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# Palladium-catalyzed double N-arylation to synthesize multisubstituted dibenzoazepine derivatives

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ABSTRACT

Palladium-catalyzed double N-arylation of primary amines with (*Z*)-1,2-bis(2-bromophenyl)ethenes was investigated. A variety of dibenzoazepine derivatives were synthesized in good to excellent yields.



Double heteroatom-arylation of conjugated di-halo compounds is a strong tool to construct the heterocyclic compounds.[1–5] Thus, useful synthesis of N-heterocyclic compounds was developed by applying double N-arylation of conjugated di-halo compounds with primary amines. For example, Nozaki and co-workers reported the synthesis of carbazoles via double N-arylation of the 2,2′-dihalobiphenyl compounds.[2] Willis and co-workers developed a series of methods to synthesize indoles using 2-(2-haloalkenyl)-aryl halides as substrates.[3] Buchwald,[4a] Li[4b] and Xi,[4c] respectively, used conjugated 1,4-dihalo-1,3-dienes to synthesize pyrroles by Cu catalyzed tandem C–N bond formation. Recently, we used *o*-halo-(2,2-dihalovinyl)benzenes, alkynes, and amines as substrates to construct α-alkynyl indoles in one pot.[5] Therefore, we envisioned that conjugated di-halo compounds such as 1,2-bis(2-bromophenyl)ethene might be useful building blocks for the construction of seven-membered nitrogen-containing heterocyclic compounds via double N-arylation. Herein, we would like to disclose a useful application of (*Z*)-1,2-bis(2-bromophenyl)ethene and a novel synthetic method for the production of dibenzoazepine derivatives.

Dibenzoazepines are important building blocks for the synthesis of anticonvulsant, antidepressant, and antiepileptic drugs.[6] Consequently, the research and development of synthetic methods for dibenzoazepines continues to be one of the most active areas in synthetic chemistry. Classical methods usually apply the dehydrogenation of iminobibenzyls[7] and the rearrangement of arylindoles[8] to the synthesis of dibenzoazepines. Due to required harsh, functional group-intolerant conditions and low yields, the synthetic application of these approaches is limited. Although transition-metal-catalyzed synthesis of dibenzoazepines would be ideal for overcoming the limitation, only a few examples have been reported. Guy and co-workers developed a novel palladium-catalyzed Heck-amination reaction sequence giving access to dibenzoazepines using *o*-iodoaniline and *o*-bromostylene as substrate.[9] Recently, Buchwald demonstrated a similar method to synthesize dibenzoazepines from *o*-choloaniline with *o*-bromostylene in high yields.[10] Derat and Catellani reported a new palladium-catalyzed reaction that leads to dibenzoazepine derivatives when starting with aryl iodides, *o*-bromoanilines, and either norbornene or norbornadiene.[11] Although these reported methods are useful and interesting, synthetic methods for the synthesis of dibenzoazepine, especially for synthesis of N-substituted dibenzoazepine with various functional groups, are still limited. In addition, diversified starting materials and synthetic strategies are desired to make dibenzoazepine derivatives more readily accessible. Nevertheless, the development of new and efficient procedures for the selective synthesis of N-substituted (functionalized) dibenzoazepine with various functional groups continues to represent an important and challenging goal.

In our present work, 5-phenyl-5*H*-dibenzo[*b*,*f*]azepine was formed in good yields from (*Z*)-1,2-bis(2-bromophenyl)ethene[12] **1a** and aniline in one-pot, via a Pd-catalyzed double amination reaction.[13] Two $Csp^2$-N bonds are constructed in the one-pot process. Table 1 shows the results of reaction optimization conditions screening. Double N-arylation of coupling reaction between **1a** and aniline **2a** was investigated using $Pd_2(dba)_3$ as the catalyst. Firstly,

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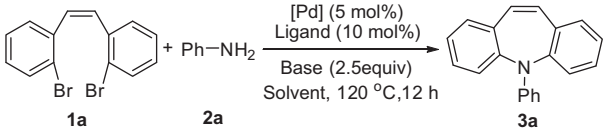
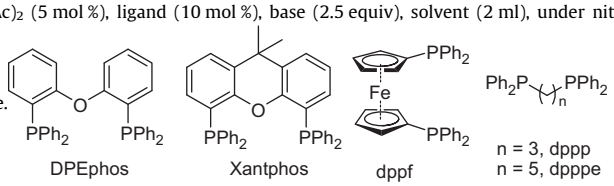
**Table 1**
Reaction optimization[a]




1a 2a 3a

| Entry | [Pd] | Ligand | Base | Solvent | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | $Pd_2(dba)_3$ | DPEphos | $Cs_2CO_3$ | Toluene | 96 |
| 2 | $Pd_2(dba)_3$ | Xantphos | $Cs_2CO_3$ | Toluene | 52 |
| 3 | $Pd_2(dba)_3$ | dppf | $Cs_2CO_3$ | Toluene | 74 |
| 4 | $Pd_2(dba)_3$ | dppp | $Cs_2CO_3$ | Toluene | 75 |
| 5 | $Pd_2(dba)_3$ | dpppe | $Cs_2CO_3$ | Toluene | 66 |
| 6 | $Pd_2(dba)_3$ | $PPh_3$ | $Cs_2CO_3$ | Toluene | 67 |
| 7 | $Pd_2(dba)_3$ | P*t*-$Bu_3$ | $Cs_2CO_3$ | Toluene | 12 |
| 8 | $Pd_2(dba)_3$ | DPEphos | NaO*t*-Bu | Toluene | 53 |
| 9 | $Pd_2(dba)_3$ | DPEphos | $Cs_2CO_3$ | Dioxane | 72 |
| 10 | $Pd(OAc)_2$ | DPEphos | $Cs_2CO_3$ | Toluene | 75 |
| 11[c] | $Pd(OAc)_2$ | Xantphos | $Cs_2CO_3$ | Toluene | 95 |
| 12[d] | $Pd_2(dba)_3$ | DPEphos | $Cs_2CO_3$ | Toluene | 0 |

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), $Pd_2(dba)_3$ (2.5 mol %) or $Pd(OAc)_2$ (5 mol %), ligand (10 mol %), base (2.5 equiv), solvent (2 ml), under nitrogen atmosphere in sealed Schlenk tube, at 120 °C, 12 h.
[b] Isolated yields.
[c] 24 h.
[d] (*Z*)-1,2-bis(2-bromophenyl)ethene was replaced by (*E*)-1,2-bis(2-bromophenyl)ethene.



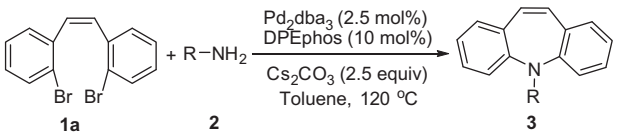

we screened the efficiency of ligands. Results indicated that DPEphos ligand is the best for this coupling reaction (entries 1–7). Next, we changed the base to NaO*t*-Bu (from $Cs_2CO_3$) (entry 8), or the solvent to dioxane (from toluene) (entry 9), all resulting in decreased yields of the product. Finally, $Pd(OAc)_2$ was found to be an efficient catalyst in the double amination of (*Z*)-1,2-bis(2-bromophenyl)ethene **1a** with aniline (entry 11). The reaction became slower, however, and longer reaction times were required (24 h to obtain compound **3a** in 95% yield). To our surprise, When (*Z*)-1,2-bis(2-bromophenyl)ethene was replaced by (*E*)-1,2-bis(2-bromophenyl)ethene, the target product **3a** could not be detected (entry 12). Thus, the optimized reaction condition was as follows: **1a** (0.3 mmol), **2a** (0.3 mmol), $Pd_2(dba)_3$ (2.5 mol %), DPEphos (10 mol %), and $Cs_2CO_3$ (0.75 mmol), in toluene (2 mL) at 120 °C.

The double amination of (*Z*)-1,2-bis(2-bromophenyl)ethene with various amines were next investigated using the optimized reaction conditions. As shown in Table 2, a variety of N-substituted dibenzoazepines were prepared. The substituent of N moiety (R) could be Aryl (*Type I*), Benzyl (*Type II*), alkyl, or allyl (*Type III*). For *type I* (R = Ar), the phenyl ring could be substituted with either electron-withdrawing groups such as F, or $NO_2$ (**3b–d**) or electron-donating groups Me, OMe, or $OCF_3$ (**3e–h**). Importantly, compounds bearing the acetylene bond of aniline could be efficiently reacted with 1,2-bis(2-bromophenyl)ethene to obtain corresponding product in model yields (**3j**, **3k**). These results showed that the variety of groups could be tolerated in this palladium-catalyzed system. Similarly, *N*-benzyl dibenzoazepines (**3l–o**) could be obtained in good to perfect isolated yields. For example, 5-(furan-2-ylmethyl)-5*H*-dibenzo[*b*,*f*]azepine was achieved in 98% yield under the optimized reaction conditions. For *type III*, *N*-alkyl and *N*-allyl dibenzoazepines (**3p–s**) could be obtained in moderate to good isolated yields. This protocol was however found to be general since a wide range of aliphatic and allylic amines reacted successfully.

Meanwhile, we focused our attention on the reactivity of (*Z*)-1,2-bis(2-bromophenyl)ethene with different groups (Table 3). As expected, the reaction was found to be efficiently performed under optimized reaction conditions. The benzene ring of (*Z*)-1,2-bis(2-bromophenyl)ethene bearing of either electron-withdrawing groups such as F, Cl, or CN(**1b–g**) or electron-donating groups Me or OMe (**1h–i**) gave the corresponding dibenzoazepines in moderate to high isolated yields. Significantly, medicinally attractive fluorine-substituted dibenzoazepines (**4a–h**) could be readily introduced in good yields.

In conclusion, we have described a novel and efficient route for the synthesis of N-substituted dibenzoazepine with various functional groups via a palladium-catalyzed double amination coupling of (*Z*)-1,2-bis(2-bromophenyl)ethene with amines. The transformation is distinguished by its mild conditions, allowing the

**Table 2**
Double amination coupling of (*Z*)-1,2-bis(2-bromophenyl)ethene




1a 2 3

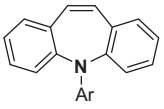
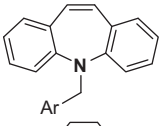
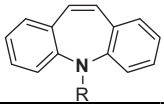
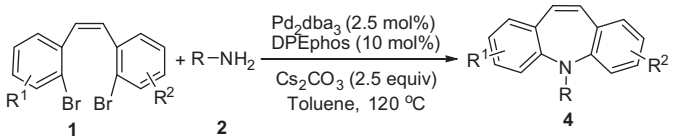
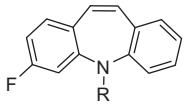
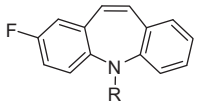
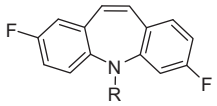
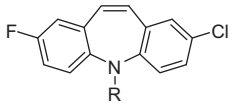
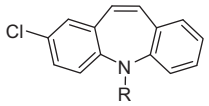
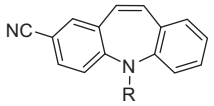
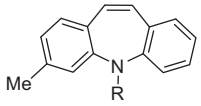
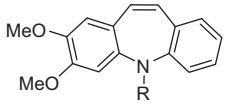
| | | |
|---|---|---|
| *Type I* |  | **3a**: Ar = Ph, (96%, 12 h)<br>**3b**: Ar = 4-F-Ph, (81%, 10 h)<br>**3c**: Ar = 3, 4-2F-Ph, (66%, 9 h)<br>**3d**: Ar = 3-$NO_2$-Ph, (67%, 20 h)<br>**3e**: Ar = 4-Me-Ph, (99%, 14 h)<br>**3f**: Ar = 2-Me-Ph, (69%, 13 h)<br>**3g**: Ar = 4-OMe-Ph, (92%, 14 h)<br>**3h**: Ar = 2-$OCF_3$-Ph, (72%, 10 h)<br>**3i**: Ar = 1-naphthalenyl, (72%, 11 h)<br>**3j**: Ar = 4-trimethylsilylethynyl)-Ph (63%, 10 h)<br>**3k**: Ar = 4-(4-phenylethynyl)-Ph (62%, 10 h) |
| *Type II* |  | **3l**: Ar = Ph, (99%, 9 h)<br>**3m**: Ar = 4-F-Ph, (88%, 11 h)<br>**3n**: Ar = 4-OMe-Ph, (81%, 12 h)<br>**3o**: Ar = 2-furanyl, (98%, 9 h) |
| *Type III* |  | **3p**: R = Propyl, (69%, 15 h)<br>**3q**: R = Amyl, (87%, 18 h)<br>**3r**: R = $C_8H_{17}$, (87%, 18 h)<br>**3s**: R = Allyl, (48%, 14 h) |

**Table 3**
Double amination coupling of substituted (*Z*)-1,2-bis(2-bromophenyl)ethene




1 2 4

| | |
|---|---|
|  | **4a**: R = Ph, (73%, 12 h)<br>**4b**: R = Bn, (78%, 12 h) |
|  | **4c**: R = Ph, (73%, 19 h)<br>**4d**: R = Bn, (90%, 19 h) |
|  | **4e**: R = Ph, (81%, 16 h)<br>**4f**: R = Bn, (83%, 17 h) |
|  | **4g**: R = Ph, (66%, 13 h)<br>**4h**: R = Bn, (81%, 13 h) |
|  | **4i**: R = Ph, (74%, 17 h)<br>**4j**: R = Bn, (80%, 16 h) |
|  | **4k**: R = Ph, (76%, 24 h) |
|  | **4l**: R = Ph, (67%, 24 h)<br>**4m**: Bn, (71%, 24 h) |
|  | **4n**: R = Ph, (62%, 11 h)<br>**4o**: R = Bn, (76%, 11 h) |

tolerance of a wide variety of functional groups in a range of substitution patterns. Efforts to extend the application of this protocol in organic synthesis are underway.

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## Supplementary data

Supplementary data associated (experimental procedures and characterization data for all new compounds and copies of NMR spectra) with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.042.

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