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Palladium-Catalyzed Domino C−C/C−N Coupling Using a Norbornene Template: Synthesis of Substituted Benzomorpholines, Phenoxazines, and Dihydrodibenzoxazepines

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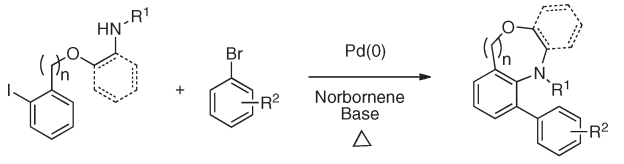
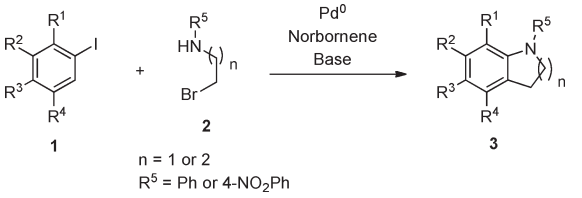


A rapid, four-step approach to alkyl- and aryl-substituted benzomorpholines is accomplished by a Pd-catalyzed domino C−C/C−N bond coupling using a norbornene template. Extension to phenoxazines and dihydrodibenzoxazepines is presented.

Benzomorpholines have been intensively studied as important scaffolds for pharmaceutically active compounds.[1] However, there are only a handful of reports describing the utility and synthesis of aryl-substituted benzomorpholines, even though they are desirable constituents of pharmaceuticals for the treatment of central nervous system disorders.[2] A modern synthetic strategy toward these compounds would be desirable to make them readily available for biological studies.

The ability to control the formation of multiple bonds in a single process is an efficient approach to maximize the value of a synthetic operation.[3] Our group has long been interested in the development of one such process, the norbornene-mediated palladium-catalyzed reaction initially reported by Catellani[4] which can form up to three C−C bonds in one synthetic sequence. In this process, both of the *ortho*-positions of an iodoarene can be functionalized with alkyl or aryl groups, and the reaction is terminated with a palladium-catalyzed coupling. The scope of this reaction has broadened considerably since its discovery.[5,6] Recently, we have reported a highly modular approach to synthesize indolines **3** by a palladium-catalyzed domino C−C/C−N coupling (Scheme 1).[7]

SCHEME 1. Synthesis of Indolines by a Domino C−C/C−N Coupling

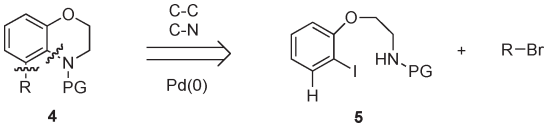


Though good yields of indoline products were achieved, the most successful examples of this approach suffered from the requirement of using *p*-nitrophenyl as the group on nitrogen.

This report was the first example of the use of a reactive heteroatom in the palladium-catalyzed, norbornene-mediated domino sequence. We wished to further explore the use of this novel feature within new substrate classes, and herein we report our findings. A common byproduct of the indoline methodology was the formation of an aziridine from bromoalkylamine **2** or the formation of other products from **2** (i.e., alkylation) that prevented the substrate from reacting. Thus, we wished to explore substrates with separate alkyl halide and amine moieties that when reacted would provide a valuable approach to useful synthetic targets.

In this manner, we envisaged the formation of substituted benzomorpholine **4** from 2-(2-iodophenoxy)ethanamine **5** (Scheme 2). The alkyl halide is now part of an intermolecular component and the amine is part of a tethered chain that does not bear a leaving group. The substrate **5** can be synthesized in three straightforward steps using standard procedures.[8] Notably, these steps combined with the key transformation can produce substituted benzomorpholines **4** in only four steps.

SCHEME 2. Proposed Retrosynthesis of Alkylbenzomorpholines



We started our investigations by studying the synthesis of 1-alkylbenzomorpholine **6**. The optimized reaction conditions for the indoline synthesis[7] were found to work well in

(1) Ilas, J.; Anderluh, P. S.; Dolenc, M. S.; Kikelj, D. *Tetrahedron* **2005**, *61*, 7325.
(2) Stack, G. P.; Hatzenbuhler N. T.; Dahui, Z. International Patent PCT/US2007/082421, **2007**.
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(6) (a) Ca', N. D.; Sassi, G.; Catellani, M. *Adv. Synth. Catal.* **2008**, *350*, 2179. (b) Mariampillai, B.; Alliot, J.; Li, M.; Lautens, M. *J. Am. Chem. Soc.* **2007**, *129*, 15372. (c) Candito, D. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6713.
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(8) See the Supporting Information.

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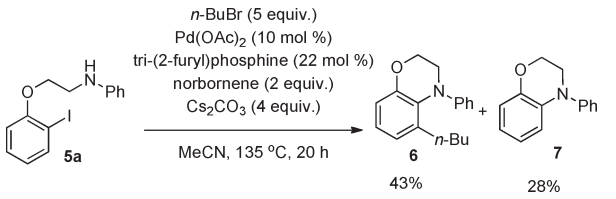
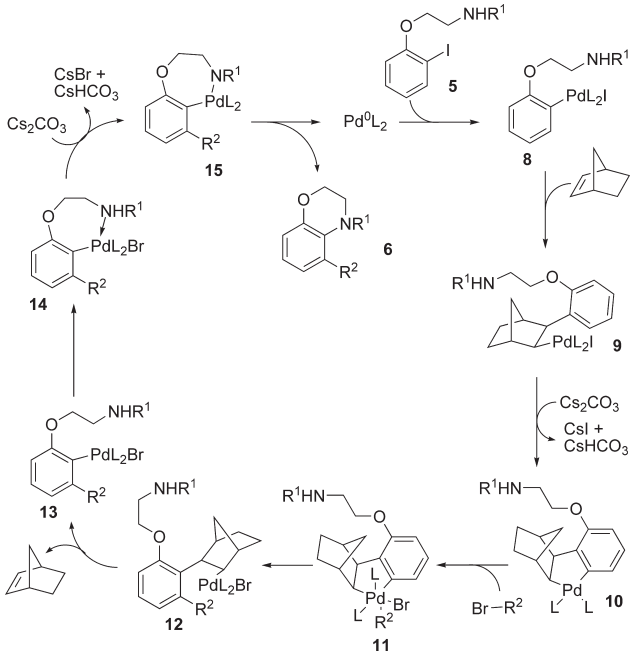
SCHEME 3. Synthesis of Alkylbenzomorpholine 6



SCHEME 4. Mechanism of the Transformation



this case. Benzomorpholine **6** can be synthesized from precursor **5a** in 43% yield (Scheme 3). The major byproduct of this benzomorpholine synthesis was the simple intramolecular amination product **7** in 28% yield. Given the ease of formation of this byproduct, it was remarkable that *ortho*-functionalization could successfully compete with intramolecular amination.

The mechanism of this reaction involves palladium alternating between three different transition states: Pd(0), Pd(II), and Pd(IV) (Scheme 4).[4,9] The mechanism begins with palladium(0) oxidatively inserting into the aryl iodide to give arylpalladium(II) species **8** (Scheme 4). Carbopalladation with norbornene leads to **9**, followed by intramolecular C−H functionalization to give **10**. Oxidative addition of 1-bromobutane leads to the palladium(IV) complex **11**, which reductively eliminates to the palladium(II) species **12**. Retrocarbopalladation of norbornene, a result of the steric constraints imposed by the two *ortho* substituents, leads to the formation of **13** which undergoes an aromatic amination to furnish the benzomorpholine **6**.

The success of substrate **5a** in the domino C−C/C−N coupling suggests that aniline-type substrates are necessary for the reaction. When Boc, Ts, Ac, Bz, and Cbz protecting groups were tested, no desired products were

(9) (a) Catellani, M.; Cugini, F. *Tetrahedron* **1999**, *55*, 6595. (b) Bocelli, G.; Catellani, M.; Ghelli, S. *J. Organomet. Chem.* **1990**, *390*, 251. (c) Catellani, M.; Mann, B. E. *J. Organomet. Chem.* **1993**, *458*, C12. (d) Catellani, M.; Fagnola, M. C. *Angew. Chem., Int. Ed.* **1994**, *33*, 2421.

SCHEME 5. Byproduct 17 from Intermediate 16

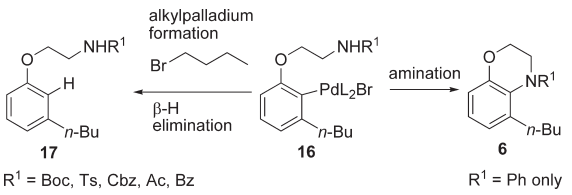
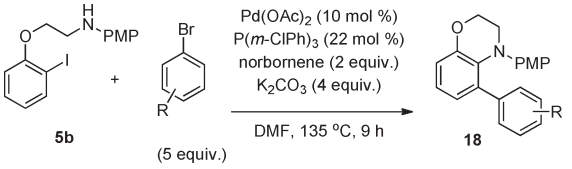


TABLE 1. Scope for the Synthesis of Benzomorpholines 18[a]



entry	R	product	yield (%)
1	4-CF_3	**18a**	62
2	3-CF_3	**18b**	44
3	2-CF_3	**18c**	2[b]

[a] *p*-Methoxyphenyl abbreviated as PMP. [b] Product identified by high-resolution mass spectrometry.

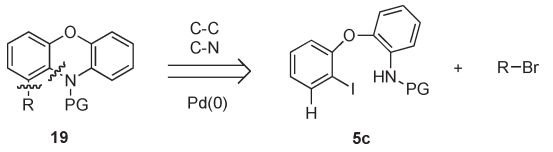
seen. These protecting groups resulted mainly in the formation of the C−C/C−H product **17** (Scheme 5). The terminal C−N coupling presumably happens from intermediate **16**, and the required conformation for C−N coupling to produce **6** may be achievable only in the case of aniline substrates.[10]

Upon discovery of the importance of aniline-type substrates for this transformation, we tested aryl iodide **5b** in the domino sequence. The use of the *p*-methoxyphenyl (PMP) group on nitrogen adds value as it can be more readily removed from the amine than the phenyl group. A switch from *ortho*-alkylation to *ortho*-arylation was necessary to avoid competing *N*-alkylation of the electron-rich amine. Using similar reaction conditions, 1-arylbenzomorpholine **18** can be synthesized in 62% yield from iodide **5b** (Table 1, entry 1). In comparison with the alkylbenzomorpholine synthesis, optimization studies showed that DMF was the better solvent, P(*m*-ClPh)$_3$ was the better ligand, and the reaction time could be reduced. However, attempts to expand the scope of the synthesis of benzomorpholines such as **6** and **18** were met with limited success. We did, however, study the effect of substituent position on the aryl bromide (Table 1). Moving from a *p*-CF_3 to a *m*-CF_3 substituent decreased the yield to 44% (entry 2). An *o*-CF_3 substituent gave only a trace of product (entry 3), illustrating the negative effect of steric bulk for oxidative addition onto the palladacycle **10** (Scheme 4).

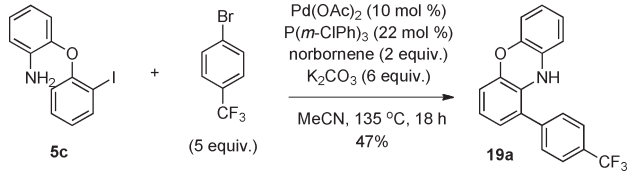
Given the importance of aniline nitrogens in this domino sequence, we turned our focus to substrate **5c** (Scheme 6). We had anticipated that the aromatic linker would reduce the degrees of freedom to promote the final cyclization. In

(10) Preliminary DFT calculations (B3LYP/SDD) of **5a**, **5b**, *N*-Ac-**5**, and *N*-Bz-**5** suggest that after *ortho*-alkylation, only aniline substrates **5a** and **5b** possess the correct geometry for C−N coupling. *N*-Ac-**5** and *N*-Bz-**5** have the Pd and N atoms too far apart for amination to occur, resulting instead in the C−C/C−H product **17** from intermediate **16**. Although substrate **5b** possessed the correct geometry, the electron richness of the nitrogen caused *N*-alkylation to occur faster than amination. See the Supporting Information for more details.

SCHEME 6. Proposed Retrosynthesis of Arylphenoxazines



SCHEME 7. Optimized Conditions for Phenoxazine 19a



addition, the product of the C−C/C−N transformations would be desirable phenoxazines.

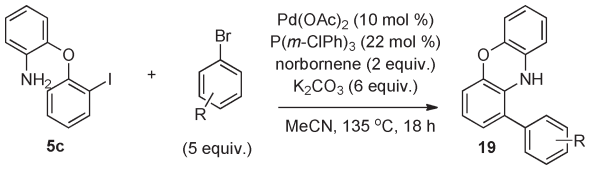
Phenoxazines are ubiquitous pharmacophores in a variety of important compounds, including anticancer,[11] antiviral,[12] and antimicrobial[13] agents. In addition, they are also used as dyes and pigments[14] and biological probes.[15] However, 1-arylphenoxazines have been largely unexplored, perhaps due to the limited number of procedures available for their preparation. To the best of our knowledge, there are only two reported methods for the construction of 1-arylphenoxazines, which both require multistep transformations and were published over 30 years ago.[16]

Given the necessity for protecting groups in the previous cases, we were delighted to find that the synthesis of **19** was successful using unprotected anilines. Optimization of the reaction of aniline **5c** produced phenoxazine **19a** in 47% yield (Scheme 7). Palladium acetate and tri(*m*-chlorophenyl)-phosphine provided the best catalyst system. Two equivalents of norbornene was required for *ortho*-arylation as its absence resulted in only amination products. A large excess of base and high temperatures were required for the domino sequence, and acetonitrile provided the best solvent medium. Though the yield of **19a** was modest, protection and deprotection steps were eliminated, and the nitrogen atom can be directly further functionalized. In addition, substrate **5c** can be recovered from the reaction in some cases.

We explored the scope of this methodology by the reaction of **5c** with a variety of commercially available aryl bromides (Table 2).

Strongly electron-withdrawing aryl bromides were most compatible with the reaction, giving between 47 and 60% of the desired phenoxazine products (entries 1−6). The use of 1-bromo-2-nitrobenzene gave 60% yield of **19c** (entry 3), though most other *ortho*-substituted aryl bromides did not react (entries 12 and 13). Less activated aryl bromides were more problematic. Using 1-bromo-3-fluorobenzene resulted in 45% yield of **19g** (entry 7), but only with a very large excess of aryl bromide (1:1 with the solvent). Similarly, using 1-bromo-3,4-difluorobenzene and 5-bromo-2-fluorotoluene resulted in 27% of **19h** and 20% of **19i**, respectively, using a 1:1 ratio of aryl bromide to acetonitrile (entries 8 and 9). Reactions with electron-neutral or electron-donating aryl bromides also resulted in very low yields of phenoxazines (entries 10 and 11). A noteworthy result occurred with the use of methyl-2-bromobenzoate. The expected phenoxazine further reacted with the *ortho*-ester moiety in situ to produce lactam **19l** in 60% yield (Scheme 8).

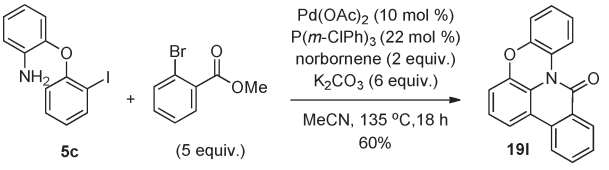
TABLE 2. Scope for the Synthesis of Phenoxazines 19



entry	R	product	yield (%)
1	4-CF_3	**19a**	47
2	4-CO_2Me	**19b**	34
3	2-NO_2	**19c**	60[a]
4	4-NO_2	**19d**	26[b]
5	4-C(O)Me	**19e**	30
6	4-CN	**19f**	40[c]
7	3-F	**19g**	45[d]
8	3,4-diF	**19h**	27[d]
9	3-Me, 4-F	**19i**	20[d]
10	4-Me	**19j**	15[d]
11	4-OMe	**19k**	9[d]
12	2-F	**19c**	0
13	2-CN	**19d**	0

[a]With 1.5 equiv of aryl bromide. [b]With 2.5 equiv of aryl bromide. [c]With 10 equiv of aryl bromide. [d]With 1:1 aryl bromide/acetonitrile.

SCHEME 8. One-Pot Synthesis of Lactam 19l



These results suggest that the substituent of the aryl bromide largely influences these reactions. Initially in the catalytic cycle, the aryl iodide **5c** must be more reactive than the aryl bromide toward Pd(0). However once C−H functionalization of the aryl iodide has occurred, the resulting Pd(II) palladacycle **10** (Scheme 4) must be selective for the aryl bromide for the desired *ortho*-arylation to happen. The full details governing this selectivity are unclear. However, the insertion of the aryl bromide onto the Pd(II) palladacycle has been shown to be aided by a directing group *ortho* to the bromide.[6] Thus, phenoxazines **19c** and **19l** are formed in higher yields. Strongly electron-withdrawing groups on the aryl bromides also fare well in this chemistry since they are reactive enough for oxidative addition and subsequent *ortho*-functionalization. In contrast, aryl bromides that are not reactive for the Pd(II) palladacycle **10** are required in large excess (entries 6−11). In these reactions, the aryl iodide **5c**

(11) Miyano-Kuraski, N.; Ikegami, K.; Kurosaki, K.; Endo, T.; Aoyagi, H.; Hanami, M.; Yasumoto, J.; Tomoda, A. *J. Pharmacol. Sci.* **2009**, *110*, 87.
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(13) Foley, J. W.; Song, X.; Demidova, T. N.; Jilal, F.; Hamblin, M. R. *J. Med. Chem.* **2006**, *49*, 5291.
(14) (a) Bruyneel, F.; Payen, O.; Rescigno, A.; Tirant, B.; Marchand-Brynaert, J. *Chem.—Eur. J.* **2009**, *15*, 8283. (b) Porcal, G. V.; Previtali, C. M.; Bertolotti, S. G. *Dyes Pigm.* **2009**, *80*, 206.
(15) Frade, V. H. J.; Coutinho, P. J. G.; Moura, J. C. V. P.; Gonçalves, M. S. T. *Tetrahedron* **2007**, *63*, 1654.
(16) (a) Sen, A. B.; Sharma, R. C. *J. Indian Chem. Soc.* **1956**, *33*, 671. (b) Reid, W.; Stratz, A. *Justus Liebigs Ann. Chem.* **1972**, *764*, 11.

SCHEME 9. Byproduct with Weakly Electron-Withdrawing Arenes

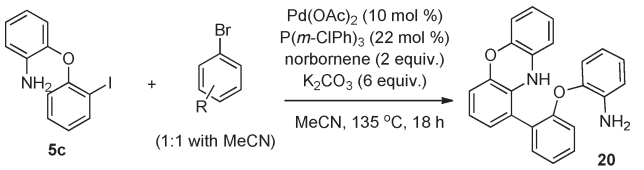
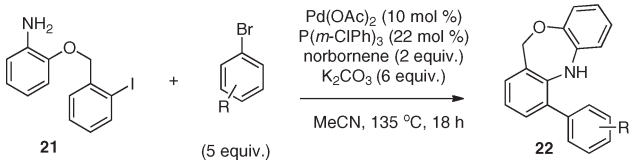


TABLE 3. Scope for the Synthesis of Dihydrodibenzoxazepines 22



entry	R	product	yield (%)
1	4-CF_3	**22a**	17
2	4-NO_2	**22b**	50
3	4-C(O)H	**22c**	17
4	2-NO_2	**22d**	48
5	4-CN	**22e**	27

becomes the more reactive *ortho*-arylation component for oxidative addition onto the palladacycle and dimeric species **20** becomes the major product (Scheme 9).

Dihydrodibenzoxazepines are also important pharmacophores for a variety of drugs including antipsychotic,[17] anticancer,[18] and anticonvulsant[19] agents. Despite their prevalence and numerous previously reported approaches,[20] 1-aryldihydrodibenzoxazepines **22** are unknown in the literature. This new class of benzoxazepines can be synthesized from substrate **21** using the analogous one-pot *ortho*-arylation/aromatic amination sequence in 17−50% yields (Table 3). In general, the yields of these products were lower than those of the corresponding phenoxazines. However, 4-bromobenzaldehyde was a successful substrate for this reaction (entry 3), which was not true for the phenoxazine case. Notably, the use of methyl-2-bromobenzoate did not produce a lactam similar to **19l**, and no desired dihydrodibenzoxazepines were obtained. The byproducts in these cases were not amenable to isolation and characterization.

In summary, we reveal a novel synthesis of alkyl- and arylbenzomorpholines using an extension of our previously reported palladium-catalyzed *ortho*-functionalization/aromatic amination. A variety of arylphenoxazines and a novel class of dihydrodibenzoxazepines can also be synthesized in moderate yields via this approach. Notably, unprotected anilines are compatible with the latter two reactions.

Experimental Section

General Procedure for the Synthesis of Phenoxazines. Compound **5a** (62 mg, 0.20 mmol), aryl bromide (1.5−10 equiv as specified), $Pd(OAc)_2$ (4.5 mg, 10 mol %), tri(3-chloro)-phosphine (16.0 mg, 22 mol %), norbornene (37.7 mg, 0.40 mmol), cesium carbonate (6.0 equiv, 1.2 mmol), and dry CH_3CN (2 mL, 0.10 M) were combined in a 0.5−2.0 mL microwave tube. The tube was purged with argon for 30 s and sealed with a Teflon cap. The resulting mixture was stirred at 135 °C for 18 h. After being cooled to room temperature, the reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (25−50% DCM in hexanes).

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Supporting Information Available: Specific experimental details and characterization data for all unknown compounds. Optimization tables and computational data are provided where appropriate. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Mc Gee, M. M.; Gemma, S.; Butini, S.; Ramunno, A.; Zisterer, D. M.; Fattorusso, C.; Catalanotti, B.; Kukreja, G.; Fiorini, I.; Pisano, C.; Cucco, C.; Novellino, E.; Nacci, V.; Clive Williams, D.; Campiani, G. *J. Med. Chem*. **2005**, *48*, 4367.
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