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Synthetic Applications of Pd(II)-Catalyzed C−H Carboxylation and Mechanistic Insights: Expedient Routes to Anthranilic Acids, Oxazolinones, and Quinazolinones

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Abstract: A Pd(II)-catalyzed reaction protocol for the carboxylation of *ortho*-C−H bonds in anilides to form *N*-acyl anthranilic acids has been developed. This reaction procedure provides a novel and efficient strategy for the rapid assembly of biologically and pharmaceutically significant molecules, such as benzoxazinones and quinazolinones, from simple anilides without installing and removing an external directing group. The reaction conditions are also amenable to the carboxylation of *N*-phenyl pyrrolidinones. A monomeric palladacycle containing *p*-toluenesulfonate as an anionic ligand has been characterized by X-ray crystallography, and the crucial role of *p*-toluenesulfonic acid in the activation of C−H bonds in the presence of carbon monoxide is discussed. Identification of two key intermediates, a mixed anhydride and benzoxazinone formed by reductive elimination from organometallic Ar(CO)Pd(II)−OTs species, provides mechanistic evidence for a dual-reaction pathway.

1. Introduction

Carbonylation of organic compounds is an attractive synthetic goal since it utilizes carbon monoxide (CO) as a carbon-atom source for the formation of a new carbon−carbon (C−C) bond with concomitant introduction of a highly oxidized functional group. Since the studies of Heck in 1974, concerning the reaction of aryl and vinyl halides with CO,[1] this reactivity has evolved to include organic triflates, tosylates, mesylates, and fluorosulfonates as the substrates to generate products such as carboxylic acids, esters, and amides.[2] A more straightforward strategy toward the construction of these carbonylated molecules, however, would be to utilize ubiquitous C−H bonds as a halide surrogate.[3] As early as the 1980s, carbonylation of C−H bonds thus emerged as a viable possibility since typical carbonylation protocols are amenable to C−H activation conditions and because both reactions (i.e., beginning with either C−X or C−H bonds) proceed through similar organopalladium intermediates.[4]

Arenes were first carbonylated by Fujiwara in 1980[4] with $Pd(OAc)_2$ under 15 atm of CO in an autoclave[5] wherein the arene substrates were used as solvent, providing carboxylic acids with a 26−48% yield relative to $Pd(OAc)_2$. The reaction procedure proved to be compatible with heterocyclic systems such as indoles, furans and thiophenes.[6] Later, it was found that the reaction was promoted by trifluoroacetic acid (TFA) and benzene could be converted to benzoic acid under 1 atm of CO at room temperature with catalytic amounts of $Pd(OAc)_2$ and $K_2S_2O_8$ as the oxidant.[7] While the reports by Fujiwara demonstrated the impressive reactivity of Pd(II) in carboxylating aryl C−H bonds, two major drawbacks largely hampered the application of this catalytic reaction. First, a large excess of arene, often used as a solvent, is required. Second, there is a lack of control over regioselectivity when substituted benzenes are used as the substrate. In fact, these two problems are pervasive challenges in the field of C−H activation and are often overcome through application of a directing group approach. For example, Orito developed a Pd(II)-catalyzed, alkylamine-directed regioselective carbonylation of aryl C−H bonds in *N*-alkyl-ω-arylalkylamines

(1) (a) Schoenberg, A.; Bartoleti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318–3326. (b) Schoenberg, A.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3327–3331.

(2) (a) Munday, R. H.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2008**, *130*, 2754–2755. (b) Barnard, C. F. *J. Organometallics* **2008**, *27*, 5402–5422.

(3) (a) Yu, J. Q.; Giri, R.; Chen, X. *Org. Biomol. Chem.* **2006**, *4*, 4041–4047. (b) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439–2463. (c) Daugulis, O.; Zaitsev, V. G.; Shabashov, D.; Pham, Q. N.; Lazareva, A. *Synlett* **2006**, *338*, 2–3388. (d) Hartwig, J. F.; Cook, K. S.; Hapke, M.; Incarvito, C. D.; Fan, Y. B.; Webster, C. E.; Hall, M. B. *J. Am. Chem. Soc.* **2005**, *127*, 2538–2552. (e) Hartwig, J. F. *Nature* **2008**, *455*, 314–322. (f) Du Bois, J. *Chemtracts* **2005**, *18*, 1–13. (g) Periana, R. A.; Bhalla, G.; Tenn, W. J.; Young, K. J. H.; Liu, X. Y.; Mironov, O.; Jones, C. J.; Ziatdinov, V. R. *J. Mol. Catal. A—Chem.* **2004**, *220*, 7–25. (h) Crabtree, R. H. *J. Organomet. Chem.* **2004**, *689*, 4083–4091. (i) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861–2903. (j) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180–2192. (k) Sen, A. *Acc. Chem. Res.* **1998**, *31*, 550–557. (l) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879–2932. (m) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403–424.

(4) Fujiwara, Y.; Kawauchi, T.; Taniguchi, H. *J. Chem. Soc., Chem. Commun.* **1980**, 220–221.

(5) Fujiwara, Y.; Takaki, K.; Taniguchi, Y. *Synlett* **1996**, 591–599.

(6) (a) Itahara, T. *Chem. Lett.* **1983**, 127–128. (b) Itahara, T. *Chem. Lett.* **1982**, 1151–1152. (c) Ugo, R.; Chiesa, A.; Nardi, P.; Psaro, R. *J. Mol. Catal.* **1990**, *59*, 23–31.

(7) (a) Taniguchi, Y.; Yamaoka, Y.; Nakata, K.; Takaki, K.; Fujiwara, Y. *Chem. Lett.* **1995**, *34*, 5–346. (b) Lu, W. J.; Yamaoka, Y.; Taniguchi, Y.; Kitamura, T.; Takaki, K.; Fujiwara, Y. *J. Organomet. Chem.* **1999**, *580*, 290–294.

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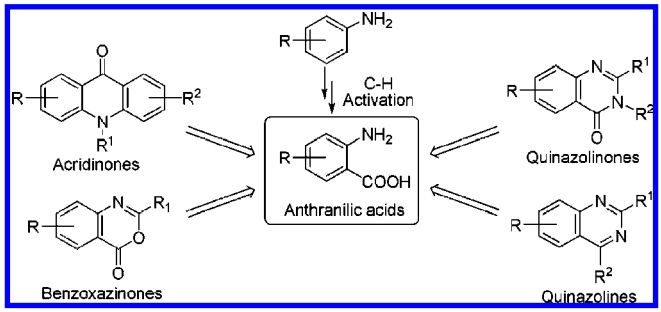
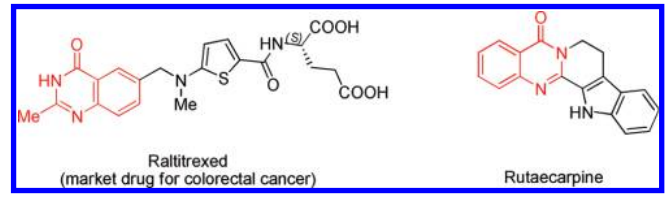
Scheme 1. Anthranilic Acids as Precursors of Heterocyclic Frameworks



at 1 atm of CO to prepare benzolactams where the substrate was used as the limiting reagent.[8] Despite this new development and other previous reports,[9] Pd(II)-catalyzed C−H activation/carbonylation under a CO environment remains an outstanding challenge since Pd(II) catalysts are readily reduced by CO[10] and alternate catalytic systems are often adopted.[11] For example, Chan et al. have recently reported an elegant Pd(II)-catalyzed esterification of sp^2 C−H bonds in a variety of aromatic substrates using diethyl azodicarboxylate as the ethoxycarbonylating reagent.[11a]

With our success in the Pd(II)-catalyzed regioselective carboxylation of aryl and vinyl carboxylic acids under 1 atm of CO,[12] we embarked on extending the scope of this reaction protocol to other molecular structures. We were specifically interested in streamlining the protocol toward the synthesis of molecules of biological and medicinal importance. As such, we primarily focused our research on the construction of anthranilic acid derivatives since they are widely utilized in the synthesis of heterocyclic natural products and molecules of biological significance. Anthranilic acid derivatives also constitute an essential motif in the heterocyclic framework of quinazoline, quinoline, and acridinone alkaloids (Scheme 1).[13] These heterocyclic scaffolds are privileged structures[14] in medicinal chemistry, and therapeutic agents with such cores are on the market or in clinical trials for the treatment of cancer (Scheme 2).[15] Moreover, anthranilic acids

Scheme 2. Examples of Drugs and Natural Products Arising from Anthranilic Acids



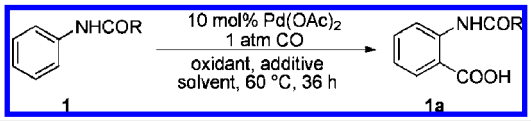
serve as precursors for benzoxazinone natural products, which display a variety of biological activities.[16] In addition, readily available acyl-protected aniline derivatives can be utilized as substrates for their synthesis via carboxylation, in which case the acyl protecting group is incorporated into the target molecule, thereby avoiding additional steps which are generally required for the installation and removal of directing groups in various C−H activation methodologies.[17] In light of their growing promise in drug discovery,[18] diverse synthetic methods have been developed with anthranilic acids as one of the crucial constituents to access these heterocyclic cores.[19] The development of synthetic analogues is, unfortunately, restricted to only a few targets due to the lack of general procedures to prepare anthranilic acid derivatives.[20] Herein, we disclose an unprecedented carboxylation reaction of anilides using a C−H activation/CO insertion sequence to give *N*-acyl-protected anthranilic acids. The use of simple anilide substrates also allows for atom-economical, expedient, and diversifying preparations of benzoxazinones and quinazolinones from a combination of readily available starting materials: anilines and benzoic acid derivatives (Scheme 1).

2. Results

2.1. Preparation of Anthranilic Acid Derivatives. Early investigations were discouraging since acetanilide **1** failed to undergo *ortho*-carboxylation under the standard conditions recently developed in our laboratory for carboxylic acids (Table 1, entry 1).[12] It is well known from the pioneering works of Tremont,[21] de Vries,[22] and Daugulis[23] that anilides are amenable to *ortho*-C−H cleavage with Pd(II) catalysts under a number

(8) Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342–14343.
(9) For the carbonylation of C−H bonds by other metals, see: (a) Mori, Y.; Tsuji, J. *Tetrahedron* **1971**, *27*, 3811–3819. (b) Kunin, A. J.; Eisenberg, R. *J. Am. Chem. Soc.* **1986**, *108*, 535–536. (c) Moore, E.; Pretzer, W. R.; O'Connell, J. H.; LaBounty, L.; Chou, L.; Grimmer, S. S. *J. Am. Chem. Soc.* **1992**, *114*, 5888–5890. (d) Choi, J.-C.; Kobayashi, Y.; Sakakura, T. *J. Org. Chem.* **2001**, *66*, 5262–5263. (e) Funk, J. K.; Yennawar, H.; Sen, A. *Helv. Chim. Acta* **2006**, *89*, 1687–1695. (f) Imoto, S.; Uemura, T.; Kakiuchi, F.; Chatani, N. *Synlett* **2007**, 170–172.
(10) Moiseev, I. I. *Pure Appl. Chem.* **1989**, *61*, 1755–1762.
(11) For the use of diethyl azodicarboxylate as the ethoxycarbonylating reagent, see: (a) Yu, W. Y.; Sit, W. N.; Lai, K. M.; Zhou, Z. Y.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304–3306. For carboxylation with CO_2, see: (b) Reference 5. (c) Sugimoto, H.; Kawata, I.; Taniguchi, H.; Fujiwara, Y. *J. Organomet. Chem.* **1984**, *266*, C44–C46. For carboxylation with formic acid, see: (d) Shibahara, F.; Kinoshita, S.; Nozaki, K. *Org. Lett.* **2004**, *6*, 2437–2439. (e) Sakakibara, K.; Yamashita, M.; Nozaki, K. *Tetrahedron Lett.* **2005**, *46*, 959–962.
(12) Giri, R.; Yu, J. Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082–14083.
(13) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 166–187.
(14) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
(15) For example, Raltitrexed (Tomudex, marketed for colorectal cancer), Ispinesib (phase II for solid tumors), and Tempostatin (phase II for bladder cancer).
(16) (a) Hsieh, P. W.; Chang, F. R.; Chang, C. H.; Cheng, P. W.; Chiang, L. C.; Zeng, F. L.; Lin, K. H.; Wu, Y. C. *Bioorg. Med. Chem. Let.* **2004**, *14*, 4751–4754. (b) Krantz, A.; Spencer, R. W.; Tam, T. F.; Liak, T. J.; Copp, L. J.; Thomas, E. M.; Rafferty, S. P. *J. Med. Chem.* **1990**, *33*, 464–479.
(17) (a) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2005**, *44*, 2112. (b) 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. (c) Giri, R.; Wasa, M.; Breazzano, S. P.; Yu, J.-Q. *Org. Lett.* **2006**, *8*, 5685.
(18) Tilloquin, F. *Phytochem. Rev.* **2007**, *6*, 65–79.
(19) (a) Pereira, M. D.; Thiery, V.; Besson, T. *Tetrahedron* **2007**, *63*, 847–854. (b) Gil, C.; Brase, S. *Chem.—Eur. J.* **2005**, *11*, 2680–2688. (c) Griffin, R. J.; Srinivasan, S.; Bowman, K.; Calvert, A. H.; Curtin, N. J.; Newell, D. R.; Pemberton, L. C.; Golding, B. T. *J. Med. Chem.* **1998**, *41*, 5247–5256.
(20) (a) Kamal, A.; Shankaraiah, N.; Markandeya, N.; Reddy, C. S. *Synlett* **2008**, *129*, 7–1300. (b) Zhou, Z. L.; Kher, S. M.; Cai, S. X.; Whittemore, E. R.; Espitia, S. A.; Hawkinson, J. E.; Tran, M.; Woodward, R. M.; Weber, E.; Keana, J. F. W. *Bioorg. Med. Chem.* **2003**, *11*, 1769–1780.
(21) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759–5760.
(22) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; van Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586–1587.
(23) Zaitsev, V. G.; Daugulis, A. *J. Am. Chem. Soc.* **2005**, *127*, 4156–4157.

Table 1. Optimization of Reaction Conditions



entry	R	oxidant	additive	solvent	% yield[a]
1	Me	Ag_2CO_3	K_2CO_3/NaOAc	dioxane	0[b]
2	Me	none	none	TFA	80[c]
3	Me	BQ	none	TFA	32[d,e]
4	Me	BQ	*p*-TsOH (0.5 equiv)	HOAc/dioxane (2:1)	90[d]
5	Me	BQ	*p*-TsOH (0.5 equiv)	HOAc/toluene (2:1)	86
6	Me	BQ	*p*-TsOH (0.5 equiv)	dioxane	70
7	Me	BQ	*p*-TsOH (0.5 equiv)	HOAc	60
8	Me	BQ	*p*-TsOH (0.5 equiv)	toluene	70
9	Me	BQ	*p*-TsOH (0.5 equiv)	DCE	60
10	Me	BQ	*p*-TsOH (0.5 equiv)	t-BuOH	65
11	Me	BQ	TfOH	dioxane	<10
12	Me	BQ	HBF_4	dioxane	<10
13	Me	BQ	(±)-camphor sulfonic acid	dioxane	<10
14	H	BQ	*p*-TsOH (0.5 equiv)	dioxane	0
15	*t*-Bu	BQ	*p*-TsOH (0.5 equiv)	dioxane	0

[a] ^{1}H NMR yields. [b] 120 °C, 18 h. See ref 12. [c] 1 equiv of $Pd(OAc)_2$ [d] Isolated yields. [e] 25 °C.

of conditions;[21−24] however, *ortho*-C−H activation of acetanilide **1** was initially unsuccessful in the presence of CO (Scheme 3). It became evident to us that the presence of CO impedes the C−H activation process and effects the reduction of $Pd(OAc)_2$ to Pd(0) in both stoichiometric and catalytic experiments.[10]

To overcome this problem, we searched for reaction conditions that would promote the cleavage of C−H bonds over the reduction of $Pd(OAc)_2$. Highly electrophilic cationic Pd(II) species generated under strongly acidic conditions are known to be more reactive toward C−H activation;[7b] thus, we began our investigation with the reaction of acetanilide **1** with stoichiometric $Pd(OAc)_2$ in TFA under 1 atm of CO. Gratifyingly, the reaction proceeded at room temperature, and *N*-acetylanthranilic acid **1a** was obtained in 80% yield (Table 1, entry 2). The reaction could also be run catalytically with 10 mol % $Pd(OAc)_2$ using 1 equiv of benzoquinone (BQ) as the terminal oxidant, affording product **1a**, albeit in meager yield (Table 1, entry 3). Further optimization of the reaction conditions in the presence of different acids established that the reaction was most productive using a solvent mixture of acetic acid (HOAc)/dioxane (2:1) in the presence of 0.5 equiv of *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) while heating at 60 °C. Other acids are not effective, suggesting the counteranion TsO^- is crucial for this reaction (Table 1, entries 11−13). *N*-Acetylanthranilic acid **1a** was obtained in 90% isolated yields (Table 1, entry 4).[25] The carboxylation also proceeds in a variety of other solvents in good yields under these conditions (Table 1, entries 5−10). The crucial effect of *p*-toluenesulfonic acid in assisting in the cleavage of acetanilide *ortho*-C−H bonds by Pd(II) was first realized by de Vries, van Leeuwen, and coworkers in 2002.[22] Recently, a similar effect of *p*-TsOH has been reported by Lloyd-Jones, Booker-Milburn, and co-workers in a urea-directed *ortho*-carbonylation[26] and 1,2-dicarboamination of dienes via *ortho*-C−H activation of phenylurea derivatives.[27]

A variety of anilides underwent carboxylation in good to excellent yields to give *N*-acyl anthranilic acids (Table 2). While HOAc/dioxane (2:1) was the solvent of choice for acetanilide and a few other substrates (Table 2, entries 1, 3, 7), dioxane was the best solvent for the majority of substrates (Table 2, entries 2, 5, 6, 8−11), and HOAc/toluene (2:1) provided higher product yields for substrates **5** and **15**. Addition of 0.5 equiv of NaOAc is essential for the best product yields with substrates **9**−**12** (Table 2, entries 8−11), as significantly less product (30−40%) was obtained in the absence of NaOAc. This result indicates that the formation of Pd−OAc species is beneficial for the C−H activation step.

Substituents on the arene ring also exhibited significant steric and electronic effects on reactivity. *Ortho*-substituted acetanilides, in general, afforded lower product yields than *meta*- and *para*-substituted derivatives (Table 2, entries 1, 2, 7). The carboxylation reaction proceeded efficiently with electron-rich substrates, which is consistent with an electrophilic palladation mechanism.[28] The reaction tolerates a variety of oxygenated substrates, and excellent product yields are consistently obtained (Table 2, entries 8−11). Excellent levels of regioselectivity were observed in the carboxylation of *meta*-substituted anilides, in which cases carboxylation of the more hindered C−H bonds was not observed (Table 2, entries 3, 6, 8, 10, 11). The carboxylation protocol is also amenable to *N*-phenyl pyrrolidinone **15**. However, electron-deficient substrates containing halogens gave less than 20% products. Due to the importance of the availability of a halogen on the aryl ring for further transformations, we developed an improved catalytic system to overcome this limitation by using $Pd(OTf)_2(CH_3CN)_4$ as the catalyst (Table 2, entries 12, 13). Substrates bearing strong electron-withdrawing groups such as *p*-NO_2 and *p*-COOMe afforded less than 10% products under the current carboxylation conditions. Intermolecular competition experiments containing a 1:1 mixture of electron-rich and electron-deficient substrates **1** and **13**, respectively, also showed that the latter is much less reactive (see the Experimental Section for details).

2.2. Syntheses of Benzoxazinones and Quinazolinones. We were excited to find that this newly developed carboxylation protocol could be extended to benzanilide substrates **16**−**18**. The *ortho*-C−H bond of the aniline fragment in benzanilide was carboxylated selectively in the presence of C−H bonds on the benzoyl ring[29] to give *N*-benzoylanthranilic acids **16a**−**18a** in 73−96% yield (Scheme 4), which could be cyclized by treating with Ac_2O to afford the corresponding benzoxazinones **16b**−**18b** in one pot (Scheme 5).[30] Furthermore, *N*-benzoylanthranilic acids **16a** and **17a** could be treated with PCl_3 in the

(24) (a) Horino, H.; Inoue, N. *J. Org. Chem.* **1981**, *46*, 4416–4422. (b) Yang, S. D.; Li, B. J.; Wan, X. B.; Shi, Z. J. *J. Am. Chem. Soc.* **2007**, *129*, 6066–6067. (c) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717–4720.

(25) Formation of dicarboxylated product was not observed. The exclusive monoselectivity is due to the lack of reactivity of the electron-deficient arenes in the carboxylated products. Furthermore, bis-chelation of Pd(II) catalyst with the acetyl and the newly generated carboxyl groups also makes it difficult for the Pd(II) to reach the remaining *ortho*-C−H bonds.

(26) While our work on the synthesis of benzoxazinones and quinazolinones via the activation of *ortho*-C−H bonds in aniline derivatives was in progress, Lloyd-Jones, Booker-Milburn, and co-workers reported a C−H carbonylation protocol using phenylurea as the directing group: Houlden, C. E.; Hutchby, M.; Bailey, C. D.; Ford, J. G.; Tyler, S. N. G.; Gagne, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2009**, *48*, 1830–1833.

(27) Houlden, C. E.; Bailey, C. D.; Ford, J. G.; Gagné, M. R.; Lloyd-Jones, G. C.; Booker-Milburn, K. I. *J. Am. Chem. Soc.* **2008**, *130*, 10066–10067.

(28) Martín-Matute, B.; Mateo, C.; Cárdenas, D. J.; Echavarren, A. M. *Chem.—Eur. J.* **2001**, *7*, 2341–2348.

(29) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655.

Scheme 3. Interference by CO on *Ortho*-C−H Cleavage by $Pd(OAc)_2$

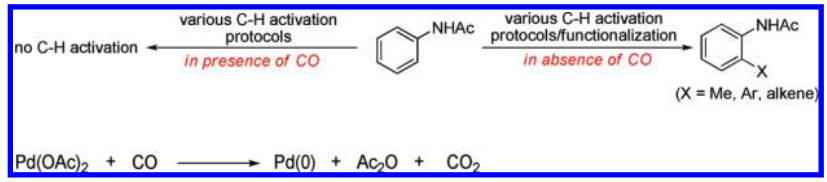
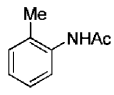
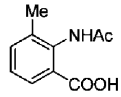
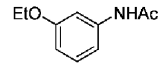
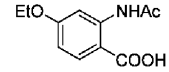
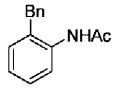
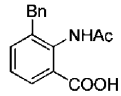
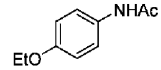
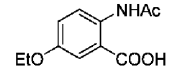
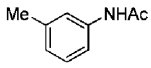
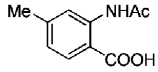
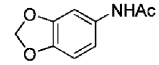
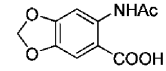
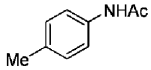
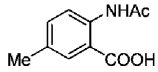
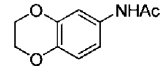
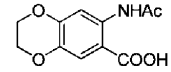
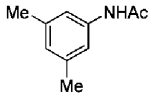
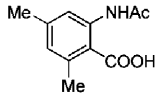
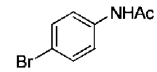
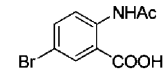
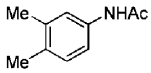
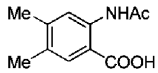
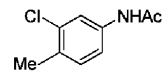
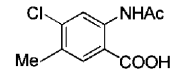
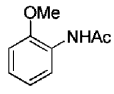
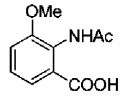
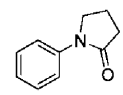
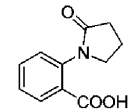


Table 2. *Ortho*-Carboxylation of Anilides via C−H Activation[a,b]

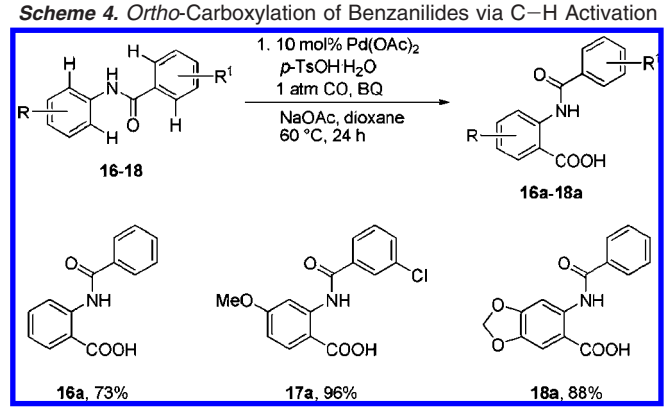
Entry	Substrate	Product	% Yield	Entry	Substrate	Product	% Yield
1	 **2**	 **2a**	60	8	 **9**	 **9a**	96[c,e]
2	 **3**	 **3a**	53[c]	9	 **10**	 **10a**	85[c,e]
3	 **4**	 **4a**	94	10	 **11**	 **11a**	97[c,e]
4	 **5**	 **5a**	70[d]	11	 **12**	 **12a**	86[c,e]
5	 **6**	 **6a**	67[c]	12	 **13**	 **13a**	62[c,f]
6	 **7**	 **7a**	68[c]	13	 **14**	 **14a**	83[c,f]
7	 **8**	 **8a**	53	14	 **15**	 **15a**	69[d]

[a] 10 mol % $Pd(OAc)_2$, 0.5 equiv of *p*-TsOH·H_2O, 1 equiv of benzoquinone, 1 atm of CO, HOAc/dioxane (2:1), 60 °C (entries 1, 4−6, 8, 10, and 11) or 80 °C (entries 2, 3, 7, 9, and 12−14), 18 h (entries 3−6 and 14), 24 h (entries 1, 2, and 7−11), or 36 h (entries 12 and 13), Hi-Vac valve Schlenk tube. [b] Isolated yields. [c] Dioxane was used as a solvent. [d] HOAc/toluene (2:1) was used as a solvent. [e] 0.5 equiv of NaOAc was used as an additive. [f] 15 mol % $Pd(OTf)_2(MeCN)_4$ was used.

presence of aniline to generate quinazolinones **16c−e** and **17c−e**, respectively, in high yields (85−96%) (Scheme 6).[31,32] These reaction sequences showcase the utility of our C−H bond carboxylation protocol in the rapid synthesis of natural product analogues and biologically active molecules from readily available aniline derivatives.

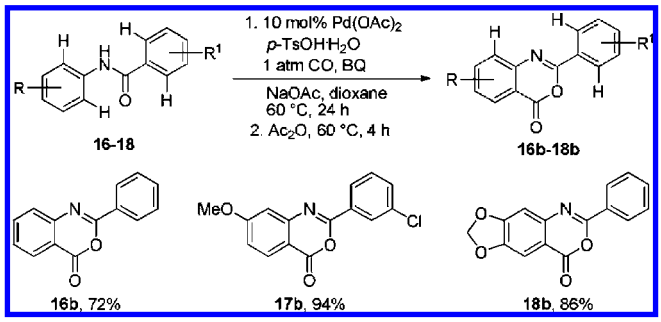
2.3. Mechanistic Consideration and Catalytic Cycle. During the course of our investigation, we also characterized a cyclopalladated intermediate complex and carried out further experiments in order to gain insight into the role of *p*-TsOH

Scheme 4. *Ortho*-Carboxylation of Benzanilides via C−H Activation



(30) Afsah, S. A.; Ahmad, J.; Purbey, R.; Kumar, A. *Asian J. Chem.* **2003**, *15*, 552–554.
(31) Xue, S.; McKenna, J.; Shieh, W.-C.; Repic, O. *J. Org. Chem.* **2004**, *69*, 6474–6477.

Scheme 5. Syntheses of Benzoxazinones via C−H Activation of Benzanilides



and the mechanism of acetanilide carboxylation. Treatment of acetanilide **1** with 1 equiv of $Pd(OAc)_2$ in the presence of 1 equiv of *p*-TsOH·H_2O in CH_2Cl_2 or dioxane at 40 °C instantly gave a faint yellow cyclopalladated intermediate in quantitative yield. Its structure is consistent with the dimeric complex **1b** as determined by ^1H and ^{13}C NMR (Scheme 7). Complex **1b** is insoluble in organic solvents such as diethyl ether and CH_2Cl_2 and partially dissolves in THF but with the loss of dimeric integrity to give an off-white monomer **1c** with the incorporation of one solvent molecule as a ligand. The monomer **1c** was crystallized from THF at room temperature, and its structure was confirmed by X-ray crystallography. Interestingly, a similar structure has been observed by ^1H NMR; however, the *p*-toluenesulfonate anion is not directly coordinated to the Pd(II) center in the crystal structure.[26,33]

The structure of **1c** lends support to a number of mechanistic hypotheses. First, the presence of OTs in **1b** and **1c** suggests that the OTs anion is likely to be attached to Pd(II) in the form of $L_2Pd(OTs)X$ on the C−H activation step, thereby enhancing the reactivity. Second, the C−H insertion intermediate **1c** or **1d** inserts CO to generate palladacycle **1e**, which then undergoes reductive elimination with *p*-toluenesulfonate to give a mixed anhydride species **1f** (Scheme 8, catalytic cycle A). Alternatively, intermediate **1e** could release a molecule of *p*-TsOH via enolization of the acidic N−H bond to generate a second intermediate **1g**, which subsequently undergoes reductive elimination to generate benzoxazinone **1h** (Scheme 8, catalytic cycle B). The final carboxylic acid product **1a** arises from the subsequent hydrolysis of these anhydride and benzoxazinone intermediate products by water present in the reaction system (Scheme 8).[12] Operation of these dual-reaction pathways was supported by the observation of a 1:1 mixture of the mixed anhydride **1f** and benzoxazinone **1h** when a reaction of dimeric palladacycle **1b** with carbon monoxide was carried out in a glovebox under anhydrous conditions in CD_2Cl_2 (Scheme 9). The formation of these products was confirmed by ^1H NMR and GC-MS analysis of the reaction mixture and comparison with either an authentic sample or a product generated in situ.[34] Simultaneous operation of both catalytic cycles is also plausible under the catalytic reaction conditions. Finally, benzoquinone reoxidizes Pd(0) to $Pd(OTs)_2$ in the presence of *p*-TsOH.[35]

Under non-anhydrous conditions, a suspension of palladacycle **1b** in dioxane or CH_2Cl_2 reacts quantitatively with CO at room temperature to produce *N*-acetylanthranilic acid **1a** (Scheme 10). Carboxylation could also be carried out directly by stirring a solution of acetanilide **1** with stoichiometric amounts of $Pd(OAc)_2$ and *p*-TsOH·H_2O under 1 atm of CO to give *N*-acetylanthranilic acid **1a** in nearly quantitative yield (90%). Notably, while the acetate-bridged palladacycle **1i** prepared from acetanilide **1** in the absence of *p*-TsOH was also carboxylated efficiently under 1 atm of CO at room temperature,[24a] the stoichiometric reaction starting directly with acetanilide and $Pd(OAc)_2$ failed to afford any product in the absence of *p*-TsOH (Scheme 10). These experiments indicate that *p*-TsOH is critical for the activation of C−H bonds under a CO environment.

3. Summary

We have developed a Pd(II)-catalyzed reaction protocol for the direct *ortho*-carboxylation of anilides to form *N*-acyl anthranilic acids. We have also characterized by X-ray crystallography a monomeric palladacycle containing *p*-toluenesulfonate as a ligand, formed from the cyclometalation of acetanilide. Further mechanistic investigations have revealed the involvement of a mixed anhydride and benzoxazinone as key intermediates, formed by reductive elimination from an Ar(CO)Pd(II)−OTs species, which lead to the generation of a carboxylic acid product after hydrolysis with traces of H_2O. The reaction conditions can also be applied to the carboxylation of *N*-phenyl pyrrolidinones. This reaction protocol allows us to rapidly generate an array of biologically active benzoxazinone and quinazolinone derivatives from simple anilides without installing and removing an external directing group.

4. Experimental Section

4.1. General Information. Solvents were obtained from Acros and used directly without further purification. Infrared spectra were recorded on a Perkin-Elmer FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian instrument (400 and 100 MHz, respectively) and internally referenced to the $SiMe_4$ signal. High-resolution mass spectra for new compounds were recorded at the Mass Spectrometry Facilities, The Scripps Research Institute. X-ray crystallographic analysis of palladacycle **1c** was done at the X-ray crystallography facility, Department of Chemistry and Biochemistry, University of California, San Diego. Palladium acetate, sodium acetate, and *p*-toluenesulfonic acid monohydrate were purchased from Sigma-Aldrich. Aniline derivatives were purchased from Acros, Sigma-Aldrich, and Alfa-Aesar. Acetanilides **3**, **6**, **11**, **12** and benzanilides **17**, **18** were prepared according to the literature procedure.[36] Carbon monoxide (99% purity) was purchased from Airgas.

(32) For other reports on the synthesis of heterocyclic compounds via C−H bond activation, see: (a) Kuninobu, Y.; Tokunaga, Y.; Kawata, A.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 202–209. (b) Méry, D.; Aranzaes, J. R.; Astruc, D. *J. Am. Chem. Soc.* **2006**, *128*, 5602–5603. (c) Kuninobu, Y.; Nishina, Y.; Nakagawa, C.; Takai, K. *J. Am. Chem. Soc.* **2006**, *128*, 12376–12377. (d) Yotphan, S.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2452–2453. (e) Jordan-Hore, J. A.; Johansson, C. C. C.; Gulias, M.; Beck, E. M.; Gaunt, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 16184–16186. (f) Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932–6933.

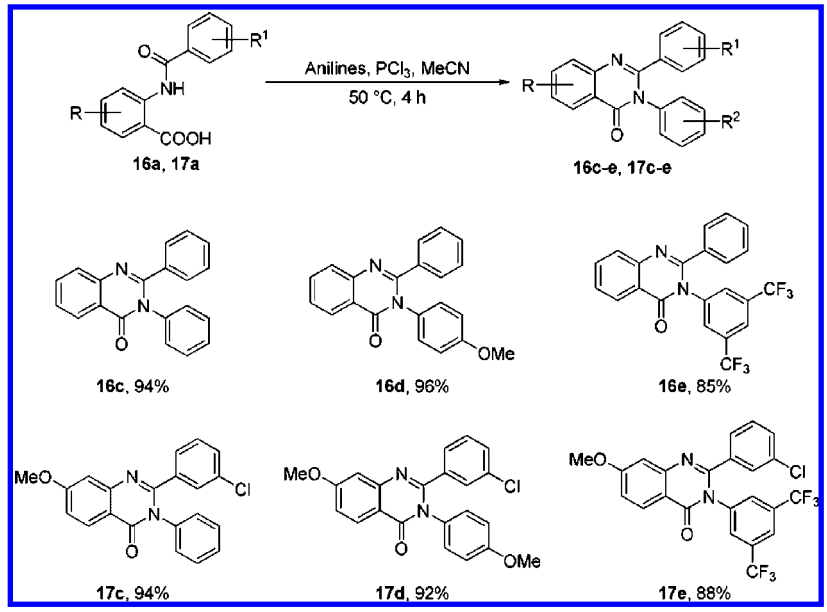
(33) Rauf, W.; Thompson, A. L.; Brown, J. M. *Chem. Commun.* **2009**, 3874–3876.

(34) For the preparation of benzoxazinone **1h**, see: (a) Nagase, T.; Mizutani, T.; Ishikawa, S.; Sekino, E.; Sasaki, T.; Fujimura, T.; Ito, S.; Mitobe, Y.; Miyamoto, Y.; Yoshimoto, R.; Tanaka, T.; Ishihara, A.; Takenaga, N.; Tokita, S.; Fukami, T.; Sato, N. *J. Med. Chem.* **2008**, *51*, 4780–4789. (b) The mixed anhydride **1f** was prepared in situ. See Experimental Section for details.

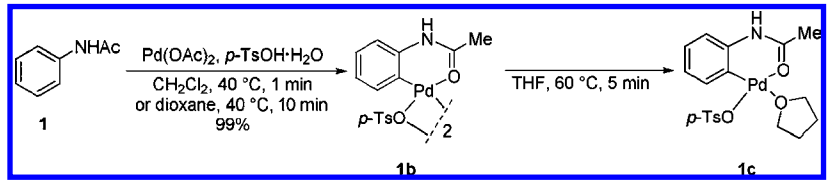
(35) Popp, B. V.; Stahl, S. S. *Top. Orgmet. Chem.* **2007**, *22*, 149–189.

(36) (a) Fang, Y. Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538–549. (b) Lyon, M. A.; Lawrence, S.; Williams, D. J.; Jackson, Y. A. *J. Chem. Soc., Perkin Trans.* **1999**, *1*, 437–442.

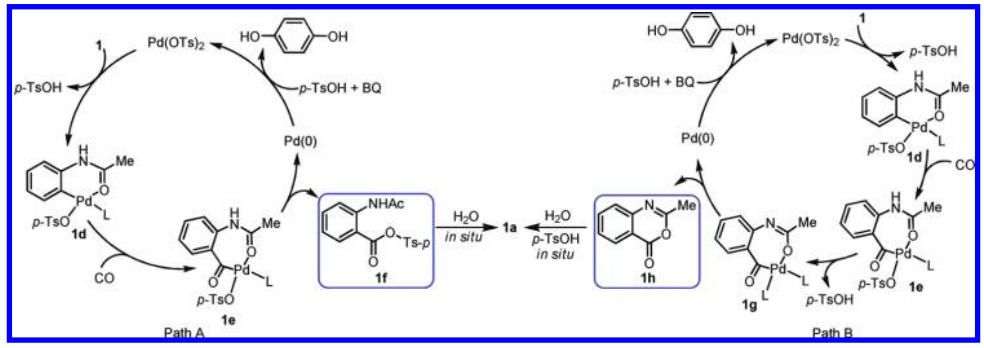
Scheme 6. Syntheses of Quinazolinones via C−H Activation of Benzanilides



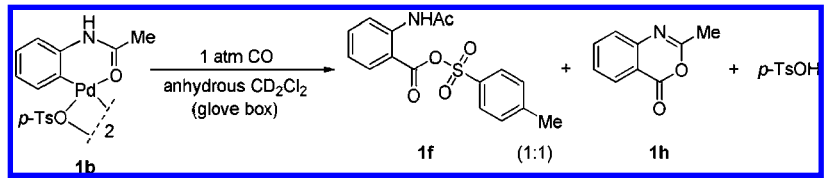
Scheme 7. Formation of **1b** and **1c**



Scheme 8. Dual-Reaction Pathways of Catalytic Carboxylation in the Presence of H_2O

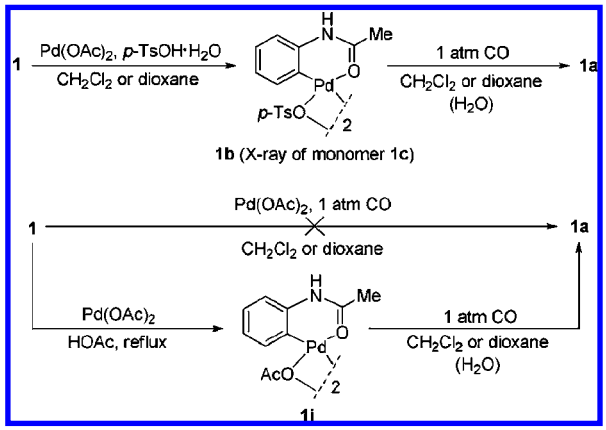


Scheme 9. Stoichiometric Reaction of Palladacycle **1b** with CO under Anhydrous Conditions



4.2. General Procedure for Preparation of Anthranilic Acid Derivatives. HOAc/dioxane (2:1, 1 mL) was added to a mixture of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), anilide (0.5 mmol), *p*-toluenesulfonic acid monohydrate (47.5 mg, 0.25 mmol), and benzoquinone (54.0 mg, 0.5 mmol) in a 50 mL Hi-Vac valve Schlenk tube. Dioxane (1 mL) was used as a solvent for substrates **3**, **6**, **7**, **9**−**14**, **16**−**18**, and HOAc/toluene (2:1, 1 mL) was used as a solvent for substrates **5** and **15**. NaOAc (20.5 mg, 0.25 mmol) was used as an additive for substrates **9**−**12** and **16**−**18**. The Schlenk tube was degassed under high vacuum and filled with carbon monoxide from a balloon at room temperature. (*Note: The use of a fresh CO-filled balloon is crucial for reproducibility of the results and high product yields*.) The reaction mixture was heated at 60 °C (substrates **2**, **5**−**7**, **9**, **11**, **12**) or 80 °C (substrates **3**, **4**, **8**, **10**, **13**−**18**) in an oil bath with vigorous stirring. After 18−36 h (18 h, substrates **4**−**7**, **15**; 24 h, substrates **2**, **3**, **8**−**12**, **16**−**18**; 36 h, substrates **13**, **14**), the reaction was cooled to room temperature, and the solvent was removed in a rotary evaporator. The residue was dissolved in saturated $NaHCO_3$ (2 mL) and washed with CH_2Cl_2 (1 mL × 3), and the aqueous fraction was acidified with dropwise addition of 6 N HCl at 0 °C and extracted with ethyl acetate (2 mL × 5). The ethyl acetate fraction was washed with water (2 mL × 3) and dried over Na_2SO_4, and the solvent was removed in a rotary evaporator. The product was purified by silica gel column chromatography using

Scheme 10. Reaction of Palladacycles **1b** and **1i** with CO



a gradient elution starting at 10% ethyl acetate in hexanes containing 5% acetic acid and ending at 30% ethyl acetate in hexanes containing 5% HOAc (10:5:85 to 30:5:65 EtOAc/HOAc/hexanes) with 5% increments unless stated otherwise.

4.3. General Procedure for Preparation of Benzoxaziones. Benzoxazinones were prepared according to the literature procedure[30] starting from the crude reaction mixture of the corresponding *N*-benzoylanthranilic acids. The carboxylation reaction was carried out in 0.2 mmol scale according to the general procedure. Solvent was then removed in a rotary evaporator, and acetic anhydride (10 mL) was added. The reaction mixture was stirred at 60 °C for 4 h. Benzoxazinones were obtained after the removal of excess solvent in a rotary evaporator and silica gel column chromatography using 5% ethyl acetate in hexanes. The benzoxazinones can also be prepared from the pure *N*-benzoylanthranilic acids in quantitative yields using the same procedure but without the need for chromatographic purification.

4.4. General Procedure for Preparation of Quinazolinones. Quinazolinones were prepared according to the literature procedure[31] starting from the corresponding *N*-benzoylanthranilic acids. Aniline (0.4 mmol) was added to a solution of *N*-benzoylanthranilic acid derivative (0.2 mmol) in CH_3CN (1.0 mL) at room temperature, followed by PCl_3 (0.4 mmol). The reaction mixture was warmed to 50 °C and stirred for 18 h, and then it was cooled to room temperature and diluted with EtOAc. The mixture was quenched by the addition of 1 N aqueous HCl solution. The organic layer was separated, washed with 10% aqueous $NaHCO_3$ solution, and dried over $MgSO_4$. The solvent was removed in a rotary evaporator.

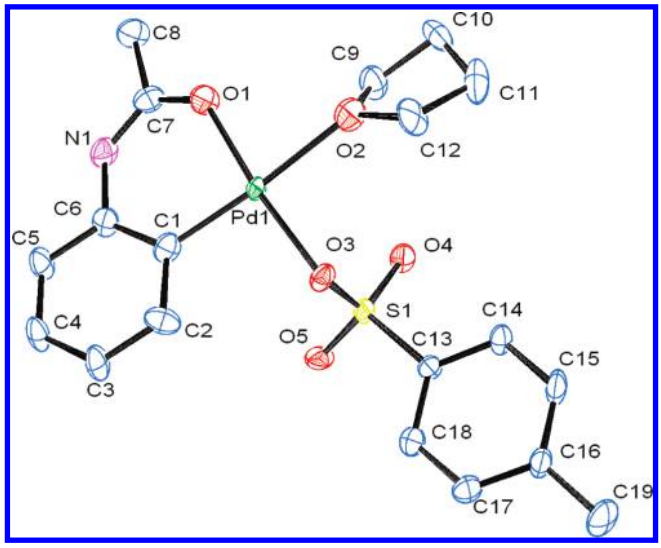


Figure 1. Crystal structure of **1c**.

The product was purified by silica gel column chromatography with gradient elution from 2% to 10% ethyl acetate in hexanes with 2% increments.

4.5. Formation and Characterization of Palladacycles 1b and 1c. A solution of acetanilide (27 mg, 0.2 mmol), *p*-toluenesulfonic acid monohydrate (38 mg, 0.2 mmol), and $Pd(OAc)_2$ (45 mg, 0.2 mmol) in CH_2Cl_2 or dioxane (2 mL) was heated at 40 °C for 1 min (CH_2Cl_2) or 10 min (dioxane). The mixture was filtered to afford a pale yellow solid which was dried under vacuum (82 mg, 99%). The complex was characterized as a dimer **1b** by ^{1}H and ^{13}C NMR: ^{1}H NMR (400 MHz, CD_3OD) δ 2.30 (s, 3H), 2.36 (s, 3H), 6.89−6.97 (m, 3H), 7.12 (t, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.0 Hz, 2H), 11.47 (s, 1H); ^{13}C NMR (100 MHz, CD_3OD) δ 21.5, 21.5, 22.1, 115.1, 115.2, 118.1, 118.2, 125.0, 127.7, 128.0, 130.6, 132.8, 132.9, 134.0, 142.5, 144.1, 168.7, 168.8.

The pale yellow solid was dissolved partially in THF (1 mL) at 60 °C, and the suspension was then filtered through a Cameo 3N syringe filter (0.45 μm, 3 mm) (Osmonics Inc.) in a glass sample vial. The complex was crystallized as yellow prisms **1c** in 24 h at room temperature. The complex **1c** was characterized by X-ray crystallography.

4.6. Competition Experiment. Dioxane (1 mL) was added to a mixture of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), acetanilide **1** (33.8 mg, 0.25 mmol), *p*-bromoacetanilide **13** (53.5 mg, 0.25 mmol), *p*-toluenesulfonic acid monohydrate (47.5 mg, 0.25 mmol), and benzoquinone (54.0 mg, 0.5 mmol) in a 50 mL Hi-Vac valve Schlenk tube. The Schlenk tube was degassed under high vacuum and filled with carbon monoxide from a balloon at room temperature. The reaction mixture was heated at 80 °C. After 3 h, the reaction was cooled to room temperature, and the solvent was removed in a rotary evaporator. The residue was dissolved in saturated $NaHCO_3$ (2 mL) and washed with CH_2Cl_2 (1 mL × 3), and the aqueous fraction was acidified with dropwise addition of 6 N HCl at 0 °C and extracted with ethyl acetate (2 mL × 5). The ethyl acetate fraction was washed with water (2 mL × 3) and dried over Na_2SO_4, and the solvent was removed in a rotary evaporator. The product was analyzed by ^{1}H NMR. The product yields of **1a** (31%) and **13a** (5%) were determined relative to the remaining starting materials.

4.7. Identification of Products after Reductive Elimination from a Pd(II) Intermediate. In a glovebox, palladacycle **1b** (82.4 mg, 0.1 mmol) was weighed into a NMR tube with a J-Young valve and suspended in anhydrous CD_2Cl_2 (1.0 mL). The NMR tube was taken out of the glovebox, frozen in liquid N_2, evacuated, and filled with 1 atm CO. The tube was tightly screw-capped and slowly warmed to room temperature with shaking, at which point the suspension turned black. The suspension was shaken for 10 min, brought into the glovebox, and filtered through a tight pad of cotton into another NMR tube with a J-Young valve. The clear solution was analyzed by ^{1}H NMR and GC-MS. A 1:1 ratio of two new products arising from acetanilide **1** was observed, along with the formation of *p*-TsOH (see the ^{1}H NMR spectra below). The formation of benzoxazinone **1h** was confirmed by comparison of the ^{1}H NMR spectrum of the reaction mixture with that of the authentic sample of benzoxazinone **1h** and by the observation of M^+ ion at 161 corresponding to the retention time of benzoxazinone **1h** at 6.63 min when an aliquot of the reaction mixture was analyzed by GC-MS.

Moreover, when a sample of benzoxazinone **1h** (10 mg) was added to the reaction mixture, intensities of one set of ^{1}H NMR peaks corresponding to benzoxazinone **1h** were enhanced. Similarly, when a sample of the mixed anhydride **1f**, generated in situ from a mixture of 1:1:1 molar ratios of *p*-TsCl, *N*-acetylanthranilic acid **1a**, and triethylamine in anhydrous CD_2Cl_2, was added to the reaction mixture, the intensities of

the remaining set of ^{1}H NMR peaks were enhanced (see the Supporting Information for details).

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Supporting Information Available: Detailed experimental procedures, characterization of new compounds, and X-ray crystallographic data for **1c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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