**	**4b**	98
3	**3a**	R^2 = ^{t}Bu **2c**	**4c**	68
4	**3b**	R^2 = Et **2a**	**4d**	80
5	**3c**	R^2 = Et **2a**	**4e**	97
6	**3d**	R^2 = Et **2a**	**4f**	85
7	**3e**	R^2 = Et **2a**	**4g**	58
8	**3f**	R^2 = ^{i}Pr **2b**	**4h**	87
9[c]	**3g**	R^2 = Et **2a**	**4i**	21[d]
10	**3h**	R^2 = Et **2a**	**4j**	84
11	**3i**	R^2 = Et **2a**	**4k**	77
12	**3j**	R^2 = ^{i}Pr **2b**	**4l**	96
13	**3k**	R^2 = ^{i}Pr **2b**	**4m**	51
14	**3k**	R^2 = ^{t}Bu **2c**	**4n**	57
15	**3l**	R^2 = Et **2a**	**4o**	91[e]
16	**3m**	R^2 = Et **2a**	**4p**	90

[a] Unless otherwise mentioned, all reactions were performed with 1 equiv of diazabicyclic alkene, 1.1 equiv of iodophenol, 1 equiv of K_2CO_3 and 5 mol % catalyst, in dry DMF under microwave for 30 min at 120 °C. [b] Isolated yields. [c] Two equivalents of DIPEA was used as base. [d] Ring opened 3,4-disubstituted cyclopentene **7d** was obtained as a major product in 66% yield (see ref 12). [e] About 1.5:1 diastereomers.

substituted iodophenols also reacted efficiently giving the cyclized products in excellent yield (entries 4 and 5). Cyclopentannulation with 4-methyl ester substituted iodophenol **3f** was very clean and provided the product **4h** in high yield (entry 8). However, when the ester is substituted *ortho* to the −OH of 2-iodophenol **3g**, only starting diazabicyclic alkene was recovered. Presumably, hydrogen bonding between phenol −OH and the ester decreases the nucleophilicity of the −OH group. After several attempts with various bases, the cyclized product **4i** (entry 9) was obtained in 21% yield along with ring-opened 3,4-disubstituted cyclopentene **7d** (see reference[12]) in 66% yield when *N*,*N*′-diisopropylethylamine (DIPEA) was used as a base. In this particular case, the ring opened product was observed while in all other cases a single diastereomer of the cyclopentannulated product was isolated. Iodophenols having methylene alcohol functionality gave the desired pentannulation products in good yields without the need to protect

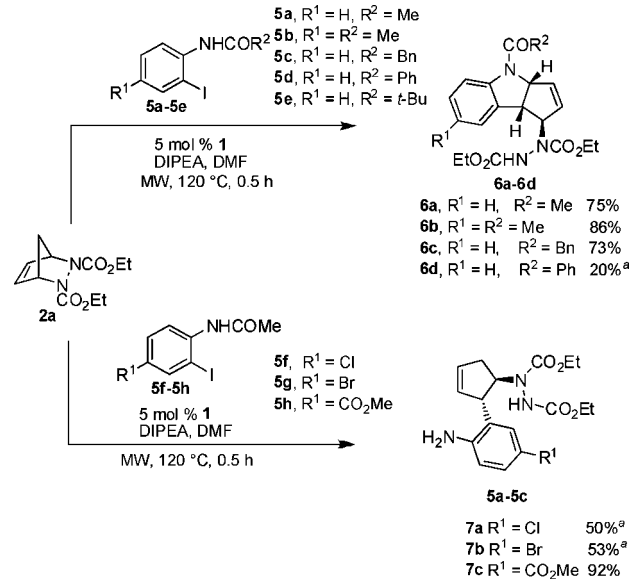
the alcohol functionality (Table 2, entries 10−14). In addition, the unprotected secondary alcohol containing iodophenol **3l** gave a ∼1.5:1 mixture of diastereomers **4o** (entry 15). Acetal protected 5-iodovanillin **3m** was stable under the reaction conditions and provided the desired cyclopenta[*b*]benzofuran **4p** in 90% yield (entry 16). Bromine substituted iodophenol **3k** gave the corresponding cyclopenta[*b*]benzofurans with **2b** and **2c** in moderate yields (Table 2, entries 13 and 14).

After the successful cyclopentannulation of diazabicyclic alkenes with 2-iodophenols, the extension of this transformation to study the synthesis of cyclopenta[*b*]indolines was undertaken. Initial attempts to perform the cyclopentannulation of diazabicyclic alkene with 2-iodoaniline were ineffective.

However, treatment of diazabicyclic alkene **2a** with acetyl protected 2-iodoaniline **5a** in presence of catalytic amount of Pd-NHC **1** and *N*,*N*′-diisopropylethylamine under microwave conditions afforded a single diastereomer of the cyclopentannulated product **6a** in 75% yield (Scheme 1). Use of benzoyl protected 2-iodoaniline **5d**, resulted in poor yield of the cyclized product **6d** whereas pivaloyl protected 2-iodoaniline **5e** did not undergo any reaction. Phenylacetyl protected 2-iodoaniline **5c** gave the cyclopentannulated product **6c** in 73% yield. Electron withdrawing groups *para*-to amide (**5f**−**5h**) gave 3,4-disubstituted cyclopentene products (**7a**−**7c**) in moderate to good yields with loss of acetyl moiety from the amine (Scheme 1).

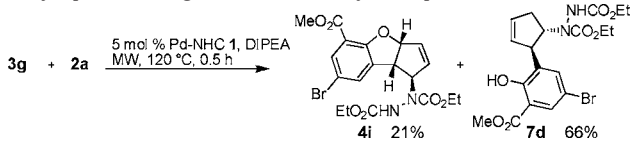
In conclusion, an efficient Pd-NHC catalyzed cyclopentannulation of diazabicyclic alkenes with 2-iodophenols has been developed. This reaction can be performed both in conventional as well as under microwave conditions. Regardless of the reaction conditions, only a single diastereomer of the cyclopentannulated product was obtained. The method has been extended to *N*-(2-iodophenyl)amides to synthesize cyclopenta[*b*]indoline derivatives. This method does not require use of excess diazabicyclic alkene, phase transfer catalyst or ionic liquids. Investigation of an asymmetric version of this reaction using chiral NHC ligands is currently underway.

Scheme 1. Cyclopentannulation of Diazabicyclic Alkenes with *N*-(2-iodophenyl)amides



[a] Unreacted starting material was recovered.

(12) Use of stronger base such as NaH or KOtBu, diazabicyclic alkene and iodophenol underwent decomposition and gave only trace amount of **4i**. However, use of DIPEA as a base the ring-opened **7d** was observed as a major product along with the desired cyclised product **4i**.



Acknowledgment. Acknowledgment is made to the National Science Foundation for partial support of this research. The Robert A. Welch Foundation is also acknowledged for partial support of this research.

Supporting Information Available: General methods, experimental procedures, and spectroscopic data for all new compounds. Copies of ^{1}H and ^{13}C NMR spectra for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102270R