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Direct *ortho*-Arylation of *ortho*-Substituted Benzoic Acids: Overriding Pd-Catalyzed Protodecarboxylation

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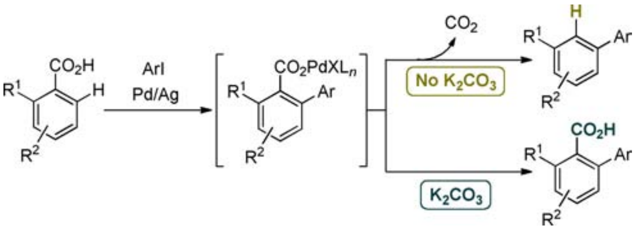
ABSTRACT



***ortho*-Arylation of *ortho*-substituted benzoic acids is a challenging process due to the tendency of the reaction products toward Pd-catalyzed protodecarboxylation. A simple method for preventing decarboxylation in sterically hindered benzoic acids is reported. The method described represents a reliable and broadly applicable entry to 2-aryl-6-substituted benzoic acids.**

Recent advances in synthetic chemistry have allowed chemists to contemplate C–H bonds as an advantageous starting point for chemical functionalization.[1] Due to the ubiquity of C–H bonds in organic molecules and their inert nature, the innovation and creativity seen in C–H functionalization processes over the past few decades have been centered on achieving C–H bond activation in a selective manner. In this regard, the presence of coordinating ligands or directing groups within the substrates has been successfully used to bind the metal catalyst and selectively deliver it to a proximal C–H bond. In particular, the commonly occurring carboxylic acids have proved to be excellent directing groups for Pd-catalyzed aromatic functionalization.[2] Despite the multiple examples of Pd-catalyzed carboxylate-directed transformations, it is surprising that the direct C–H arylation of *ortho*-substituted benzoic acids with haloarene coupling partners remains largely unexplored.[3] Given that 2-aryl-6-substituted benzoic acids (Scheme 1, bottom) are present

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(1) For a recent special issue on C–H functionalization, see: (a) Doyle, M. P.; Goldberg, K. I. *Acc. Chem. Res.* **2012**, *45*, 777. For selected reviews, see: (b) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Sun, C. -L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (e) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315. (f) McMurray, L.; O'Hara, F. O.; Gaunt, M. *Chem. Soc. Rev.* **2011**, *40*, 1885. (g) Boorman, T. C.; Larrosa, I. *Chem. Soc. Rev.* **2011**, *40*, 1910. (h) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (i) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (j) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (k) Lyons, T. W.; Sanford, M. *Chem. Rev.* **2010**, *110*, 1147. (l) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (m) Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *Acc. Chem. Res.* **2008**, *41*, 1013.

(2) (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (b) Satoh, T.; Miura, M. *Synthesis* **2010**, 3395. (c) Chen, X.; Engle, K. M.; Wang, D. H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (d) Daugulis, O.; Do, H. Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.

(3) To the best of our knowledge, only the *ortho*-arylation of 2-toluic and 2-phenylbenzoic acids with haloarenes has been reported: (a) Giri, R.; Maugel, N. L.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Chiong, H. A.; Pham, Q.-N.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 9879. For three more examples using Ar–BF_3K as the coupling partner, see: (c) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676.

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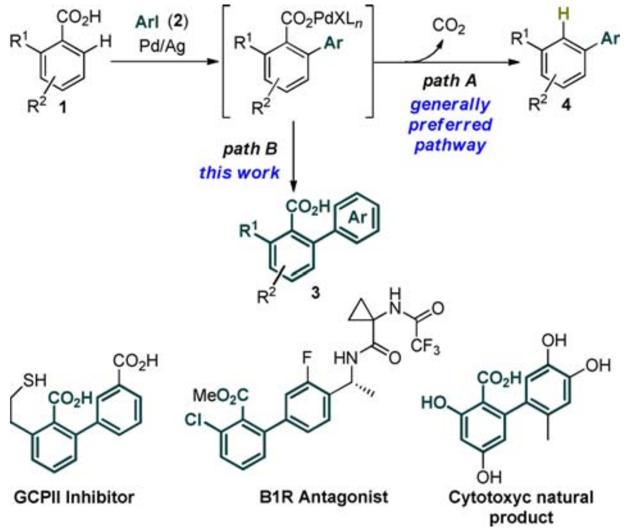
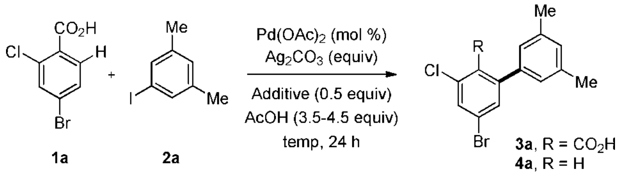
in natural products with cytotoxic activity[4a] and show promise as hGPR91 antagonists,[4b] glutamate carboxypeptidase II (GCPII) inhibitors,[4c] Bradykinin B1 receptor (B1R) antagonists,[4d,e] and 3-HAO inhibitors,[4f] a general method allowing their direct synthesis via *ortho*-arylation of *ortho*-substituted benzoic acids would be highly useful.

Scheme 1. Synthetic Approach to 2-Aryl-6-Substituted Benzoic Acids **3**



Previous studies in our group have shown that the core to the difficulty in synthesizing 2-aryl-6-substituted benzoic acids is their intrinsic instability toward Pd-catalyzed protodecarboxylation under the reaction conditions (Scheme 1, *path A*).[5] In line with our experimental observation, recent DFT studies on decarboxylation reactions have concluded that *ortho* substituents can significantly enhance metal-catalyzed protodecarboxylation.[6] To access the elusive 2-aryl-6-substituted benzoic acids it would be necessary to develop a catalytic system where the Pd-mediated decarboxylation event could be switched off after the coupling has occurred (*path B*). Herein, we disclose the development of such a method, resulting in an efficient and practical protocol for the synthesis of these highly hindered benzoic acids.

Table 1. Selected Optimization Results^{a}



entry	Pd mol %	Ag_2CO_3 equiv	additive	temp (°C)	yield (%)^{b} **3a** + **4a**
1^{c}	2	1	–	130	22 + 75
2	2	1	–	120	70 + 11
3^{d}	2	1	–	120	7 + 80
4	4	1	–	120	10 + 70
5	1	1	–	120	42 + 6
6	2	0.5	–	120	22 + 70
7	2	0.5	Li_2CO_3	120	56 + 5
8	2	0.5	Na_2CO_3	120	47 + 10.5
9	2	0.5	K_2CO_3	120	70 + 4.5
10	2	0.5	Cs_2CO_3	120	73 + 5
11	2	0.55	K_2CO_3	120	81 (76)^{e} + 5
12	2	0.55	K_2CO_3	130	78 + 5
13^{d}	2	0.55	K_2CO_3	120	81 + 5.5

[a] Unless otherwise noted, all reactions were carried out using $Pd(OAc)_2$ as the catalyst, Ag_2CO_3, 1 equiv of **1a**, and 3 equiv of **2a** in AcOH as a solvent for 24 h. [b] Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction run for 16 h. [d] Reaction run for 67 h. [e] Yield of the isolated pure product **3a** is shown in parentheses.

On the basis of our previous work[5] and Daugulis' pioneering studies,[3b] the reaction optimization was carried out with *ortho*-substituted benzoic acid **1a** and iodoarene **2a** as the coupling partner in a Pd/Ag system (Table 1). Implementation of our previously reported conditions, as expected, led to decarboxylated biaryl **4a** as the major product (entry 1). Lowering the reaction temperature to 120 °C minimized the protodecarboxylation step and allowed the formation of the desired product, **3a** (entry 2).[7] However, under these conditions benzoic acid **3a** proved to be very sensitive toward protodecarboxylation with longer reaction times favoring this undesired process (entry 3). Seeking a more robust catalytic system, we confirmed that Pd species (and not Ag) were responsible for the decarboxylation of the product **3a**: raising the catalyst loading to 4 mol % appeared to promote extrusion of CO_2, allowing good conversion to side product **4a** (entry 4). On the contrary, low catalyst loadings led to a slower decarboxylation although these conditions proved to be counterproductive as they compromise the *ortho*-arylation step (entry 5). On the other hand, decreasing the amount of Ag_2CO_3 to 0.5 equiv led to a significant increase in

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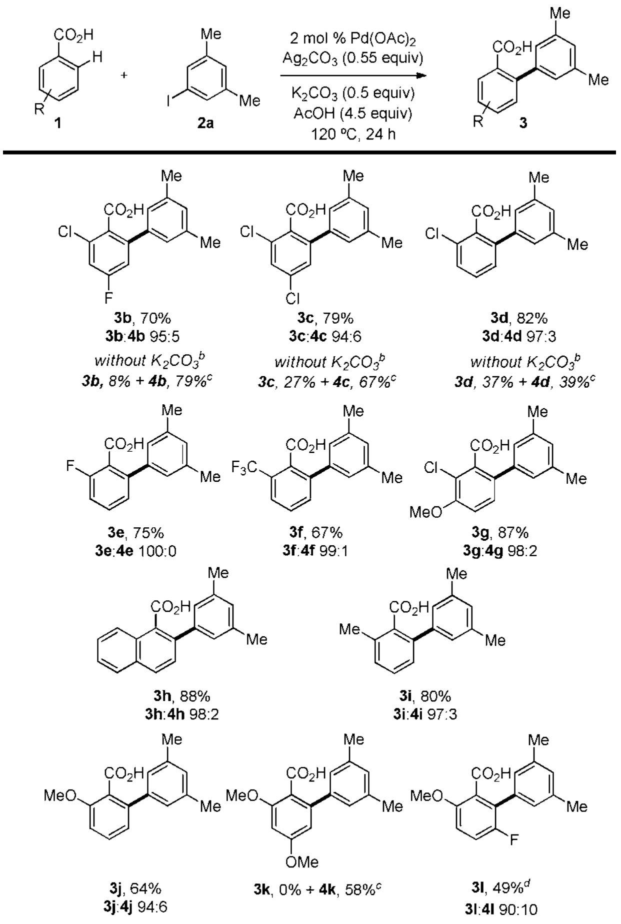
(4) (a) Aly, A. H.; Edrada-Ebel, R.; Indriani, I. D.; Wray, V.; Müller, W. E. G.; Totzke, F.; Zirrgiebel, U.; Schächtele, C.; Kubbutat, M. H. G.; Lin, W. H.; Proksch, P.; Ebel, R. *J. Nat. Prod.* **2008**, *71*, 972. (b) Bhuniya, D.; Umrani, D.; Dave, B.; Salunke, D.; Kukreja, G.; Gundu, J.; Naykodi, M.; Shaikh, N. S.; Shitole, P.; Kurhade, S.; De, S.; Majumdar, S.; Reddy, S. B.; Tambe, S.; Shejul, Y.; Chugh, A.; Palle, V. P.; Mookhtiar, K. a; Cully, D.; Vacca, J.; Chakravarty, P. K.; Nargund, R. P.; Wright, S. D.; Graziano, M. P.; Singh, S. B.; Roy, S.; Cai, T.-Q. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3596. (c) Stoermer, D.; Vitharana, D.; Hin, N.; Delahanty, G.; Duvall, B.; Ferraris, D. V; Grella, B. S.; Hoover, R.; Rojas, C.; Shanholtz, M. K.; Smith, K. P.; Stathis, M.; Wu, Y.; Wozniak, K. M.; Slusher, B. S.; Tsukamoto, T. *J. Med. Chem.* **2012**, *55*, 5922. (d) Huang, H.; Placer, M. P. *J. Med. Chem.* **2010**, *53*, 5383. (e) Kuduk, S. D.; Di Marco, C. N.; Chang, R. K.; Wood, M. R.; Schirripa, K. M.; Kim, J. J.; Wai, J. M. C.; DiPardo, R. M.; Murphy, K. L.; Ransom, R. W.; Harrell, C. M.; Reiss, D. R.; Holahan, M. A.; Cook, J.; Hess, J. F.; Sain, N.; Urban, M. O.; Tang, C. *J. Med. Chem.* **2007**, *50*, 272. (f) Linderberg, M.; Hellberg, S.; Björk, S.; Gotthammar, B.; Högberg, T. *Eur. J. Med. Chem.* **1999**, *34*, 729.

(5) Cornella, J.; Righi, M.; Larrosa, I. *Angew. Chem., Int. Ed.* **2011**, *50*, 9429.

(6) (a) Xue, L.; Su, W.; Lin, Z. *Dalton Trans.* **2011**, *40*, 11926. (b) Xue, L.; Su, W.; Lin, Z. *Dalton Trans.* **2010**, *39*, 9815.

(7) For the initial screening of solvents and various palladium and silver sources, see Table S1 in the Supporting Information.

Scheme 2. Scope of Benzoic Acids[a]



3b, 70%
3b:**4b** 95:5
without K_2CO_3[b]
***3b**, 8% + **4b**, 79%*[c]

3c, 79%
3c:**4c** 94:6
without K_2CO_3[b]
***3c**, 27% + **4c**, 67%*[c]

3d, 82%
3d:**4d** 97:3
without K_2CO_3[b]
***3d**, 37% + **4d**, 39%*[c]

3e, 75%
3e:**4e** 100:0

3f, 67%
3f:**4f** 99:1

3g, 87%
3g:**4g** 98:2

3h, 88%
3h:**4h** 98:2

3i, 80%
3i:**4i** 97:3

3j, 64%
3j:**4j** 94:6

3k, 0% + **4k**, 58%[c]

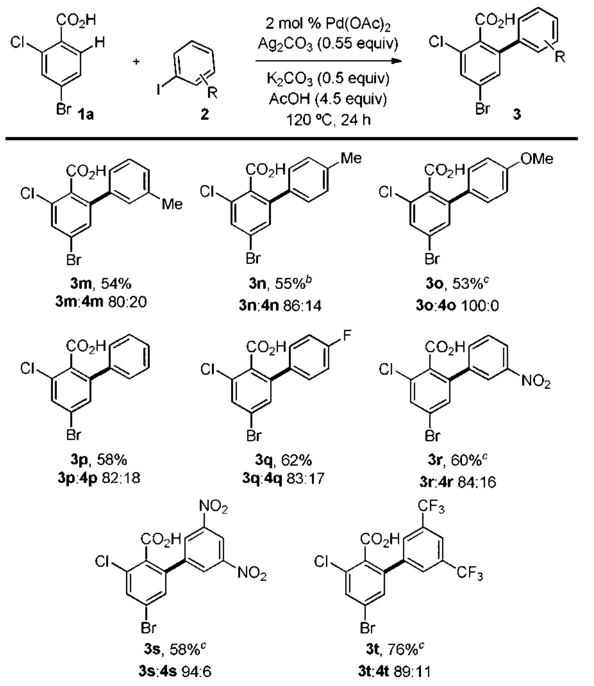
3l, 49%[d]
3l:**4l** 90:10

[a] Yields are of the isolated pure material. The ratio of **3**:**4** products was determined by ^1H NMR analysis of the reaction crude. [b] The reaction was performed in the absence of K_2CO_3. [c] Yields were determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [d] Reaction carried out at 130 °C.

protodecarboxylation, reversing the **3a**:**4a** ratio (entries 2 and 6). These results led us to hypothesize that addition of an external base might have a beneficial effect on suppressing the protodecarboxylation side reaction. The test of Li, Na, K, and Cs carbonate salts as additives (entries 7–10) highlighted that K_2CO_3 and Cs_2CO_3 were indeed able to inhibit protodecarboxylation, dramatically reducing the formation of **4a**. Ultimately, a subtle increase to 0.55 equiv of Ag_2CO_3 in the presence of K_2CO_3 as an additional base turned out to be the most effective combination for high yielding *ortho*-arylation with near-complete suppression of the undesired decarboxylation side reaction (entry 11). These optimized conditions proved to be much more robust and reliable as higher temperatures and longer reaction times barely affect product distribution (entries 12 and 13).

To explore the generality of this new method, we examined the reaction of a variety of *ortho*-substituted benzoic acids (Scheme 2). Gratifyingly, benzoic acids **1b**–**d** underwent *ortho*-arylation to **3b**–**d** in high yields with minimal protodecarboxylation. Remarkably, when these reactions were performed in the absence of K_2CO_3, the products of protodecarboxylation **4b**–**d** were obtained as the major products. Benzoic acids with other *ortho* electron-withdrawing substitutents, F and CF_3, also afforded the desired products **3e** and **3f**, respectively, with exceptional selectivity. Despite the fact that electron-donating substituents generally facilitate Pd-mediated decarboxylation,[8,9] the reaction proceeded smoothly with more electron-rich benzoic acids **1g**–**i**. Remarkably, the reaction tolerated even an *ortho* MeO group, allowing access to **3j** with little decarboxylation. On the other hand, highly electron-rich **3k** was shown to be very unstable under the present reaction conditions, and its decarboxylated side-product **4k** was exclusively detected. Of significant interest was the arylation of sterically hindered 5-fluoro-2-methoxybenzoic acid, affording 1,2,3,4-tetrasubstituted arene derivative **3l**.

Scheme 3. Scope of Iodoarenes[a]



3m, 54%
3m:**4m** 80:20

3n, 55%[b]
3n:**4n** 86:14

3o, 53%[c]
3o:**4o** 100:0

3p, 58%
3p:**4p** 82:18

3q, 62%
3q:**4q** 83:17

3r, 60%[c]
3r:**4r** 84:16

3s, 58%[c]
3s:**4s** 94:6

3t, 76%[c]
3t:**4t** 89:11

[a] Yields are of the isolated pure material. The ratio of **3**:**4** products was determined by ^1H NMR analysis of the reaction crude. [b] Reaction performed with 2 equiv of iodoarene and 0.5 equiv of Ag_2CO_3. [c] Reaction carried out at 130 °C.

The generality of this method was further demonstrated, varying the stereoelectronic properties of the coupling partner (Scheme 3). Taking into account that the nature of the newly installed aryl substituent on the *ortho* position

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(8) For reviews on transition metal mediated protodecarboxylation, see: (a) Rodriguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030. (b) Cornella, J.; Larrosa, I. *Synthesis* **2012**, 653.

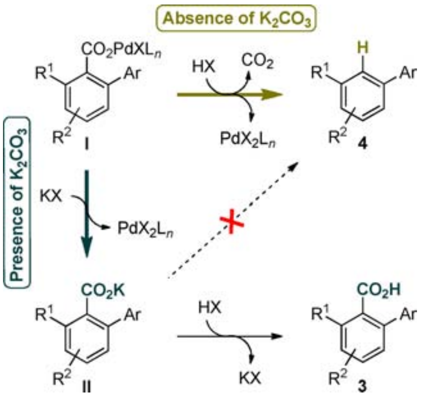
(9) For selected examples of Pd-mediated decarboxylation, see: (a) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323. (b) Dickstein, J. S.; Mulrooney, C. A.; O'Brien, E. M.; Morgan, B. J.; Kozlowski, M. C. *Org. Lett.* **2007**, *9*, 2441. (c) Hu, P.; Kan, J.; Su, W.; Hong, M. *Org. Lett.* **2009**, *11*, 2341. (d) Zhang, S.-L.; Fu, Y.; Shang, R.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 638.

may have a significant influence on the decarboxylation rate of the products, we were pleased to find that a variety of iodoarenes were tolerated with no, or very little, modification being required. Iodoarenes with electron-donating substituents in the *meta* and *para* position furnished products **3m**–**o** in good yields. Remarkably, 4-iodoanisole allowed the *ortho*-arylation process to occur with total prevention of the subsequent decarboxylation step. Despite competing protodecarboxylation, iodobenzene also provided the corresponding benzoic acid derivative **3p** in good yield. Finally, we examined iodoarenes bearing weak and strong electron-withdrawing groups. All reactions proceeded well, and products **3q**–**t** were accessed in good to very good yields.[10]

Based on our experimental observations, we postulated a reaction scenario that could explain the influence of K_2CO_3 on product distribution (Scheme 4). After the consumption of stoichiometric amounts of Ag(I) for iodide removal in the form of AgI,[11] the excess of base KX (X = OAc, HCO_3^-) could allow ligand exchange with the Pd-carboxylate intermediate **I**, thus preventing the Pd-catalyzed decarboxylation process. However, in the absence of KX (Table 1, entry 6) no transmetalation would take place, and the Pd-mediated extrusion of CO_2 would occur preferentially. On the other hand, when excess Ag_2CO_3 is used (Table 1, entries 1–3) the resulting Ag-carboxylate can also undergo protodecarboxylation, leading to a less reliable procedure.[12]

The method is practically simple, often with only an acid–base workup and/or a recrystallization being required to obtain analytically pure material. This makes the process easily scalable. As an example, the reaction of 8.40 g of **1g** (45 mmol) was directly carried out without further optimization, affording 7.67 g of pure crystalline **3g** (60%).

Scheme 4. Proposed Pathways in Either the Presence or Absence of K_2CO_3



In conclusion, we have developed a practical and general C–H functionalization protocol to access the elusive 2-aryl-6-substituted benzoic acid compounds. The pivotal role of K_2CO_3 in switching off the Pd-mediated protodecarboxylation side reaction has enabled a broad reaction scope overriding the challenging electronic and steric bias of the substrates. The process is scalable, and the sterically hindered benzoic acids formed can be easily purified by recrystallization.

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

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(10) Only iodoarenes were found to undergo the desired C–H arylation reaction, with Ph-Br and Ph-OTf affording only recovered starting materials. Further, 2- and 3-iodo substituted pyridines were also found to be unreactive under our reaction conditions.

(11) For a mechanistic discussion on the role of Ag(I) salts in the C–H arylation step, see ref 3b. For a discussion on the role of carboxylate salts on the C–H arylation step, see ref 2d.

(12) See ref 8 and: (a) Cornella, J.; Sanchez, C.; Banawa, D.; Larrosa, I. *Chem. Commun.* **2009**, 7176. (b) Lu, P.; Sanchez, C.; Cornella, J.; Larrosa, I. *Org. Lett.* **2009**, *11*, 5710. (c) Goossen, L. J.; Linder, C.; Rodriguez, N.; Lange, P. P.; Fromm, A. *Chem. Commun.* **2009**, 7173. (d) Goossen, L. J.; Rodriguez, N.; Linder, C.; Lange, P. P.; Fromm, A. *ChemCatChem* **2010**, *2*, 430.

The authors declare no competing financial interest.