Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: R. A. Daley and J. J. Topczewski, *Org. Biomol. Chem.*, 2018, DOI: 10.1039/C8OB01806E.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C8OB01806E

Organic & Biomolecular Chemistry

COMMUNICATION

Palladium-Catalyzed Salt-Free Double Decarboxylative Aryl Allylation

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

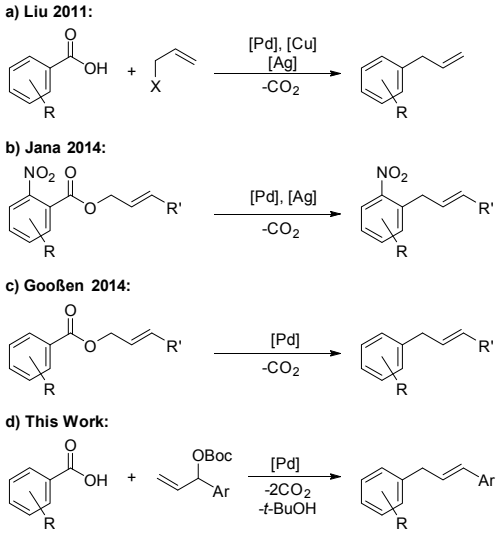
Ryan A. Daley and Joseph J. Topczewski*

This report describes a palladium-catalyzed decarboxylative aryl allylation between unactivated benzoic acids and allylic carbonates. This transformation successfully couples a variety of carbonates and benzoic acids in good yield (up to 94%) using 1 mol% palladium. This salt free allyl-arylation proceeds without added base, copper, or silver. The only stoichiometric byproducts are carbon dioxide and *tert*-butanol.

Traditional palladium catalyzed cross-coupling reactions enable the synthesis of natural products, agrochemicals, and pharmacueticals.[1,2] Classically, these transformations are limited by the use of stoichiometric organometallic nucleophiles, which can be expensive to prepare and are often unstable. Additionally, such transformations often require insoluble inorganic bases or additives to activate the catalyst for transmetalation.[3] The products are typically purified from excess base or other stoichiometric salts via liquid-liquid extraction. Solvents account for 80-90% of the mass used in the pharmaceutical industry,[4] of which a sizable percentage is used during extractions. Water, used primary for salt removal, accounts for ~20% of the mass used in synthesis even after process optimization.[5] As such, the use of preformed metal nucleophiles and inorganic bases generates a substantial amount of waste. Developing catalytic methods that do not require these additives and that can proceed without salt formation are therefore advantageous.

An alternative route to access aryl-metal intermediates for cross-coupling is through the decarboxylation of benzoic acids. Decarboxylation has emerged as an exciting alternative to both traditional cross-coupling and C-H activation because it uses simple and readily available benzoic acids and is highly site-selective.[6,7] A variety of transition metals such as copper,[8,9] silver,[10,11] gold,[12,13] and palladium[14–19] are competent for the decarboxylation of benzoic acids. Many protocols however are impractical because they use multiple metal sources, additional additives, and/or pre-activated benzoic acids (carboxylate salts or activated esters).

In aryl-decarboxylative coupling, the identity of the electrophilic coupling partner has been mostly limited to aryl halides, aryl tosylates and alkenes,[20,21] which is in contrast to the broad scope of alkyl decarboxylation reacitons.[22] A few successful allylation reactions have been reported. In 2011, Liu reported the decarboxylative allylation of electron rich benzoic acids with a mixture of catalytic palladium, catalytic copper, and stoichiometric silver (Scheme 1a).[23] The reaction relied on large quantities of silver for catalytic turnover and was not amenable to using allylic acetates, which underwent Heck coupling. In 2014, Jana[24] and Gooßen[15] independently reported intramolecular decarboxylative allylations of preformed esters (Scheme 1b and 1c respectively). Jana attempted the coupling with free benzoic acids, but was unable to attain selectivity for allylation over protodecarboxylation.[24]



Scheme 1 Palladium-Catalyzed Decarboxylative Allylations.

Herein, we report a method for the intermolecular decarboxylative allylation between *free benzoic acids* and allyl-*tert*-butyl-carbonates (Scheme 1d). This reaction likely generates an equivalent of *tert*-butoxide *in situ*, which can subsequently deprotonate the benzoic acid. As such, no exogenous base is required. The stoichiometric byproducts, carbon dioxide and *tert*-butanol, are volatile, which obviates the need for an aqueous extraction or additional solvent.

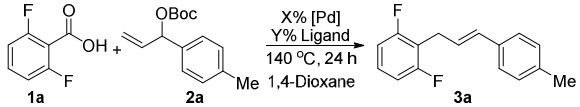
Department of Chemistry, University of Minnesota, Minneapolis MN 44544, United states of America. E-mail: jtopczew@umn.edu

† Electronic Supplementary Information (ESI) available: Experimental procedures, ^{1}H, ^{13}C, and ^{19}F NMR spectra. See DOI: 10.1039/x0xx00000x

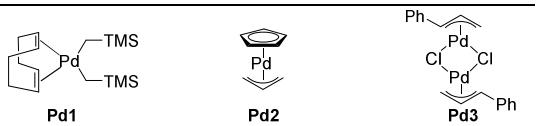
View Article Online
DOI: 10.1039/C8OB01806E

Our investigation into decarboxylative allylation began with the coupling between 2,6-difluorobenzoic acid (**1a**), which readily decarboxylates with palladium,[15] and carbonate **2a**, a preferred substrate for allylation. Conditions with 5 mol% Pd_2dba_3, 10 mol% BINAP, in anhydrous 1,4-dioxane, at 140 °C provided a modest yield of product **3a** (table 1, entry 1). In our hands, using Pd_2dba_3 as a palladium source afforded variable results. The precatalyst Pd_2dba_3 is known to form nanoparticles of Pd,[25] and this could be the cause of the observed irreproducibility. Changing the pre-catalyst to the palladium(II) complex **Pd1** improved the yield to 68% (table 1, entry 2), while the use of precatalysts **Pd2** and **Pd3** led to a significant decrease in yield (table 1, entries 3-4). Furthermore, using complex **Pd1** as the palladium source provided more reproducible outcomes. The reaction was not improved by modifying the bidentate ligand (table 1, entries 5-8) or by using a monodentate ligand (table 1, entries 9-11). Using less ligand was tolerated (table 1, entry 12). As anticipated, the reaction was inhibited by excess BINAP (table 1, entry 13) as the palladium likely becomes coordinately saturated. Lowering the catalyst loading to 5 mol% Pd and then to 1 mol% Pd increased the yield to 86% by improving the selectivity of the reaction (table 1, entries 14, 15) These conditions are the first intermolecular allylation that occurs with a low loading of a single metal and use the *free* carboxylic acid.

Table 1 Optimization of the decarboxylative allylation reaction. [a]

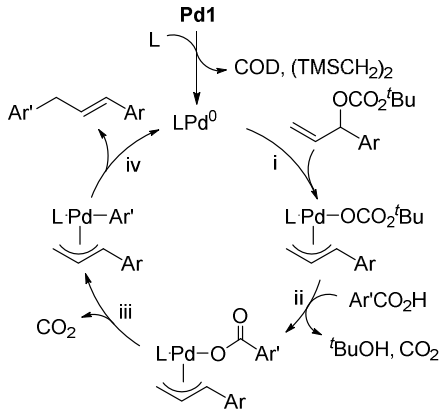


Entry	[Pd]	Ligand	mol % cat loading	Ligand:[Pd] Ratio	% 3a[b]
1	Pd_2dba_3	BINAP	5%	1:1	50%
2	**Pd1**	BINAP	10%	1:1	68%
3	**Pd2**	BINAP	10%	1:1	42%
4	**Pd3**	BINAP	5%	1:1	<5%
5	**Pd1**	Xantphos	10%	1:1	<5%
6	**Pd1**	*p*-Tol-BINAP	10%	1:1	49%
7	**Pd1**	Segphos	10%	1:1	64%
8	**Pd1**	dppb	10%	1:1	50%
9	**Pd1**	PPh_3	10%	2:1	<5%
10	**Pd1**	PCy_3	10%	2:1	49%
11	**Pd1**	$P(p\text{-Tol})_3$	10%	2:1	<5%
12	**Pd1**	BINAP	10%	1:2	78%
13	**Pd1**	BINAP	10%	2:1	<5%
14	**Pd1**	BINAP	5%	1:1	80%
15	**Pd1**	BINAP	1%	1:1	86%



[a] Reaction conditions: benzoic acid (63 µmol), carbonate (95 µmol), biphenyl standard (16 µmol), [Pd] (0.6 - 6 µmol, 1 - 10 mol %), ligand (0.6 - 6 µmol, 1 - 10 mol %), 1,4-dioxane (0.32 mL), under nitrogen, at 140 °C for 24h. [b] Yields were determined by calibrated GC−FID analysis. Reactions were carried out in triplicate, and the average value is reported.

We propose a mechanism for this transformation that is based on prior work regarding palladium catalysed decarboxylation reactions (Scheme 2).[26,27] Our reaction was not inhibited by the addition of TEMPO or BHT, which supports a two-electron pathway (see ESI for details). Without a more detailed kinetic analysis it is difficult to assign the exact sequence of events or ancillary ligands. However, our current understanding is consistent with the general mechanism shown (Scheme 2). Ligand exchange on the pre-catalysts to forms a ligated palladium (0). Oxidative addition with the allylic carbonate could generate a π-allyl palladium (II) complex (Scheme 2i). The initial complex could lose CO_2 to generate *tert*-butoxide, which would facilitate ligand exchange with the benzoic acid (Scheme 2ii). A second decarboxylation from the palladium carboxylate would generate a new palladium (II) aryl complex (Scheme 2iii). Reductive elimination would afford the product and regenerate palladium (0) (Scheme 2iv). Several by-products of this reaction where characterized throughout this work and a description is included (see ESI for details).



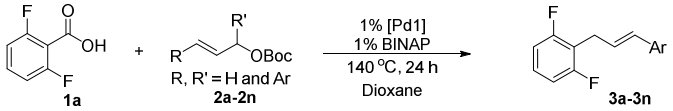
Scheme 2 Proposed Mechanism for Allylation.

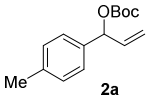
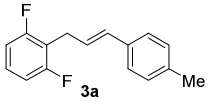
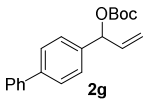
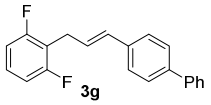
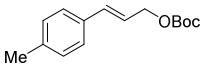
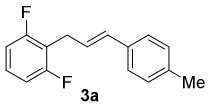
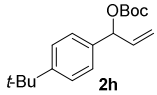
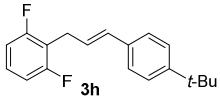
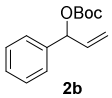
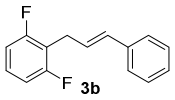
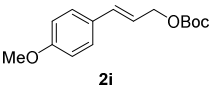
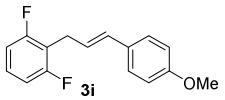
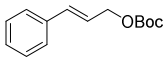
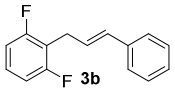
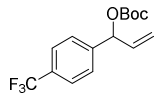
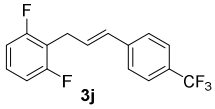
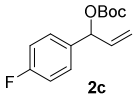
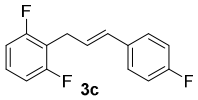
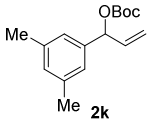
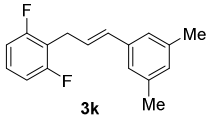
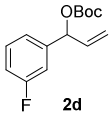
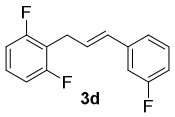
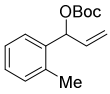
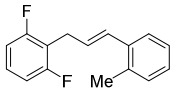
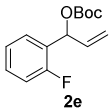
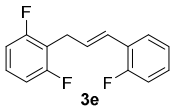
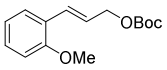
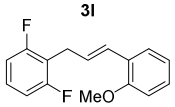
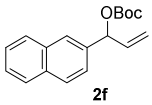
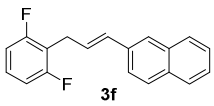
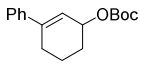
With the optimized conditions identified, we explored the substrate scope of the carbonate coupling partner using 2,6-difluorobenzoic acid (table 2). Both branched carbonates (**2a**, **2b**) and linear carbonates (**2a'**, **2b'**) gave comparable yields of products **3a** and **3b** respectively. Either carbonate presumably generates the same π-allyl-Pd intermediate. The reaction worked well with carbonates containing a fluorine atom in the *para* (**2c**), *meta* (**2**), or *ortho* (**2e**) position. Napthyl carbonate (**2f**) as well as carbonates containing additional remote alkyl or aryl groups (**2g**, **2h,** and **2k**) readily underwent the allylation in good yield. Both electron rich carbonates (**2i**, and **2m**) and electron deficient carbonate **2j** were compatible with the reaction. Electron rich carbonates (**2i** and **2m**) and an electron deficient carbonate (**2j**) underwent the reaction at significantly different rates (18h vs 5 days). Carbonates with *ortho*-groups (**2L**, **2m**) were tolerated. Unfortunately, a carbonate containing a cyclic alkene (**2n**) failed to form product under the reaction conditions.

The benzoic acid scope was more limited than the scope of allylic carbonates. Like other palladium catalyzed decarboxylations, two *ortho*-substituents are required for reactivity and to prevent competitive directed C-H activation. Benzoic acids with additional *para*- or *meta*-fluoro substituents (**3o** and **3p**) provided a good yield under the reaction conditions. However, the yield for the decarboxylation of pentaflourobenzoic acid (**3q**) was poor due to uncontrolled protodecarboxylation. The addition of an aryl chloro substituent significantly decreased the yield (**3r**), likely caused by competitive oxidative addition of palladium into the carbon-chlorine bond. The addition of electron donating groups (**3s**, **3t**, **3u**, and **3v**)

View Article Online
DOI: 10.1039/C8OB01806E
Journal Name COMMUNICATION

Table 2 Scope of the carbonate coupling partner for the decarboxylative allylation.



Starting Material	Product	% Yield[b]	Starting Material	Product	% Yield[b]
 2a	 3a	87%	 2g	 3g	81%
 2a'	 3a	80%	 2h	 3h	82%
 2b	 3b	83%	 2i	 3i	81%[c]
 2b'	 3b	79%	 2j	 3j	76%[d]
 2c	 3c	81%	 2k	 3k	76%
 2d	 3d	78%	 2l	 3l	86%
 2e	 3e	90%	 2m	 3m	94%[c]
 2f	 3f	78%	 2n		<5%

[a] Reaction conditions: benzoic acid (430 µmol), carbonate (640 µmol), **Pd1** (4.3 µmol, 1 mol %), BINAP (4.3 µmol, 1 mol %), 1,4-dioxane (2.1 mL), under nitrogen, at 140 °C for 24h. [b] Yields are of isolated and purified material. Values reported are the average of duplicate, or triplicate trials. [c] Reaction run for 18h. [d] Reaction run for 5 days.

required increased temperatures, but still provided an acceptable yield of the product. Either or both of the two *ortho*-fluorines could be replaced with methoxy groups (3w and 3x).

Conclusions

In conclusion, we report the first salt-free intermolecular decarboxylative allylation reaction between *free* benzoic acids and allylic *tert*-butyl-carbonates. The combination of precatalyst **Pd1** with BINAP was found to promote the reaction at 1 mol% catalyst loading. The transformation was successfully applied to a variety carbonates and 2,6-disubstituted benzoic acids. Further applications of our salt free approach to decarboxylation will be reported in due course.

Conflicts of interest

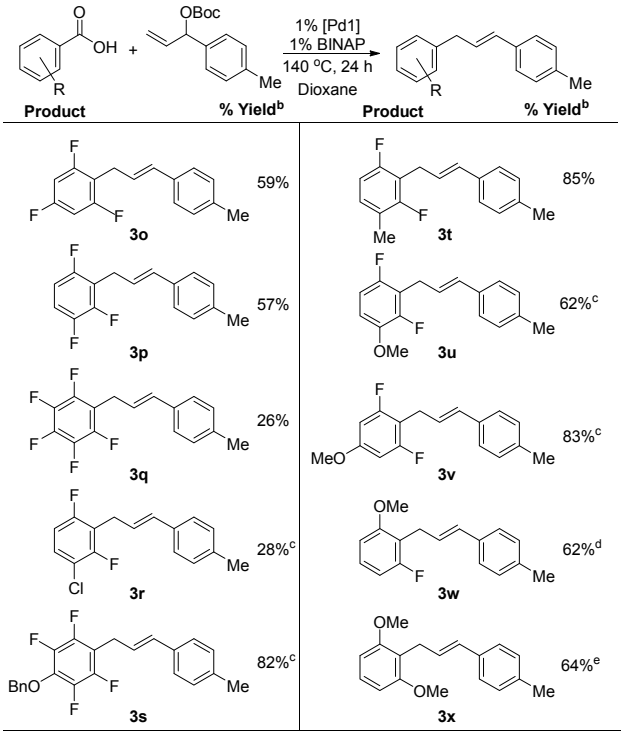
We declare no conflicts of interest.

Acknowledgements

Alanna Hildebrandt is thanked for helping with starting material synthesis. Financial support was provided by the University of Minnesota.

View Article Online
DOI: 10.1039/C8OB01806E

Table 3 Scope of benzoic acid coupling partner. [a]



[a] Reaction conditions: benzoic acid (430 µmol), carbonate (640 µmol), **Pd1** (4.3 µmol, 1 mol %), BINAP (4.3 µmol, 1 mol %), 1,4-dioxane (2.1 mL), under nitrogen, at 140 °C for 24h. [b] Yields are of isolated and purified material. Values reported are the average of duplicate or triplicate trials. [c] Reaction run at 160 °C for 48h. [d] Reaction run at 160°C for 5 days. [e] Reaction run at 180 °C for 48h.

Notes and references

1 M. Busch, M. D. Wodrich and C. Corminboeuf, *ACS Catal.*, 2017, **7**, 5643–5653.

2 C. C. C. Johansson Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chemie Int. Ed.*, 2012, **51**, 5062–5085.

3 A. A. Thomas and S. E. Denmark, *Science*, 2016, **352**, 329–332.

4 D. J. C. Constable, C. Jimenez-Gonzalez and R. K. Henderson, *Org. Process Res. Dev.*, 2007, **11**, 133–137.

5 D. Cespi, E. S. Beach, T. E. Swarr, F. Passarini, I. Vassura, P. J. Dunn and P. T. Anastas, *Green Chem.*, 2015, **17**, 3390–3400.

6 N. Rodríguez and L. J. Gooßen, *Chem. Soc. Rev.*, 2011, **40**, 5030.

7 W. I. Dzik, P. P. Lange and L. J. Gooßen, *Chem. Sci.*, 2012, **3**, 2671–2678.

8 L. J. Gooßen, G. Deng and L. M. Levy, *Science*, 2006, **313**, 662–664.

9 L. J. Gooßen, N. Rodríguez and C. Linder, *J. Am. Chem. Soc.*, 2008, **130**, 15248–15249.

10 P. Lu, C. Sanchez, J. Cornella and I. Larrosa, *Org. Lett.*, 2009, **11**, 5710–5713.

11 R. A. Crovak and J. M. Hoover, *J. Am. Chem. Soc.*, 2018, **140**, 2434–2437.

12 J. Cornella, M. Rosillo-Lopez and I. Larrosa, *Adv. Synth. Catal.*, 2011, **353**, 1359–1366.

13 S. S. Dupuy, F. F. Lazreg, A. M. Z. M. Z. Slawin, C. S. J. S. J. Cazin and S. P. P. Nolan, *Chem. Commun.*, 2011, **47**, 5455–5457.

14 A. G. Myers, D. Tanaka and M. R. Mannion, *J. Am. Chem. Soc.*, 2002, **124**, 11250–11251.

15 K. F. Pfister, M. F. Grünberg and L. J. Gooßen, *Adv. Synth. Catal.*, 2014, **356**, 3302–3306.

16 D. Nandi, Y. M. Jhou, J. Y. Lee, B. C. Kuo, C. Y. Liu, P. W. Huang and H. M. Lee, *J. Org. Chem.*, 2012, **77**, 9384–9390.

17 R. Shang, Q. Xu, Y.-Y. Jiang, Y. Wang and L. Liu, *Org. Lett.*, 2010, **12**, 1000–1003.

18 J. S. Dickstein, C. A. Mulrooney, E. M. O'Brien, B. J. Morgan and M. C. Kozlowski, *Org. Lett.*, 2007, **9**, 2441–2444.

19 J. Cornella, M. Righi and I. Larrosa, *Angew. Chemie Int. Ed.*, 2011, **50**, 9429–9432.

20 T. Patra and D. Maiti, *Chem. Eur. J.*, 2017, **23**, 7382–7401.

21 N. Rodriguez, L. J. Gooßen, N. Rodríguez and L. J. Gooßen, *Chem. Soc. Rev.*, 2011, **40**, 5030–5048.

22 J. D. Weaver, A. Recio, A. J. Grenning and J. A. Tunge, *Chem. Rev.*, 2011, **111**, 1846–1913.

23 J. Wang, Z. Cui, Y. Zhang, H. Li, L.-M. Wu and Z. Liu, *Org. Biomol. Chem.*, 2011, **9**, 663–666.

24 A. Hossian, S. Singha and R. Jana, *Org. Lett.*, 2014, **16**, 3934–3937.

25 S. S. Zalesskiy and V. P. Ananikov, *Organometallics*, 2012, **31**, 2302–2309.

26 D. Tanaka, S. P. Romeril and A. G. Myers, *J. Am. Chem. Soc.*, 2005, **127**, 10323–10333.

27 J. S. Dickstein, J. M. Curto, O. Gutierrez, C. A. Mulrooney and M. C. Kozlowski, *J. Org. Chem.*, 2013, **78**, 4744–4761.