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Facile Benzo-Ring Construction via Palladium-Catalyzed Functionalization of Unactivated sp^3 C−H Bonds under Mild Reaction Conditions

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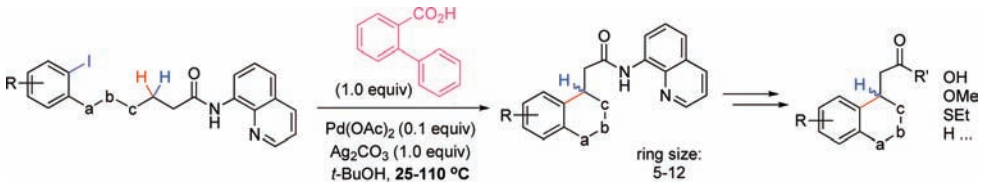
ABSTRACT



A practical synthetic method for the annulation of benzo-rings by the intramolecular coupling of an aryl iodide and a methylene C−H bond is described. The palladium-catalyzed C−H functionalization is directed by an aminoquinoline carboxamide group, which can be easily installed and removed. High yields and broad substrate scope were achieved. An additive of *ortho*-phenyl benzoic acid, identified from a systematic screening, functions as a critical ligand for the catalytic process under mild condition, even at near room temperature.

Site- and stereoselective functionalization of C−H bonds, especially of the more prevalent sp^3 C−H bonds, under mild operating conditions would offer tremendous opportunities for synthesis of complex molecules.[1] Despite the significant progress made over the past decade, the development of synthetically useful methods via the functionalization of sp^3 C−H bonds is still lacking.[2,3] Although some novel site-selective C−H functionalization strategies exploiting the intrinsic C−H reactivity difference have emerged,[4] unbiased approaches governed by intramolecular directing groups or tethered auxiliaries can provide more versatile and controllable transformations.[5] A variety of functional groups, including amines, ketones, and aldehydes, have proven viable handles for such directing purposes.[6] More recently, free carboxylic acid groups, *ortho*-methyl hydroxamic acids, oxazolines, and arylamides have been successfully utilized in palladium-catalyzed, directed C−H functionalization.[7] The aminoquinoline carboxamide, a seminal discovery of Daugulis, appears to be a well-behaved auxiliary to enable C−H functionalization at the β-methylene position.[8,9] Recently, we successfully applied it as the key C−C bond construction strategy in a streamlined synthesis of celogentin C.[10] Encouraged by the high efficiency and selectivity, we went

(1) C−H activation in synthesis: (a) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510–11511. (b) O'Malley, S. J.; Tan, K. L.; Watzke, A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 13496–13497. (c) Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72. (d) Chen, K.; Baran, P. S. *Nature* **2009**, *459*, 824–828. (e) Chaumontet, M.; Piccardi, R.; Baudoin, O. *Angew. Chem., Int. Ed.* **2009**, *48*, 179–182.

(2) C−H insertion via nitrene and carbene: (a) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936. (b) Davies, H. M.; Manning, J. R. *Nature* **2008**, *451*, 417–424.

(3) Functionalization of sp^3 C−H bonds: (a) Dyker, G., Ed. *Handbook of C-H Transformation*; Wily-VCH: Weinheim, Germany, 2005; Vols. 1−3. (b) Chen, H. Y.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995–1997. (c) Dangel, B. D.; Godula, K.; Youn, S. W.; Sezen, B.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 11856–11857. (d) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514. (e) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542–9543. (f) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420–7424. (g) Bergman, R. G. *Nature* **2007**, *446*, 391–393. (h) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654–2672.

(4) (a) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783–787. (b) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566–571.

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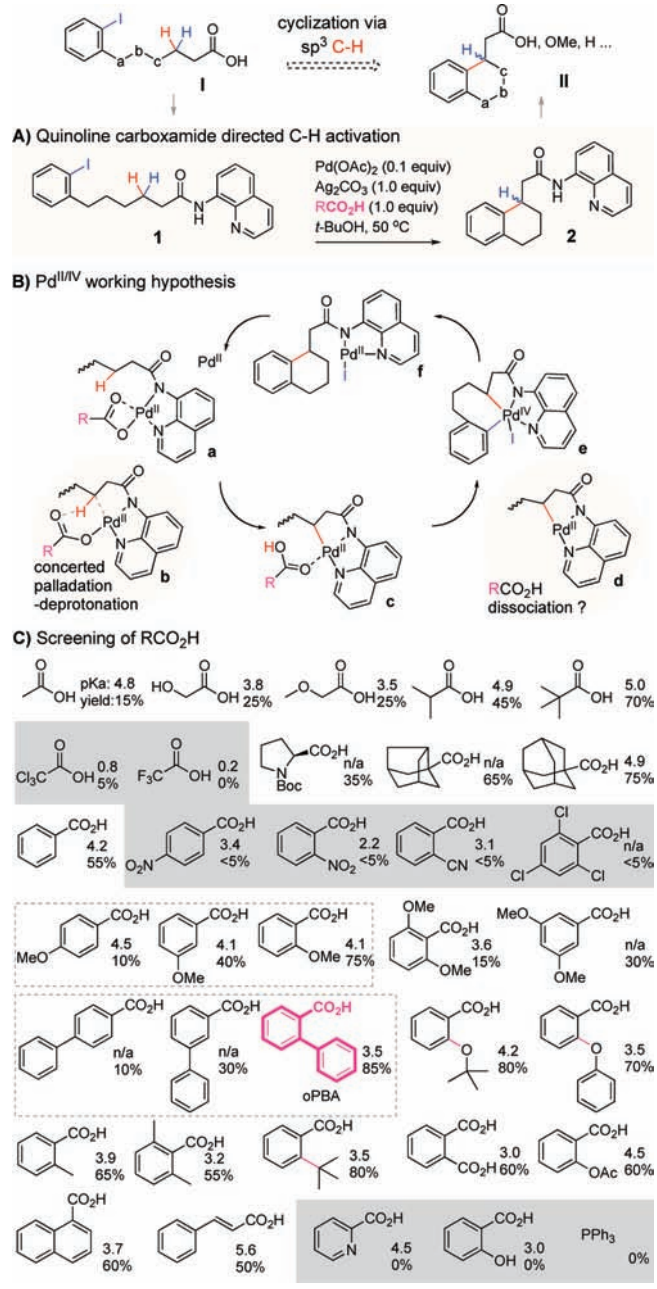
on to explore its synthetic utilization in a more delicate intramolecular setting. Herein, we report a practical benzo-ring construction method via the Pd-catalyzed aminoquinoline carboxamide directed functionalization of sp^3 C−H bonds under mild reaction conditions and the discovery of *ortho*-phenyl benzoic acid as a critical ligand to the catalytic cycle at ambient temperature.

As outlined in Scheme 1, we envisioned a new synthetic strategy for the construction of benzo-ring enabled by the aminoquinoline auxiliary (Q), which can be easily installed at the carboxyl terminus via standard amide coupling.

Evidence from Daugulis, Corey, and our previous work strongly supported the hypothesis that this C−H functionalization proceeds through a sequential C−H activation/oxidative addition $Pd^{II/IV}$ pathway.[11] This served as the initial working mechanism for our reaction development. Aiming to achieve an efficient transformation under user-friendly conditions, the cyclization of precursor **1** was set up at 50 °C, which is significantly lower than the original operating temperature, in *t*-BuOH without exclusion of air or moisture.[12]

Since the Ag^+ salt was believed to act only as an I^- scavenger, our attention was focused on the carboxylic acid additives, which are known to play the key role in the concerted palladation−deprotonation C−H activation step via a three-center agostic interaction (Scheme 1B).[13] An extensive screening of both aliphatic acid and benzoic acids with varied substituents was carried out to explore their functional roles.[14,15]

Scheme 1. Benzo-Ring Construction via the Palladium-Catalyzed Tandem C−H Activation/Intramolecular Cross Coupling with Aryl Iodide[a]



[a] Reagents and conditions: 25 μM, 50 °C, 18 h; air and moisture were not excluded; yields were determined by ^{1}H NMR analysis of the crude reaction mixture (±3%).

(5) Directed C−H activation: (a) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1958**, *80*, 2903–2904. (b) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2640–2641. (c) Breslow, R.; Corcoran, R. J.; Snider, B. B. *J. Am. Chem. Soc.* **1974**, *96*, 6791. (d) Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2000**, *122*, 6321–6322. (e) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169.

(6) (a) Dangel, B. D.; Johnson, J. A.; Sames, D. *J. Am. Chem. Soc.* **2001**, *123*, 8149–8150. (b) Shi, B.-F.; Maugel, N.; Zhang, Y.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 4882–4886. (c) Chen, K.; Richter, J. M.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*, 7247–7249. (d) Desai, L. V.; Stowers, K. J.; Sanford, M. S. *J. Am. Chem. Soc.* **2008**, *130*, 13285–13293.

(7) (a) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420–7424. (b) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Sauders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510–3511. (c) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190–7191. (d) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094–5115. (e) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 9886–9887.

(8) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154–13155. (b) Shabashov, D.; Daugulis, O. *Org. Lett.* **2005**, *7*, 3657–3659. (c) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972.

(9) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391–3394. A palladacycle intermediate was isolated and characterized.

(10) Feng, Y. Q.; Chen, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 958–961.

(11) Pd(IV) chemistry: (a) Canty, A. J. *Acc. Chem. Res.* **1992**, *25*, 83–90. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 119–122. (c) Lautens, M.; Peguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045–1046. (d) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330–7331. (e) Xu, L.; Li, B.; Yang, Z.; Shi, Z. *Chem. Soc. Rev.* **2010**, *39*, 712–733.

(12) The original condition was 110−130 °C in neat condition with 1.5 equiv of AgOAc. A newer condition without Ag salt at 90 °C was recently reported (ref 8c). Although many C−H activations in AcOH and TFA have been developed, neutral and low boiling point solvents are more favorable for practical synthesis.

(13) (a) Davies, D. L.; Donald, S. M. A.; Macgregor, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 13754–13755. (b) García-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886. (c) Lafrance, M.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2007**, *129*, 14570–14571. (d) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848–10849.

(14) (a) Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497. (b) Lebrasseur, N; Larrosa, I. *J. Am. Chem. Soc.* **2008**, *130*, 2926–2927. (c) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrehedron* **2008**, *64*, 6015–6020.

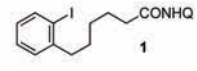
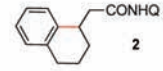
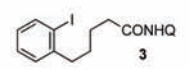
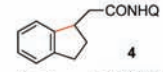
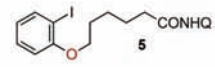
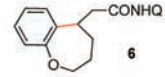
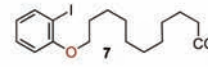
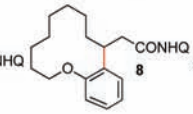
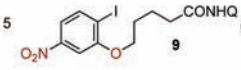
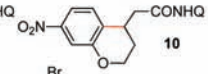
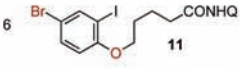
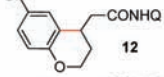
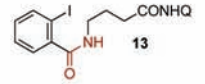
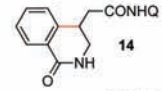
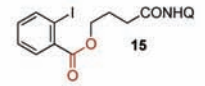
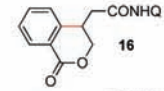
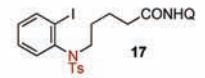
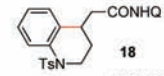
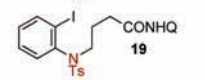
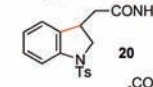
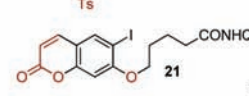
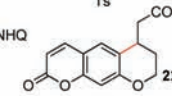
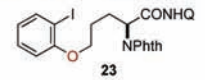
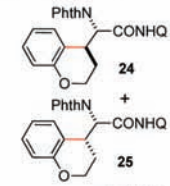
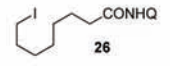
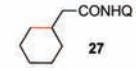
(15) research.chem.psu.edu/brpgroup/pKa_compilation.pdf. pK_a (in H_2O) data compiled by R. Wiliams.

Gratifyingly, several distinct trends in the acid ligand effect were revealed from the initial screening: (1) Aliphatic acids with strong electron-withdrawing substituents ($pK_a < 3$) resulted in failed reactions with recovery of most of **1**. (2) Benzoic acids with either strong electron-donating or electron-withdrawing substituents diminished the yield. (3) Sterically hindered acetic acid derivatives gave higher yields. (4) Ligands, including PPh_3, with strong affinity for palladium shut down the reaction completely. (5) Most interestingly, benzoic acids with one weakly electron-donating group, including methyl, methoxy, *tert*-butoxyl, phenoxyl, *tert*-butyl, and phenyl groups, on the *ortho* position gave significantly higher yields than their *meta* and *para* counterparts. The *ortho*-phenyl benzoic acid (*o*PBA) stands out as the best ligand in terms of efficiency and cost. Clearly, electronic effects alone cannot explain such dramatic differences; we posited that the steric hindrance from the *ortho* substituent must play a critical role.

Further screening revealed a clear solvent effect: strong coordinating solvents such as CH_3CN, DMF, and DMSO completely shut down the reaction; THF and dioxane were comparable to *t*-BuOH; acetone and CH_2Cl_2 gave lower yields. Ag_2CO_3 (0.6 equiv) was found to be sufficient for the reaction: excess Ag_2CO_3 (>1.5 equiv) slightly diminished the yield. Addition of K_2CO_3 (0.5 equiv) also diminished the yield.[16] The reaction was well tolerant of air and moisture. Finally, to our surprise, the cyclization reaction can take place at even lower temperature and proceeded cleanly over 72 h at 25 °C in the presence of 1.0 equiv of *o*PBA, 1.0 equiv of Ag_2CO_3, and 0.1 equiv of $Pd(OAc)_2$ in *t*-BuOH/CH_2Cl_2 (2:1) or dioxane/H_2O (20:1) (Table 1).[17] In contrast, no reaction occurred in the presence of AcOH, and much lower yield was obtained with PivOH at 25 °C.[18] The *o*PBA ligand exhibited an unprecedented level of accelerating ability to this catalytic cycle at ambient temperature.

The mild conditions of this cyclization reaction suggest that the *o*PBA ligand can substantially lower the energy barrier for the critical C−H activation and/or oxidative addition steps in this $Pd^{II/IV}$ catalytic cycle. While the cyclopalladation at ambient temperature has been precedented, the oxidative addition of aryl iodide via Pd^{IV} is usually considered kinetically unfavorable and the rate-limiting step.[19,20] We speculate that the *ortho* bulky substituent on the benzoic acid might facilitate the oxidative addition turnover via its facile dissociation from the Pd^{II} center and provide a open coordination site to the Pd^{II} intermediate (**16e**) (Scheme 1B, e−d).[21]

Table 1. Substrate Scope and Functional Group Tolerance[a]

entry	substrate	product	isolation yield
1			a) 80 °C, *t*-BuOH, 2 h, 88% b) 50 °C, *t*-BuOH, 24 h, 86% c) 25 °C, 72 h, dioxane/H_2O(20/1), 81% *t*-BuOH/CH_2Cl_2(2/1), 79%
2			80 °C, 24 h, 77%
3			110 °C, 48 h, 58%
4			90 °C, 24 h, 64%*
5			70 °C, 24 h, 80%
6			70 °C, 24 h, 82%
7			80 °C, 24 h, 81%
8			110 °C, 24 h, 0%
9			50 °C, 24 h, 83%
10			110 °C, 36 h, 75%
11			70 °C, 12 h, 77%
12			(24+25) 50 °C, 36 h, 81% 80 °C, 12 h, 78%
13			110 °C, 12 h, 13%

[a] General reaction condition: $Pd(OAc)_2$ (0.1 equiv), Ag_2CO_3 (1.0 equiv), *o*PBA (1.0 equiv), 25 μM in *t*BuOH, air and moisture were not excluded; *, 5 μM.

With the optimized conditions established, we began applying them to the cyclization of substrates with varied ring sizes and functional groups. We were pleased to observe moderate to excellent reaction yield and excellent functional group tolerance (Table 1). All the substrates can be easily prepared (see Supporting Information). In general, six-membered rings were readily formed; five and seven-membered rings were more difficult to form, and elevated temperatures were needed. Macrocyclization of the 12-membered ring **8** also worked well under more dilute conditions. Aryl ethers, tosylamides, and phthalimides at varied positions were well tolerated, and even the coumarin

(16) See discussion on proton shuttle in ref.14a

(17) CH_2Cl_2 is added to prevent *t*-BuOH from freezing.

(18) Higher yield (60−80%) can be achieved with AcOH or PivOH at 110°C.

(19) Activation of sp^3 C−H bonds at room temperature: (a) ref 3f. (b) Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391.

(20) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527–2571.

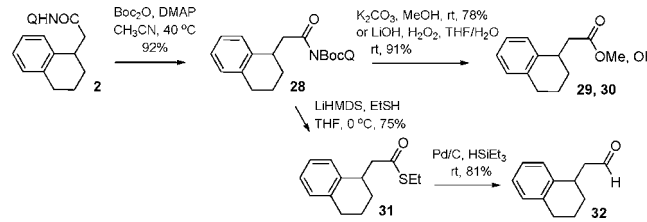
(21) The carboxylate ligand dissociation has been proposed to facilitate the reductive elimination from the Pd^{IV} intermediate, and the dissociation for oxidative addition has not been discussed. See: Racowski, J. M.; Dick, A. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 10974–10983. The strong electron-donating bis-*N* ligand might also facilitate the $Pd^{II/IV}$ oxidative addition.

substrate **21** bearing the unsaturated lactone cyclized cleanly. Aryl bromide **11** was also unaffected under the reaction conditions. Interestingly, substrate **15** bearing the ester tether completely failed the reaction, whereas its amide analogue **13** readily cyclized. The ester might act as an internal ligand to block the oxidative addition step. Cyclization of substrate **23** bearing the Phth-*N*α gave a 2:1 diastereomeric mixture of **24** and **25**. Finally, the cyclization of the alkyl iodide **26** also worked but in much lower yield.

To make this method truly applicable to the synthesis of complex molecules, the aminoquinoline auxiliary needs to be removed or transformed into other functional groups under mild conditions for further elaboration. To our delight, simple Boc activation of the amide linkage[22] followed by nucleophilic replacement provided the corresponding *O*-ester **29**, free acid **30**, and *S*-ester **31** in excellent yield under mild conditions (Scheme 2). Furthermore, the *S*-ester can be easily converted to the corresponding aldehyde **32**.

In summary, we developed a practical method for benzo-ring construction via the aminoquinoline carboxamide directed palladium-catalyzed functionalization of unactivated methylene C−H bonds. The *ortho*-phenyl benzoic acid, identified from a systematic screening, acts as a critical ligand for this catalytic process under mild condition, even at near room temperature. High yields and broad substrate scope were achieved, and the auxiliary was shown to be amenable to further transformation. Its application in the synthesis of complex molecules and development of asymmetric cyclization is currently under investigation.

Scheme 2. Facile Auxiliary Removal



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

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(22) Flynn, D. L.; Zelle, R. E.; Grieco, P. A. *J. Org. Chem.* **1983**, *48*, 2424–2426.