J|A|C|S COMMUNICATIONS

Published on Web 09/21/2010

Synthesis of Heterocycles via Pd-Ligand Controlled Cyclization of 2-Chloro-*N*-(2-vinyl)aniline: Preparation of Carbazoles, Indoles, Dibenzazepines, and Acridines

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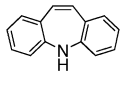
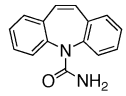
Received August 19, 2010; E-mail: sbuchwal@mit.edu

Abstract: The Pd-catalyzed condensation of 2-bromostyrene and 2-chloroaniline derivatives yields stable diphenylamine intermediates, which are selectively converted to five-, six-, or seven-membered heteroaromatics (indoles, carbazoles, acridines, and dibenzazepines). The selectivity of these intramolecular transformations is uniquely ligand-controlled and offers efficient routes to four important classes of heterocycles from a common precursor.

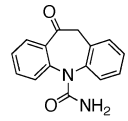
The biological activity manifested by tricyclic, nitrogen-containing heterocyclic compounds makes them attractive targets for synthetic chemists.[1] The seven-membered ring 5*H*-Dibenz[*b*,*f*]-azepine nucleus (**1**) is a pharmaceutically important structure and constitutes the key subunit in tricyclic antidepressant drug substances as Carbamazepine (**2**) and Oxcarbazepine (**3**).[2] These anticonvulsant and mood stabilizing drugs are primarily used for the treatment of epilepsy, bipolar disorder,[3] trigeminal neuralgia,[4] and other neurological disorders.[5] Currently, the most widely employed method for the construction of dibenzazepine analogs involves a gas-phase dehydrogenation of iminobibenzyls at high temperatures.[6,7] The crude product in these processes is usually contaminated with 9-methylacridine.[8] Thus, a general and efficient means for the synthesis of substituted dibenzazepines remains a challenging problem. In addition, the closely related acridine and carbazole tricyclic nuclei also feature prominently among natural products and drug substances.[9] Various methods utilizing a number of synthetic platforms and starting materials are used for the construction of such heteroaromatic systems.[1b,10] While there are many strategies available for the synthesis of carbazoles,[2,11] methods for the preparation of acridines[12c,13] are limited and typically require harsh, functional group-intolerant conditions.



1
5*H*-Dibenzazepine



2
Carbamazepine



3
Oxcarbazepine

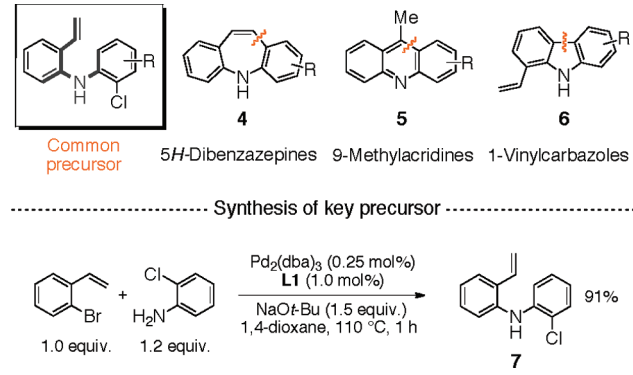
An examination of a series of tricyclic heteroaromatic compounds led us to the realization that 5*H*-dibenzazepines (**4**), 9-methylacridines (**5**), and vinylcarbazoles (**6**) might be derived from a common precursor via controlled intramolecular cyclizations. The key precursor (**7**) was prepared in 91% yield via a C−N coupling reaction[14,15] of commercially available 2-bromostyrene and 2-chloroaniline, as shown in Scheme 1.

We reasoned that four major factors would control the regioselectivity of the Pd(0)-catalyzed transformation of **7**: ligand, base, solvent, and temperature. Further examination of these variables led us to discover that the mode of heterocyclization is almost exclusively controlled by the ligand employed. We examined a variety of phosphines (**L1**−**L11**)[14a] and found that DavePhos (**L2**) was a highly effective ligand for the 7-endo cyclization of **7** to form **1**. In contrast, TrixiePhos (**L3**) and **L4**,[16] selectively furnished 1-vinylcarbazole (**8**) and 9-methylacridine (**9**), respectively (Scheme 2). An efficient catalyst for all transformations was formed from the combination of the appropriate ligand, Pd_2dba_3 and NaO*t*-Bu at 100−110 °C. Among the solvents screened, the use of 1,4-dioxane was superior in terms of conversion and selectivity for the formation of 5*H*-dibenzazepine and 1-vinylcarbazole. Regioselective 6-exo cyclization to form 9-methylacridine was achieved using **L4** in toluene. It should be noted that no other heterocycles or side products were formed under the optimized conditions. Other combinations[11b−d] of catalyst, ligand, base, and solvent led to the production of multiple products or gave low yields of the desired heterocycles.

To the best of our knowledge, our results represent the first cases of such intramolecular reactions that incorporate a 7-endo cyclization. Control experiments were performed and demonstrated that no reactions occurred in the absence of ligand. Interestingly, of all the ligands screened, **L2** was unique in promoting the cascade synthesis[17] of 5*H*-dibenzazepine (Scheme 3). This direct transformation was achieved via a tandem reaction of 2-bromostyrene with 2-chloroaniline, which proceeded smoothly in the presence of $Pd_2(dba)_3$, **L2**, and NaO*t*-Bu, to provide **1** in 99% isolated yield. Other ligands (**L1**, **L3**−**L11**) afforded a diarylamine intermediate as the only observed product. As shown in Table 1, our protocol for the tandem synthesis of 5*H*-dibenzazepine derivates is quite general.

Following the initial survey of ligands (**L3** and **L4** for the formation of carbazoles and acridines respectively) and optimization of Pd sources, we next prepared a range of vinyldiarylamines (as

Scheme 1. Proposed Common Precursor for the Synthesis of Tricyclic Nitrogen-Containing Heterocyclic Cores



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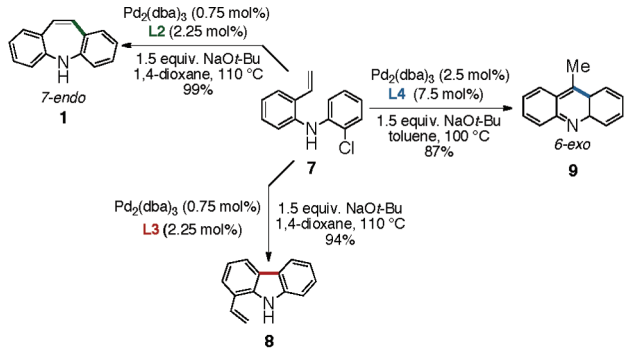
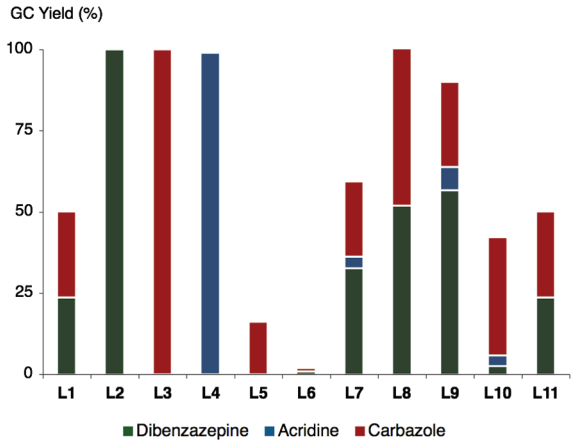
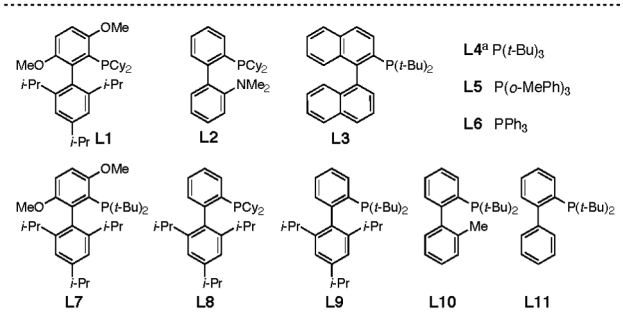
Scheme 2. Pd/Ligand Controlled Selective Cyclizations







[a] Used as salt of HBF_4

shown in Table 2). The intermediates so prepared were then subjected to Pd-catalyzed cyclization conditions to provide a range of vinylcarbazoles and acridines in a highly regioselective manner and in good to excellent yields (Table 3). Notably, both electron-rich and electron-deficient vinyldiarylamines were transformed in an efficient manner.

Scheme 3. One-Pot Direct Synthesis of 5*H*-Dibenzazepine

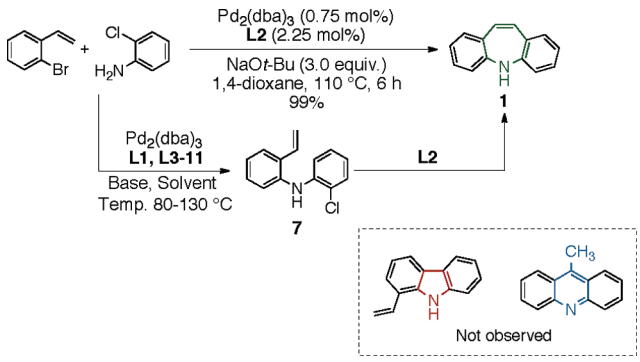
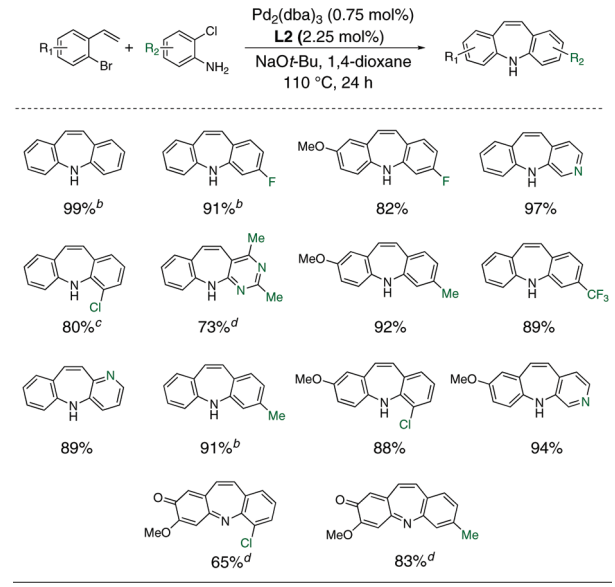
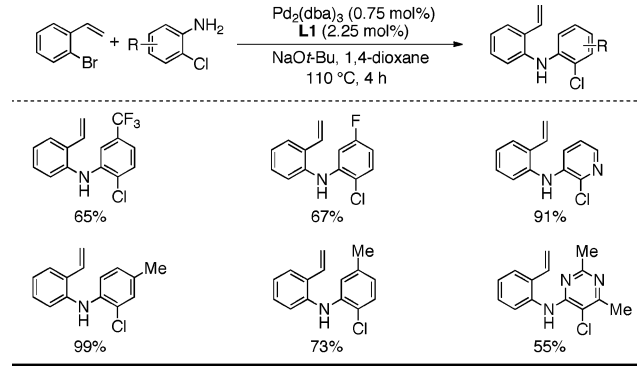


Table 1. Pd-Catalyzed Tandem Formation of Dibenzazepines



[a] Reaction conditions: Isolated yields (average of two runs). 1.0 mmol of styrene, 1.2 mmol of amine, 1 mL of dry 1,4-dioxane, 3.0 mmol of NaO*t*-Bu, 0.0075 mmol of $Pd_2(dba)_3$, 0.023 mmol of **L2**; Ar atmosphere; 110 °C, 24 h. [b] Reaction time: 6 h. [c] Reaction proceeded to 85% conversion (GC). [d] Reaction conditions: 2.5 mol % $Pd_2(dba)_3$ and 8 mol % of **L2** are required.

Table 2. Synthesis of Diarylamine Intermediates[a]

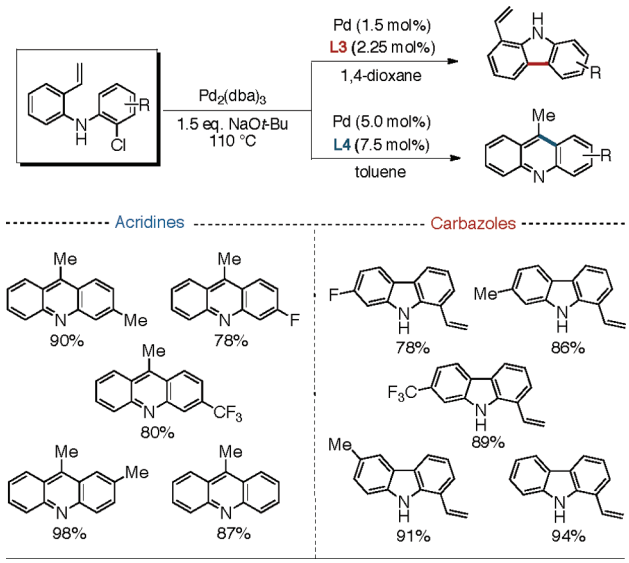


[a] Reaction conditions: 1.0 mmol of 2-bromostyrene, 1.2 mmol of amine, 0.0075 mmol of $Pd_2(dba)_3$, 0.023 mmol of **L1** (BrettPhos), 1.0 mL of dry 1,4-dioxane, 1.5 mmol of NaO*t*-Bu; Ar atmosphere; 110 °C, 4 h. Isolated yields.

As an expansion of this study, we explored the preparation of *N*-arylindoles through the use of an oxidative cyclization.[1b,18] Using the same precursors as above, the construction of arylindoles was achieved via intramolecular C−N bond formation. These reactions proceed in the presence of $Pd(OAc)_2$, $Cu(OAc)_2$, and acetic acid in DMF at 100 °C, to provide 2-chloro-*N*-arylindoles in excellent yields (Table 4).

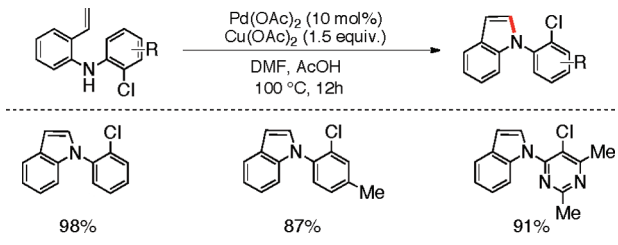
In Scheme 4 we suggest plausible mechanisms for the transformations described above. The dibenzazepine, vinylcarbazole, and acridine syntheses are likely initiated by the oxidative addition of Pd(0) to **7**. Carbon−carbon bond formation, in the construction of 5*H*-dibenzazepine, may proceed via intermediate **A** to form eight-membered palladacycle **B**, which then undergoes reductive elimination to afford **1** (pathway **I**, green).[19] With **L3**,

Table 3. Selective Formation of Acridines and Carbazoles[a]



[a] Reaction conditions: Isolated yields (average of two runs). 1.0 mmol of intermediate, 1.5 mmol of NaO*t*-Bu, 110 °C, 24 h. For acridines: 1 mL of dry toluene, 0.025 mmol of $Pd_2(dba)_3$, 0.075 mmol of **L3**. For vinylcarbazoles: 1 mL of dry 1,4-dioxane, 0.0075 mmol of $Pd_2(dba)_3$, 0.023 mmol of **L4**.

Table 4. Pd(II)-Catalyzed Synthesis of *N*-Arylindoles[a]

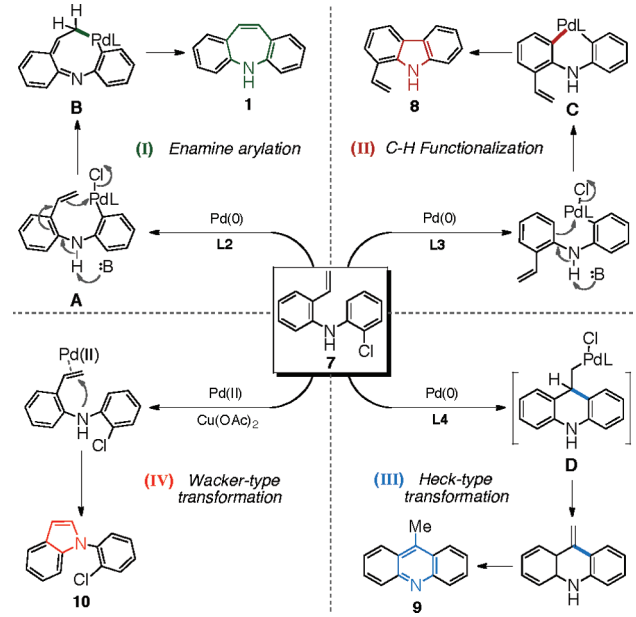


[a] Reaction conditions: Isolated yields (average of two runs). 1.0 mmol of intermediate, 1.5 mmol of $Cu(OAc)_2$, 0.1 mmol of $Pd(OAc)_2$, 1 mL of AcOH, 3 mL of DMF; 110 °C, 24 h.

the oxidative addition complex may undergo intramolecular C−H activation to give a six-membered palladacycle **C**, which yields 1-vinylcarbazole **8** after reductive elimination[11b−d] (pathway **II**, red). Acridine formation may proceed via a "normal" Heck pathway,[20] producing intermediate **C**, from which β-hydride elimination can take place to generate **9** (pathway **III**, blue). Finally, the formation of *N*-arylindole **10** presumably results from a Pd(II)-mediated intramolecular amination of olefin (Wacker-type transformation[21]), as shown in pathway **IV**, orange. Transformations of this type were reported in the pioneering work of Hegedus.[18b]

In conclusion, the Pd-catalyzed condensation of 2-bromostyrene and 2-chloroaniline derivatives yields stable diphenylamine intermediates, which are selectively converted to form, either five-, six-, or seven-membered heterocycle systems (indoles, carbazoles, acridines, and dibenzazepines). The selectivity of these intramolecular transformations appears to be completely ligand controlled and offers a unique opportunity for efficient routes to four important heterocyclic derivates from a common precursor. The novel Pd-catalyzed synthesis of dibenzazepines and 9-methylacridines developed in this study is highly efficient and should provide an access to a range of other tricyclic

Scheme 4. Possible Mechanistic Pathways



derivates. Our future efforts will be devoted to obtaining a clearer understanding of the mechanism of these highly ligand-dependent transformations.

Acknowledgment. This research was financially supported by the National Institutes of Health (NIH) (GM-58160) and Novartis AG.

Supporting Information Available: Experimental details for the synthesis of all new compounds and spectral data. This information is available free via the Internet at http://pubs.acs.org.

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JA107511G