ORGANIC
LETTERS

2007
Vol. 9, No. 13
2441−2444

Development of a Catalytic Aromatic Decarboxylation Reaction

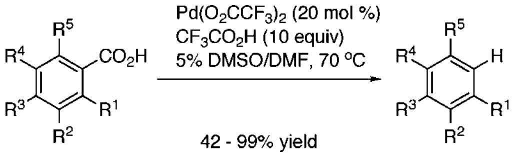
Joshua S. Dickstein, Carol A. Mulrooney, Erin M. O'Brien, Barbara J. Morgan, and Marisa C. Kozlowski*

Department of Chemistry, Roy and Diana Vagelos Laboratories, University of Pennsylvania, Philadelphia, Pennsylvania 19104

marisa@sas.upenn.edu

Received March 27, 2007

ABSTRACT



A palladium-catalyzed aromatic decarboxylation reaction has been developed. With electron-rich aromatic acids, the reaction proceeds efficiently under fairly mild conditions in good yields. The method was useful with complex functionalized substrates containing hindered carboxylic acids.

A mild and efficient method for aromatic decarboxylation has yet to be reported. In general, aromatic decarboxylation is difficult due to the unstable intermediates that are formed during the course of the reaction. As a result, the methods available for decarboxylation all require harsh, forcing conditions.

Prototypical methods include heating in the presence of a strong acid[1] and heating with a copper catalyst and quinoline.[2] The first method proceeds through ipso protonation of the aromatic ring and thus requires electron-rich systems and temperatures of at least 100 °C. In the copper/quinoline method, the copper catalyst coordinates to the aromatic ring and helps stabilize the anion that results upon loss of carbon dioxide. Again these reactions only proceed at very high temperatures (>160 °C).[3] While mercury mediated decarboxylations can proceed under milder conditions, the requirement for stoichiometric mercury salts and the intervention of toxic organomercury(II) intermediates is restrictive.[4] The Barton protocol does not permit direct protonation in aromatic systems although an indirect approach via radical decarboxylative bromination is viable.[5] This three-step protocol (ester formation, decarboxylative bromination, and bromine hydrogenolysis) still requires high temperatures and is not suitable for highly hindered esters or substrates with hydrogenolytically sensitive functionality.

In this Letter, we report the development of a single-step palladium-catalyzed decarboxylation utilizing trifluoroacetic acid as the proton source that proceeds at <100 °C. Our investigations were motivated by the need to remove efficiently the carboxylate groups from **1** as part of our studies[6] of the perylenequinone natural products[7] (Scheme 1). Unfortunately, decarboxylation reactions with protic acid were unsuccessful and those under the copper/quinoline conditions resulted in low yields and racemization of the biaryl stereochemistry.

---

[1] (a) Olah, G. A.; Laali, K.; Mehrotra, A. K. *J. Org. Chem.* **1983**, *48*, 3359−3360. (b) Horper, W.; Marner, F.-J. *Phytochemistry* **1996**, *41*, 451−456.

[2] (a) Cohen, T.; Schambach, R. A. *J. Am. Chem. Soc.* **1970**, *92*, 3189−3190. (b) Cohen, T.; Berninger, R. W.; Wood, J. T. *J. Org. Chem.* **1978**, *43*, 837−848. (c) Pulgarin, C.; Tabacchi, R. *Helv. Chim. Acta* **1988**, *71*, 876−880.

[3] Microwave heating can also be employed: Frederiksen, L. B.; Grobosch, T. H.; Jones, J. R.; Lu, S. Y.; Zhao, C. C. *J. Chem. Res. Synop.* **2000**, 42−43.

[4] (a) Gilman, H.; Wright, G. F. *J. Am. Chem. Soc.* **1933**, *55*, 3302−3314. (b) Deacon, G. B.; O'Donoghue, M. F.; Stretton, G. N.; Miller, J. M. *J. Organomet. Chem.* **1982**, *233*, C1−C3.

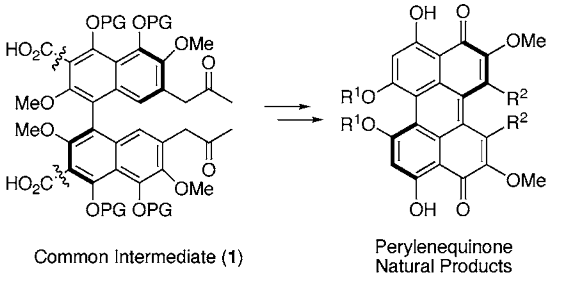
[5] (a) Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron Lett.* **1985**, *26*, 5939−5942. (b) Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron* **1987**, *43*, 4321−4328.

[6] Mulrooney, C. A.; Li, X.; DiVirgilio, E. S.; Kozlowski, M. C. *J. Am. Chem. Soc.* **2003**, *125*, 6856−6857.

[7] Review: Weiss, U.; Merlini, L.; Nasini, G. *Prog. Chem. Org. Nat. Prod.* **1987**, *52*, 1−71.

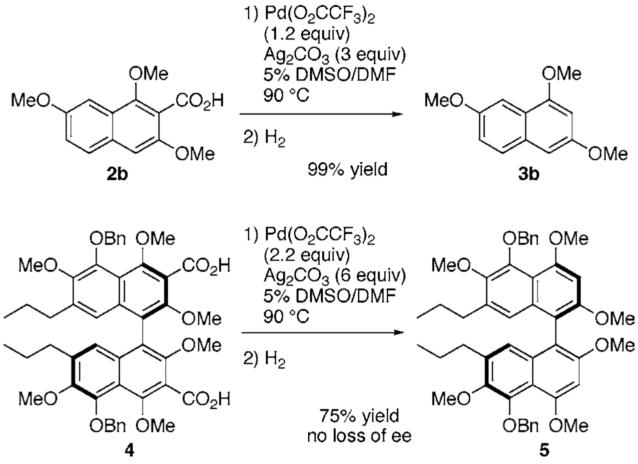
10.1021/ol070749f CCC: $37.00

Scheme 1. Perylenequinone Family Common Intermediate



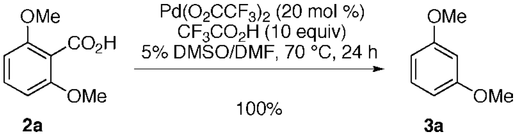
Recently, the Myers group reported a palladium-catalyzed decarboxylative Heck coupling.[8,9] Inspired by this precedent; we proposed that a catalytic decarboxylation could be achieved if an appropriate hydride or proton source could be discovered. To begin with, we explored stoichiometric palladium decarboxylation by treatment with palladium(II) trifluoroacetate and silver carbonate followed by introduction of a hydrogen atmosphere to reduce the resultant aryl palladium species. Rewardingly, this protocol produced high yields of decarboxylated product in model systems (Scheme 2) at *much lower temperatures* compared to classical methods,[1,2] and to another report with a palladium catalyst.[10] As a result, no loss of enantioselectivity was seen with these conditions in thermally atroposensitive substrates such as **4**.

Scheme 2. Initial Decarboxylation Results



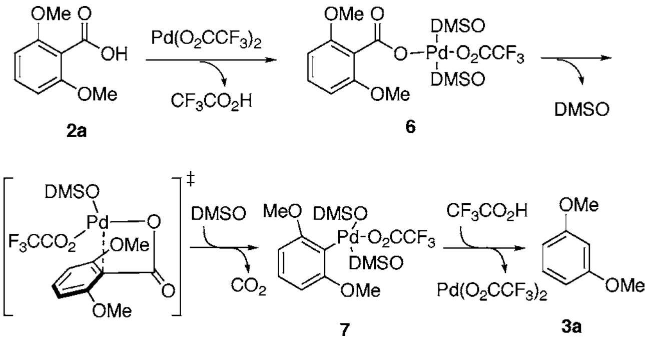
Having solved the atropoisomerization issues that were our initial concern, our attention turned to reducing the amount of palladium required for an effective reaction. To do this required identification of a hydride or proton source that (1) can be employed in the presence of palladium(II) and (2) will allow catalytic turnover. The former condition excludes most hydride sources such as hydrogen, borohydrides, etc. which cause rapid reduction of palladium(II) to palladium(0) before decarboxylation can occur. The latter condition either requires a reoxidation step if a reductive elimination pathway occurs or Brønsted acid to allow protonolysis of the aryl palladium intermediate. This last proposal proved to be the most effective. Upon generation of the aryl palladium intermediate from **2a** with stoichiometric palladium(II) trifluoroacetate, addition of trifluoroacetic acid produced the decarboxylated material **3a** (Scheme 3). Since a closed catalytic cycle was anticipated, we were gratified that the amount of palladium catalyst could indeed be lowered to 20 mol % without any effect on the yield of **3a** (Scheme 3).

Scheme 3. Decarboxylation of the Model System



On the basis of a number of mechanistic experiments performed in our lab as well as work reported by the Myers group,[8] the following mechanism for catalytic decarboxylation is proposed (Scheme 4). Coordination of the palladium to two molecules of DMSO and the substrate (**2a**) results in the loss of a molecule of trifluoroacetic acid. A four-membered transition state with loss of carbon dioxide provides an avenue for palladium insertion onto the aryl ring to give the aryl palladium species (**7**). At this point the aryl palladium intermediate (**7**) can undergo protonolysis with trifluoroacetic acid to yield the product (**3a**) and reform the palladium(II) trifluoroacetate catalyst.

Scheme 4. Proposed Mechanism



To further optimize and extend this process, the rate-determining step in the above mechanistic cycle needed to

---

(8) (a) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250−11251. (b) Tanaka, D.; Myers, A. G. *Org. Lett.* **2004**, *6*, 433−436. (c) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323−10333.

(9) For recent related work on decarboxylative cross-coupling reactions, see: (a) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem., Int. Ed.* **1997**, *36*, 155−156. (b) Goossen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662−664. (c) Forgione, P.; Brochu, M. C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350−11351. (d) Goossen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824−4833. For decarboxylation as a side reaction with palladium catalysts, see: (e) Lee, J. M.; Chang, S. *Tetrahedron Lett.* **2006**, *47*, 1375−1379.

(10) Matsubara, S.; Yokota, Y.; Oshima, K. *Org. Lett.* **2004**, *6*, 2071−2073.

be determined. Thus, ^{1}H NMR spectroscopy was employed to monitor the formation of the aryl palladium intermediate (**7**) and the product (**3a**) during the course of the reaction. In the first experiment, substrate **2a** was treated with stoichiometric palladium(II) trifluoroacetate in the presence of excess methanesulfonic acid. Under these conditions, carboxylate exchange occurred rapidly and adduct **6** was the only species observed at the beginning of the reaction. Upon heating to 65 °C, formation of the aryl palladium species (**7**) was directly related to the disappearance of adduct **6** during the initial stages of the reaction (Figure 1). The disappearance of **6** was a first-order process ($k = 0.25$ h^{-1}, $t_{1/2} = 2.8$ h). As the reaction progressed, aryl palladium species **7** began to react forming the product **3a** via a zero-order process ($k = 2.73$ mM/h, $t_{1/2} = 17.7$ h). Overall, formation of aryl palladium **7** is much faster than the final protonolysis step (**7** to **3a**). This result clarifies the need for excess acid to achieve a reasonable reaction time. While the mechanism in Scheme 4 does not require any additional acid for turnover, the slow step (**7** to **3a**) does depend on the acid concentration.

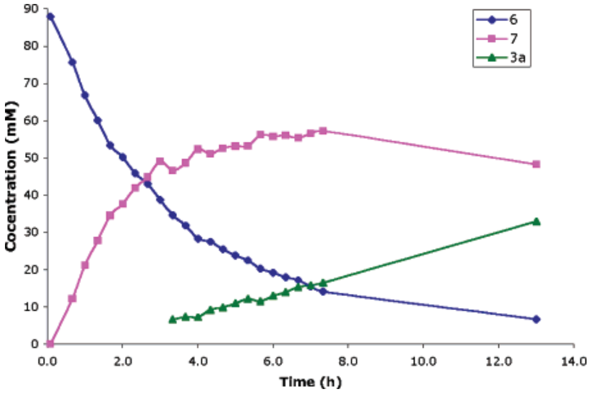


Figure 1. NMR monitoring of the decarboxylation of **2a** (reaction conditions: initial concentration [**2a**] = 88 mM and [Pd(O_2CCF_3)$_2$] = 105 mM, CH_3SO_3H (10 equiv), 0.75 mL d_6-DMSO, 65 °C).

To further probe the protonation reaction, the aryl palladium intermediate (**7**) was generated in the absence of acid and then treated with 10 equiv of methanesulfonic acid. Monitoring by ^{1}H NMR spectroscopy revealed a linear relationship between formation of product (**3a**) and consumption of intermediate **7** (Figure 2). The much slower rate of this reaction (reaction of **7** was apparently zero order, $k = 2.69$ mM/h, $t_{1/2} = 13$ h) even with excess acid explains why the decarboxylative Heck reaction[8] can be so successful.

Namely, the aryl palladium species is sufficiently stable that migratory insertion into the alkene can occur before protonation. Additionally, the basic Ag_2CO_3 employed in the Heck process[8] likely serves to scavenge any free acid further preventing protonation. Overall, the results of the ^{1}H NMR experiments indicated that protonation is the slow step. On this basis, the following general parameters were developed: ≤20 mol % of palladium(II) trifluoroacetate, an excess of a strong acid such as trifluoroacetic acid, and no base such as Ag_2CO_3.

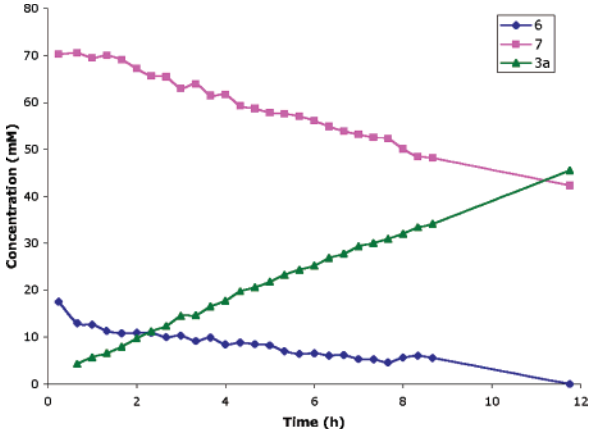
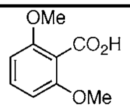
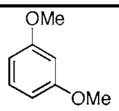
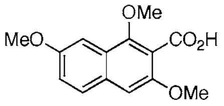
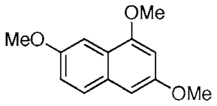
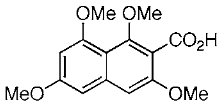
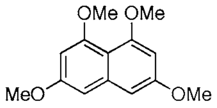
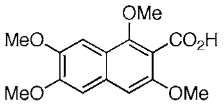
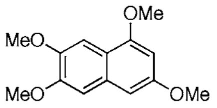
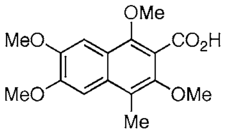
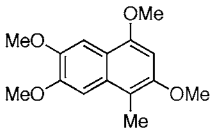


Figure 2. Protonolysis of the aryl palladium intermediate corresponding to **7** from **2a** (reaction conditions: initial concentration [**2a**] = 88 mM and [Pd(O_2CCF_3)$_2$] = 105 mM, CH_3SO_3H (10 equiv), 0.75 mL d_6-DMSO, 65 °C (aryl palladium formed at 70 °C but protonolysis at 65 °C)).

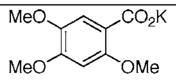
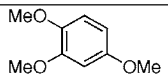
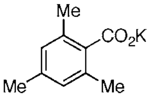
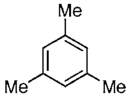
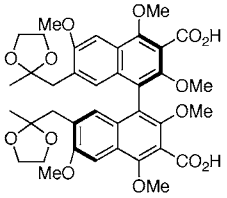
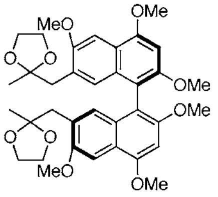
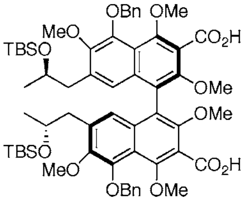
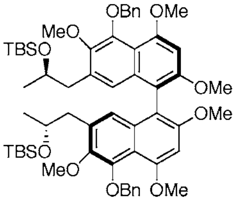
Surprisingly, when the methodology was extended to other substrates it was found that two *ortho* substituents were required to obtain high yields of the decarboxylation

Table 1. Catalytic Palladium Decarboxylation

entry	substrate	product[a]	yield (%)[b]
1	 **2a**	 **3a**	100
2	 **2b**	 **3b**	71[c]
3	 **2c**	 **3c**	72
4	 **2d**	 **3d**	74
5	 **2e**	 **3e**	75[c]

[a] Reaction conditions: Pd(O_2CCF_3)$_2$ (0.2 equiv), 70 °C, CF_3CO_2H (10 equiv), 5% DMSO/DMF. [b] Isolated yield. [c] 80 °C.

Table 2. Stoichiometric Palladium Decarboxylation

entry	substrate	product[a]	yield (%)[b]
6	 **2f**	 **3f**	55
7	 **2g**	 **3g**	42
8	 **2h**	 **3h**	64[c,d]
9	 **2i**	 **3i**	55[c,e]

[a] Reaction conditions: $Pd(O_2CCF_3)_2$ (1.2 equiv), 70 °C, CF_3CO_2H (10 equiv), 5% DMSO/DMF. [b] Isolated yields. [c] $Pd(O_2CCF_3)_2$ (2.5 equiv), Ag_2CO_3 (6 equiv), 75 °C, followed by $NaBH_4$. [d] No loss of enantioselectivity. [e] No loss of diastereoselectivity.

products. Further NMR experiments elucidated a secondary pathway with mono-*ortho*-substituted substrates comprised of C−H insertion into positions adjacent to the carboxyl group. Unfortunately, no conditions were found to completely prevent this undesired reaction from occurring. Nevertheless, the substrate scope of bis-*ortho*-substituted compounds was found to be good with use of the catalytic palladium conditions as illustrated in Table 1.

Further substrates were also explored with stoichiometric palladium as shown in Table 2. For entries 6 and 7, the potassium carboxylate salts were employed which precluded turnover. Even so, these salts were found to undergo more rapid reaction than the free acid under comparable conditions. The substrates from entries 8 and 9 were not explored with catalytic palladium as they are very late stage intermediates. For these compounds, the aryl palladium species was deliberately formed and then reduced with sodium borohydride. In fact, many other hydrogen sources were found to be effective when this approach was employed. For example, methanesulfonic acid, acetic acid, nitric acid, and *p*-nitrobenzoic acid were all effective with catalytic palladium. With stoichiometric palladium, diethylsilane, triethylsilane, triisopropylsilane, triphenylsilane, diethylmethylsilane, borane−THF complex, PHMS/KF, Mg/NH_4OAc, sodium formate, ammonium formate, sodium methoxide, and potassium carbonate/methanol were all found to be viable.

In conclusion, a catalytic decarboxylation method has been realized for electron-rich bis-*ortho*-substituted aromatic compounds. This mild and efficient decarboxylation can be employed with sensitive substrates. This method works especially well with substrates that contain sterically hindered carboxylic acids. Further details about this and other aspects will be reported in due course.

Acknowledgment. This research was supported by the National Institutes of Health (CA-109164). We thank 3D Pharmaceuticals (C.A.M.), the Division of Organic Chemistry of the ACS (C.A.M.), Eli Lilly (E.M.B), and the Department of Chemistry at the University of Pennsylvania (E.M.B) for graduate fellowships.

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

OL070749F