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Zipper-Mode Double C–H Activation: Palladium-Catalyzed Direct Construction of Highly-Fused Heterocyclic Systems

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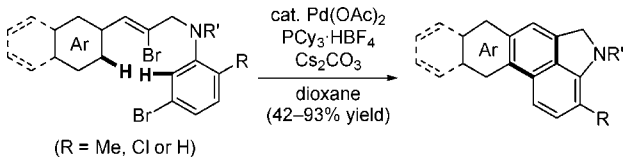
ABSTRACT



(R = Me, Cl or H)

Direct construction of fused aromatic ring systems by "zipper-mode" double C–H bond activation is described. Treatment of (*Z*)-3-bromo-*N*-(2-bromo-3-phenylprop-2-enyl)aniline derivatives with a catalytic amount of $Pd(OAc)_2$ and $PCy_3{\cdot}HBF_4$ in the presence of Cs_2CO_3 in dioxane affords 4,5-naphtho[3,2,1-*cd*]indole derivatives in good yields. Introduction of heterocycles such as benzofuran, benzothiophene, or indole moieties into the substrates leads to the efficient construction of highly fused heterocyclic aromatic ring systems via C–H bond activation of the heteroaromatic rings.

Efficient construction of highly fused heterocyclic aromatic ring systems is an important research area in organic synthesis. A number of highly fused aromatic compounds with interesting biological activities have been reported to date, including aristolactams,[1] aporphines,[2] naphthofurans,[3] benzonaphthothiophenes,[4] and benzocarbazoles[5,6] (Figure 1). Since synthetic routes to these complex molecules often suffer from lengthy reaction steps of redundancy with a considerable amount of waste, reliable synthetic methods for this class of compounds in direct and atom-economical manners are strongly required. Construction of novel heteroaromatic ring systems would also lead to the development of promising templates for drug discovery.

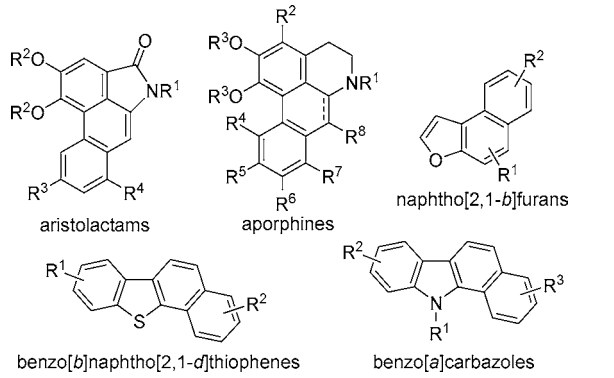


Figure 1. Biologically-active heterocyclic compounds with highly fused aromatic ring systems.

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(2) (a) Cava, M. P.; Watanabe, Y.; Bessho, K.; Mitchell, M. J. *Tetrahedron Lett.* **1968**, *9*, 2437−2442. (b) Wright, C. W.; Marshall, S. J.; Russell, P. F.; Anderson, M. M.; Phillipson, J. D.; Kirby, G. C.; Warhurst, D. C.; Shiff, P. L., Jr. *J. Nat. Prod.* **2000**, *63*, 1638−1640. (c) Lan, Y.-H.; Chia, Y.-C.; Chang, F. R.; Hwang, T.-L.; Liaw, C.-C.; Wu, Y.-C. *Helv. Chim. Acta* **2005**, *88*, 905−909.

(3) (a) Huang, K.-S.; Lin, M.; Cheng, G.-F. *Phytochemistry* **2001**, *58*, 357−362. (b) Braña, M. F.; Cacho, M.; García, M. A.; de Pascual-Teresa, B.; Ramos, A.; Domínguez, M. T.; Pozuelo, J. M.; Abradelo, C.; Rey-Stolle, M. F.; Yuste, M.; Báñez-Coronel, M.; Lacal, J. C. *J. Med. Chem.* **2004**, *47*, 1391−1399.

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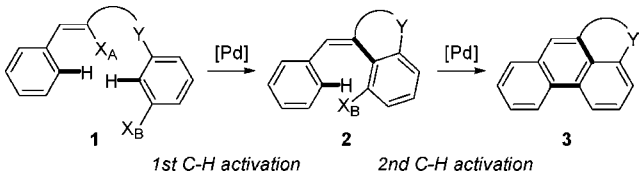
In modern organic chemistry, both tandem reactions and C−H activation are considered as efficient tools for synthesis of complex molecules in terms of atom economy. On the basis of our recent studies on palladium-catalyzed tandem cyclization of allenes and enynes via C−H activation,[7] we envisioned that double aromatic C−H activation in the presence of a palladium catalyst would become one promising approach to various types of fused aromatic ring systems from readily available substrates. Our concept is depicted in Scheme 1. The first intramolecular C−H activation via

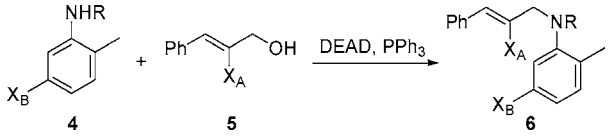
Scheme 1. Construction of Tetracyclic Ring Systems via Palladium-Catalyzed Tandem C−H Activation



oxidative addition of C−X_A bond of dihalides **1** would lead to halostilbene-type intermediates **2**, which could be transformed to fused aromatic compounds **3** by the second C−H activation. It is apparent that preferential oxidative addition of C−X_A bond over C−X_B is the key to the desired "zipper-mode" double C−H activation.[8] Herein we demonstrate construction of tri- or tetracyclic fused aromatic ring system by successful tandem C−H activation of dihalides **1** (X_A = X_B = Br, Y = NR or O, Scheme 1). Although there are some precedents for tandem C−H activation processes to consecutively form multiple C−C bonds,[9] to the best of our knowledge, this is the first example of palladium-catalyzed bis-cyclization that activates two C−H bonds in the desired order.[10]

Preparation of representative dihalides is shown in Scheme 2. Mitsunobu reaction of *N*-protected 5-halo-2-methylaniline **4** and 2-halo-3-phenylpropan-1-ol **5**, obtained by Wittig olefination of the corresponding aldehyde and DIBAL-H reduction, readily afforded requisite dihalides in good to

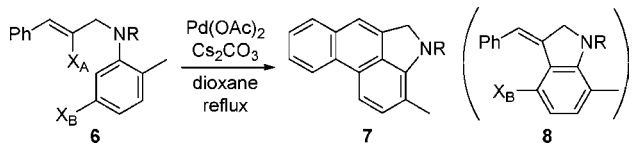
Scheme 2. Preparation of Representative Substrates



excellent yields. Other substrates including heterocyclic analogues and phenol derivatives were also prepared in a similar manner.

We first investigated the tandem cyclization of dibromide **6a** having an *o*-methylaniline moiety to avoid the regioselectivity issue on the first cyclization. After considerable experimentation using various solvents, bases, and additives, we found that the reaction of dibromide **6a** in the presence of $Pd(OAc)_2$, PPh_3, and Cs_2CO_3 in refluxed dioxane gave the desired tetracyclic compound **7a** in 46% yield (Table 1,

Table 1. Optimization of Reaction Conditions and Substrate Structure[a]



entry	substrate	R	X_A	X_B	ligand	time (h)	yield (%)[b] 7	8
1					PPh_3	3	46	
2	**6a**	Ts	Br	Br	PCy_3	9	81	
3					$PCy_3{\cdot}HBF_4$	20	81	
4	**6b**	Ts	Br	Cl	$PCy_3{\cdot}HBF_4$	24	36	63
5	**6c**	Ts	Br	I	$PCy_3{\cdot}HBF_4$	24	ND[c]	
6	**6d**	Ts	I	Br	$PCy_3{\cdot}HBF_4$	24	16	34
7	**6e**	Ms	Br	Br	$PCy_3{\cdot}HBF_4$	21	63	
8	**6f**	Ns	Br	Br	$PCy_3{\cdot}HBF_4$	12	41	
9	**6g**	Piv	Br	Br	PCy_3	3	55	

[a] Unless otherwise noted, the reaction was carried out in the presence of $Pd(OAc)_2$ (20 mol %), phosphine ligand (50 mol %), Cs_2CO_3 (4 equiv) in dioxane under reflux.[11] [b] Yields of isolated products. [c] Not determined; a complex mixture of unidentified compounds was obtained.

entry 1). Among various phosphine ligands examined, tricyclohexylphosphine (PCy_3) was most effective to give **7a** in 81% yield (entry 2). A more handy ligand $PCy_3{\cdot}HBF_4$ gave a comparable good result (81% yield) by refluxing for 20 h (entry 3). We expected that the use of a different halogen atom in the substrate **6** might improve reactivity and/or selectivity of the oxidative addition; however, other dihalides **6b**−**6d** gave unsatisfactory results, and a considerable amount of monocyclized intermediates **8** was detected

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(6) (a) Gábelová, A.; Farkašová, T.; Bačová, G.; Robichová, S. *Mutat. Res*. **2002**, *517*, 135−145. (b) Routier, S.; Peixoto, P.; Mérour, J.-Y.; Coudert, G.; Dias, N.; Bailly, C.; Pierré, A.; Léonce, S.; Caignard, D.-H. *J. Med. Chem*. **2005**, *48*, 1401−1413.

(7) (a) Ohno, H.; Miyamura, K.; Takeoka, Y.; Tanaka, T. *Angew. Chem., Int. Ed*. **2003**, *42*, 2647−2650. (b) Ohno, H.; Yamamoto, M.; Iuchi, M.; Tanaka, T. *Angew. Chem., Int. Ed*. **2005**, *44*, 5103−5106. (c) Ohno, H.; Miyamura, K.; Mizutani, T.; Kadoh, Y.; Takeoka, Y.; Hamaguchi, H.; Tanaka, T. *Chem. Eur. J*. **2005**, *11*, 3728−3741.

(8) For an excellent review on cyclic carbopalladation including "zipper-mode" cyclization, see: Negishi, E.; Coperet, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev*. **1996**, *96*, 365−394.

(9) (a) Zhao, J.; Campo, M.; Larock, R. C. *Angew. Chem., Int. Ed*. **2005**, *44*, 1873−1875. (b) Zhao, J.; Yue, D.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc*. **2007**, *129*, 5288−5295.

(10) For recent reviews for C-H activation, see: (a) Dyker, G. *Angew. Chem., Int. Ed*. **1999**, *38*, 1698−1712. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res*. **2001**, *34*, 633−639. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev*. **2002**, *102*, 1731−1769. (d) Miura, M.; Satoh, T. *Top. Organomet. Chem*. **2005**, *14*, 55−83. (e) Zeni, G.; Larock, R. C. *Chem. Rev*. **2006**, *106*, 4644−4680.

in the reaction mixture after 24 h (entries 4−6).[12] The reaction of the corresponding mesylamide **6e**, nosylamide **6f**, or pivalamide **6g** gave lower yields of **7e**−**g** (41−63%, entries 7−9).

Next, the reaction of substituted dibromides **9a**−**c** was investigated. As shown in Table 2, the desired tetracyclic compounds **10a**−**c** bearing an electron-donating or -withdrawing substituent were obtained in slightly decreased yields (42−63%; entries 1−3). The reaction of the oxygen congener **11** afforded 5*H*-phenanthro[1,10-*bc*]furan derivative **15** in 60% yield (entry 4). Particularly notable is that introduction of heterocycles into the substrate led to direct construction of various heterocyclic aromatic ring systems: for example, the zipper-mode tandem cyclization of dibromides **12**−**14** with a benzofuran, benzothiophene, or indole moiety directly afforded pentacyclic fused heterocycles in 67−93% yields (entries 5−7).[13] Some of these heterocycles have the same core structures of a fused aromatic ring system as the biologically active compounds shown in Figure 1.

Finally, we investigated formation of 3-unsubstituted 4,5-naphtho[3,2,1-*cd*]indole derivative **21** (Scheme 3). The zipper-mode cyclization of 5-bromo-2-chloroaniline derivative **19** followed by reductive dechlorination in the presence of Pd/C gave **21** in 63% yield in two steps. Quite interestingly, the tandem cyclization of 3-bromoaniline derivative **22** directly afforded **21** in 48% yield. Since no monocyclized compounds were isolated from the reaction mixture even with shorter reaction time, it has been proven that the first cyclization of **22** preferentially proceeds at the more hindered 2-position of the aniline moiety.[14]

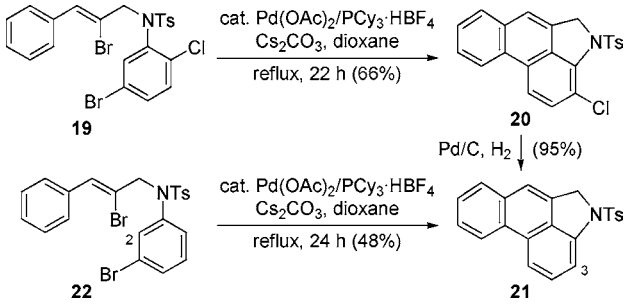
In conclusion, we have developed a zipper-mode double C−H activation leading to fused aromatic compounds. Since all the dibromides can be readily prepared starting from the corresponding aryl aldehydes in a straightforward manner, this tandem cyclization is extremely useful for construction of fused aromatic compounds with complex structures.

Table 2. Construction of Various Fused Aromatic Compounds[a]

entry	substrate	time	product (yield)[b]
1	**9a**: R = OMe	30 h	**10a**: R = OMe (42%)
2	**9b**: R = Me	14 h	**10b**: R = Me (63%)
3	**9c**: R = CO_2Me	14 h	**10c**: R = CO_2Me (45%)
4	**11**	8 h	**15** (60%)
5	**12**	2 h	**16** (93%)
6	**13**	8 h	**17** (87%)
7	**14**	7 h	**18** (67%)

[a] All reactions were carried out in the presence of $Pd(OAc)_2$ (20 mol %), $PCy_3{\cdot}HBF_4$ (50 mol %), Cs_2CO_3 (4 equiv) in dioxane under reflux. [b] Yields of isolated products.

Scheme 3. Synthesis of 3-Unsubstituted Compound **21**



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Supporting Information Available: Representative experimental procedures and characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Unfortunately, decreased loading of the catalyst (10 mol %) and $PCy_3{\cdot}HBF_4$ (25 mol %) afforded **7a** in lower yield (46%) as well as monocyclized compound **8a** (16%).

(12) Although the exact reason for the unsuccessful result with the iodide **6d** (entry 6), a promising substrate for the selective oxidative addition of the vinyl halide moiety, is unclear, the liberating iodide ion might inhibit the desired transformation. This hypothesis is supported by the result that the reaction of dibromide **6a** in the presence of Bu_4NI led to complete recovery of the starting material.

(13) The arylation of heteroaromatic C−H bonds shown in entries 5−7 can be considered as a Heck-type reaction, see ref 10e.

(14) The rest of the material was a complex mixture of many products which was difficult to analyze. Accordingly, formation of a small amount of side products generated by the first cyclization at the less hindered position cannot be ruled out.