

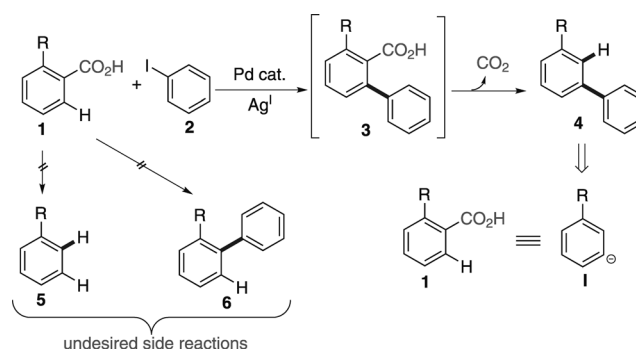
Carboxylic Acids as Traceless Directing Groups for Formal *meta*-Selective Direct Arylation**

Josep Cornella, Marika Righi, and Igor Larrosa*

The synthesis of biaryl compounds is of high importance as these structures form part of numerous natural products, pharmaceuticals, and organic materials.^[1,2] The most commonly used method for their synthesis is the traditional cross-coupling reaction, and this requires the use of organometallic aryl donors. This results in large amounts of waste as well as low atom and step economy, especially when *meta*-substituted aryl donors are required as their preparation usually involves several steps.^[3] In recent years, direct C–H arylation methods have emerged, in which a simple arene is arylated at a C–H bond, thus avoiding the use of an organometallic aryl donor.^[4] However, controlling the regioselectivity of arylation in substituted benzenes is still a great challenge. Recent advances in this area have shown that several types of substituents, including 2-pyridyls, amides, and carboxylic acids among others, can act as directing groups for the direct arylation on the *ortho* position.^[4] *meta*-Selective arylation, on the other hand, is much more difficult to achieve. In 2009, a pioneering report by Gaunt and co-workers described the first method for *meta*-selective direct arylation.^[5] This system, however, is limited exclusively to the use of 2-oxo-substituted directing groups, and the noncommercially available Ar₂IOTf species as the coupling partner. All of these strategies to control the regioselectivity of direct arylation rely on a limited number of directing groups, which require subsequent modification if a different substituent is present in the target molecule. On the contrary, the ideal direct arylation system would allow regioselective coupling regardless of the nature of the substituents present on the arene. This is particularly important in the case of *meta*-selective direct arylations as, to date, only one class of directing group has been reported.

It should be possible to access *meta*-substituted adducts by the use of a strategically placed removable *ortho*-directing group, a concept recently reviewed by Breit.^[6] Indeed, this approach has been successfully applied by Satoh, Miura et al. to the formal *meta* olefination of arenes by *ortho* vinylation of benzoic acids followed by decarboxylation.^[7] However, the

application of this concept to the synthesis of *meta*-substituted biaryl compounds has not been achieved. Herein we report our strategy for performing direct arylation in the *meta* position to a variety of electron-withdrawing and electron-donating substituents, thus bypassing any electronic preferences from such substituents (Scheme 1). Through the use of



Scheme 1. Tandem *ortho*-selective arylation/protodecarboxylation process leading to formal *meta*-selective C–H arylation.

this tandem process, *ortho*-substituted benzoic acid **1** becomes a synthetic equivalent of the *meta* anion **I**, therefore allowing the synthesis of *meta*-substituted biaryl compounds (**4**) that would otherwise be difficult to obtain. This one-pot method is operationally simple, requires low catalyst loadings, uses readily available iodoarenes as coupling partners, and, importantly, is compatible with a wide variety of substituents.

Our group, as well as Goossen's, have recently reported that a wide variety of benzoic acids can be easily protodecarboxylated under Ag catalysis provided that they bear an electron-withdrawing or electron-donating substituent in the *ortho* position.^[8] These results place carboxylic acid substituents as the ideal candidates for our *meta*-selective direct arylation strategy. Daugulis and co-workers, and Yu and co-workers have reported two methods for the *ortho*-selective direct arylation of benzoic acids with iodoarenes mediated by a Pd/Ag system.^[9] However, only one of the reported examples contained a substituent (Me) *ortho* to the carboxylic acid, thus suggesting general lack of compatibility. Despite this potential hurdle we decided to explore the possibility of carrying out the tandem C–H arylation/protodecarboxylation process (Scheme 1). To achieve the desired *meta*-selective arylation a number of crucial challenges had to be overcome: 1) Can highly hindered adducts **3** be protodecarboxylated? 2) Can protodecarboxylation of the starting *ortho*-substituted benzoic acid (**1**→**5**) be prevented? 3) Can the alternative decarboxylative *ipso*-arylation process, which would lead to *ortho*-substituted adducts **6**, be avoided?

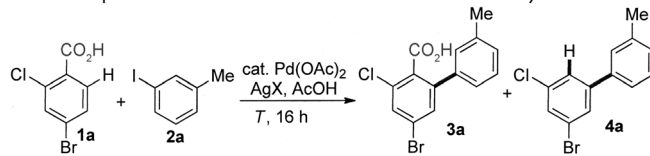
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Initially, we tested the reaction of 4-bromo-2-chlorobenzoic acid, **1a**, with the *ortho*-arylation conditions reported by Daugulis and co-workers,^[9] and employing 3-iodotoluene, **2a**, as the coupling partner (Table 1). Perhaps unsurprisingly owing to the lack of precedent, only 29% of the *ortho*-arylated benzoic acid **3a** was obtained (Table 1, entry 1).

Table 1: Optimization of the formal *meta*-selective C–H arylation.

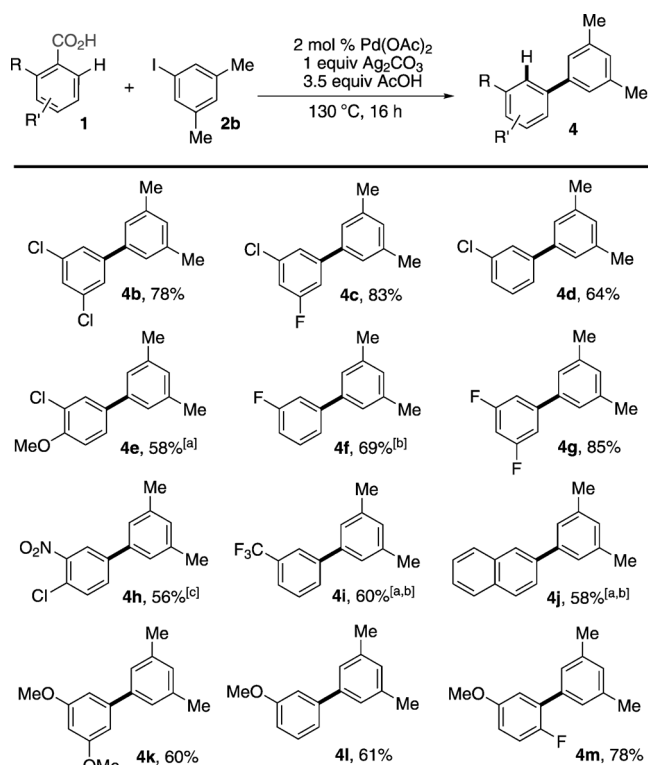


Entry ^[a]	Pd mol %	AgX (equiv)	T [°C]	3a [%] ^[b]	4a [%] ^[b]
1	5	AgOAc (1.3)	120	29	20
2	10	AgOAc (2)	120	33	28
3	2	AgOAc (2)	120	17	44
4	1	AgOAc (2)	120	16	41
5	2	Ag ₂ CO ₃ (1)	120	65	9
6 ^[c]	2	Ag ₂ CO ₃ (1)	120	20	0
7	2	Ag ₂ CO ₃ (1)	130	0	73

[a] Unless otherwise noted, all reactions were carried out using Pd(OAc)₂ as catalyst, a silver salt (AgX), 1.0 equiv of **1a**, 3.0 equiv of **2a** and 3.5 equiv of AcOH, for 16 h. [b] Yields were determined by ¹H NMR analysis using mesitylene as an internal standard. [c] 10 equiv of H₂O were added.

Interestingly, 20% of **4a** was also observed, thus suggesting that the desired tandem *ortho*-arylation/protodecarboxylation was feasible. Optimization of this reaction showed that lower catalyst loadings led to higher overall yield (**3a** + **4a**), with 2 mol % of Pd(OAc)₂ being the optimum (entries 2–4). Replacing AgOAc with Ag₂CO₃ further increased the overall yield (**3a** + **4a**), although the protodecarboxylation step was greatly reduced (entry 5).^[10] Gratifyingly, increasing the temperature from 120 to 130 °C allowed the tandem process to occur, thus producing the *meta*-arylated adduct **4a** in 73% overall yield (entry 7). It is remarkable that under these reaction conditions the protodecarboxylation step seems to be chemoselective for **3a** in the presence of **1a**.

Since decarboxylative transformations are in general highly dependent on the substitution pattern in the benzoic acid,^[11,12] our next concern was to examine the scope of this method in regard to the acid starting material **1**. Gratifyingly, a wide range of substituents and substitution patterns are tolerated with none or minimal changes in the reaction conditions (Scheme 2). Thus, C–H arylation *meta* to a Cl substituent, which would offer an entry for further cross-couplings to be performed, occurs in high yields (**4b–e**). Other electron-withdrawing groups, such as F, NO₂, and CF₃ are also tolerated, and lead to the corresponding *meta*-arylated adducts (**4f–i**). This tandem transformation is not limited to electron-withdrawing groups in the *ortho* position to the starting benzoic acid: MeO is also compatible with our protocol, leading to *meta*-substituted biaryl compounds **4k–m** in good yields. This protocol can also be applied to 1-naphthoic acid, which selectively affords 2-aryl-naphthalene **4j**.^[13] In a few cases (**4e** and **4h–j**), protodecarboxylation does

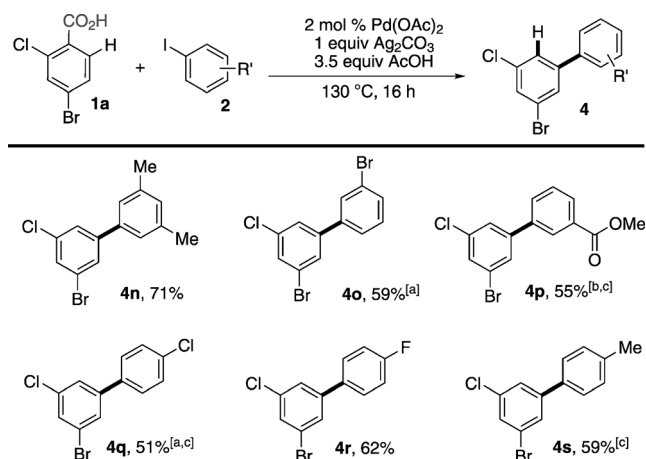


Scheme 2. Tandem *ortho*-selective arylation/protodecarboxylation process leading to formal *meta*-selective C–H arylation. Yields are of the isolated pure material. [a] Reaction carried out at 150 °C for 16 h, followed by the addition of 1.0 equiv of Ag₂CO₃ in 2.5 mL of DMSO and stirring for a further 4 h at 170 °C. [b] 2.0 equiv of iodoarene were used. [c] After 16 h, 1.0 equiv of Ag₂CO₃ in 2.5 mL of DMSO were added and the reaction was stirred for 3 h.

not occur fully during the reaction. This problem was solved by adding an extra equivalent of Ag₂CO₃ in DMSO after the first 16 hours of the reaction.^[14]

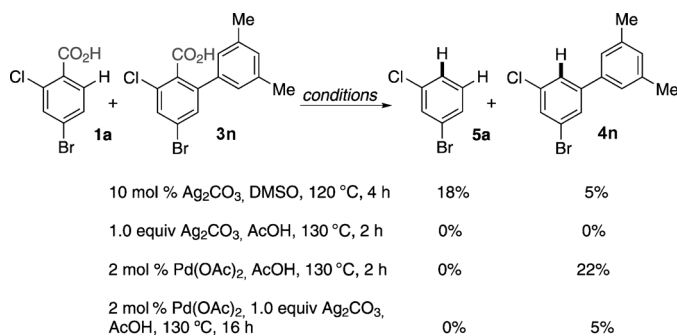
We then examined the scope of the reaction with respect to the iodoarene coupling partner (Scheme 3). Iodoarenes substituted with F, Cl, Me, Br, and CO₂Me in *para* and *meta* positions are compatible with the procedure, and lead to the corresponding *meta*-substituted biaryl compounds in good yields. In all cases the *meta*-arylated adduct was the only regioisomer observed.

Notably most of these *meta* adducts **4** could not have been prepared selectively by direct C–H arylation of the parent arene in the absence of the removable directing group. This is particularly striking for the parent arenes of biaryl compounds **4a–d**, **4f–g**, and **4k–l**, which in an electrophilic aromatic substitution would be substituted at the *ortho* and/or *para* positions. The inherent electronic biases of the different substituents are therefore irrelevant with our *meta*-selective arylation strategy. The only other straightforward approach to this important class of compounds is by Suzuki coupling using the corresponding *meta*-substituted aryl boronic acids. However, the synthesis of these starting materials generally involves several steps, which is reflected in their higher cost (ca. 500–1000 times more expensive than the equivalent benzoic acid).^[15]



Scheme 3. Scope of the formal *meta*-selective C–H arylation of a variety of arenes. Yields are of the isolated pure material. [a] After 16 h, 1.0 equiv of Ag_2CO_3 in 2.5 mL DMSO were added and the reaction stirred for further 3 h. [b] After 16 h, 0.25 equiv of Ag_2CO_3 in 2.5 mL DMSO were added and the reaction was stirred for further 3 h. [c] 7.0 equiv of AcOH were used.

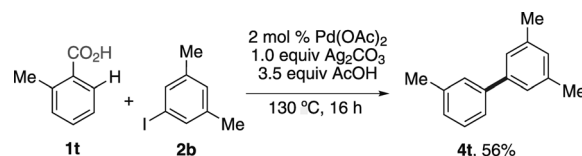
This process is likely to proceed by a tandem *ortho*-arylation/protodecarboxylation, as depicted in Scheme 1. To explain the high selectivity displayed for the protodecarboxylation step (**1** versus **3**) we hypothesized that the decarboxylation of the more-hindered **3** is much faster than that of **1**. Surprisingly, when a mixture of **1a** and **3n** was treated under our previously reported Ag-mediated protodecarboxylation conditions (10 mol % Ag_2CO_3 in DMSO),^[8] the opposite trend was observed: **1a** decarboxylates more than three times faster than **3n** (Scheme 4). Furthermore, when AcOH was



Scheme 4. Attempts at protodecarboxylation of **1a** and **3n**. DMSO = dimethylsulfoxide.

used as the solvent, no protodecarboxylation was observed for either substrate, suggesting that Ag is not responsible for the decarboxylation step in this process. On the other hand, when **1a** and **3n** were treated with 2 mol % of $\text{Pd}(\text{OAc})_2$ in AcOH, protodecarboxylation of **3n** was observed with complete selectivity.^[16] This remarkable selectivity suggests that electronics are not the only factor controlling the Pd-mediated decarboxylation of benzoic acids. Based on computational studies, Su, Lin, and Xue have previously hypothesized that Pd-mediated decarboxylation may be influenced by

steric factors.^[17] Notably Pd^{II} salts have only been reported to mediate the protodecarboxylation of highly electron-rich benzoic acids,^[18] whereas our system seems to be independent of the electronic nature of the initial *ortho* substituent. To further explore this new hypothesis, we attempted the *meta*-arylation protocol on *ortho*-toluic acid (**1t**) which, lacking a strong electron-withdrawing or electron-donating *ortho* substituent, does not decarboxylate with either Ag or Pd catalysts. To our delight, after 16 hours at 130 °C, 56 % of the corresponding *meta*-substituted biaryl compound **4t** was obtained (Scheme 5), thus showing that the scope of this



Scheme 5. *meta*-Selective arylation of *o*-toluic acid (**1t**).

method is not limited to the traditional activating *ortho* groups for Ag- or Pd-mediated decarboxylation.^[12] Further mechanistic studies to explore the effect of the *ortho*-aryl group on the decarboxylation step are under way and will be reported in due course.

In summary, we have reported the first method for the formal *meta*-selective direct C–H arylation using iodoarenes as coupling partners. This process, which is compatible with a wide range of *meta* substituents, utilizes carboxylic acids as traceless directing groups to afford exquisite control upon the regioselectivity of the direct C–H arylation. Benzoic acids are cheap and readily available starting materials, and provide an efficient alternative to the sometimes prohibitively expensive Suzuki couplings, to access *meta*-substituted biaryl compounds. Furthermore, we have demonstrated that Pd salts (and not Ag) are able to perform the decarboxylation of *ortho*-arylated disubstituted benzoic acids under the reported reaction conditions. Notably this decarboxylation occurs with complete chemoselectivity over the starting *ortho*-monosubstituted benzoic acids.

Experimental Section

Representative *meta*-selective direct arylation of **4b** (Scheme 1): A mixture of $\text{Pd}(\text{OAc})_2$ (2.2 mg, 0.01 mmol), Ag_2CO_3 (138 mg, 0.5 mmol), 2,4-dichlorobenzoic acid (96.0 mg, 0.5 mmol), and **2b** (0.218 mL, 0.75 mmol) in 0.1 mL of AcOH was heated at 130 °C for 16 h. The reaction mixture was filtered through a plug of celite with CH_2Cl_2 . The filtrate was washed with 5 % aqueous KOH and extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4 , filtered, and evaporated to dryness. The crude product was purified by flash column chromatography on silica gel (hexanes) to afford 3,5-dichloro-3',5'-dimethyl-1,1'-biphenyl (**4b**) as a white solid (98 mg, 78 %).

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- [1] a) J. Hassan, M. Sevignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359; b) D. A. Horton, G. T. Bourne, M. L. Smythe, *Chem. Rev.* **2003**, *103*, 893.
- [2] The biological activity of more than 51 000 biaryl compounds has been reported (Reaxys).
- [3] a) L. Anastasia, E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis* (Ed.: E. Negishi), Wiley, New York, **2002**; b) J.-P. Corbet, G. Mignani, *Chem. Rev.* **2006**, *106*, 2651; c) C. Torborg, M. Beller, *Adv. Synth. Catal.* **2009**, *351*, 3027.
- [4] a) L. Ackermann, R. Vicente, A. R. Kapdi, *Angew. Chem.* **2009**, *121*, 9976; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792; b) F. Bellina, R. Rossi, *Tetrahedron* **2009**, *65*, 10269; c) L. Joucla, L. Djakovitch, *Adv. Synth. Catal.* **2009**, *351*, 673; d) X. Chen, K. M. Engle, D.-H. Wang, J.-Q. Yu, *Angew. Chem.* **2009**, *121*, 5196; *Angew. Chem. Int. Ed.* **2009**, *48*, 5094; e) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174; f) L.-C. Campeau, D. R. Stuart, K. Fagnou, *Aldrichimica Acta* **2007**, *20*, 35; g) T. Satoh, M. Miura, *Chem. Lett.* **2007**, *36*, 200; h) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173.
- [5] a) R. J. Phipps, M. J. Gaunt, *Science* **2009**, *323*, 1593; b) H. A. Duong, R. E. Gilligan, M. L. Cooke, R. J. Phipps, M. J. Gaunt, *Angew. Chem.* **2011**, *123*, 483; *Angew. Chem. Int. Ed.* **2011**, *50*, 463.
- [6] a) G. Rousseau, B. Breit, *Angew. Chem.* **2011**, *123*, 2498; *Angew. Chem. Int. Ed.* **2011**, *50*, 2450, for recent examples of traceless directing groups in C–H functionalization, see: b) H. Ihara, M. Sugimoto, *J. Am. Chem. Soc.* **2009**, *131*, 7502; c) N. Chernyak, A. S. Dudnik, C. Huang, V. Gevorgyan, *J. Am. Chem. Soc.* **2010**, *132*, 8270; d) A. S. Dudnik, N. Chernyak, C. Huang, V. Gevorgyan, *Angew. Chem.* **2010**, *122*, 8911; *Angew. Chem. Int. Ed.* **2010**, *49*, 8729; e) A. García-Rubia, M. A. Fernandez-Ibanez, R. G. Arrayas, J. C. Carretero, *Chem. Eur. J.* **2011**, *17*, 3567; f) H. Richter, S. Beckendorf, O. G. Mancheño, *Adv. Synth. Catal.* **2011**, *353*, 295.
- [7] a) S. Mochida, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 5776; b) S. Mochida, K. Hirano, T. Satoh, M. Miura, *J. Org. Chem.* **2011**, *76*, 3024; c) A. Maehara, H. Tsurugi, T. Satoh, M. Miura, *Org. Lett.* **2008**, *10*, 1159.
- [8] a) J. Cornella, C. Sanchez, D. Banawa, I. Larrosa, *Chem. Commun.* **2009**, 7176; b) P. Lu, C. Sanchez, J. Cornella, I. Larrosa, *Org. Lett.* **2009**, *11*, 5710; c) L. J. Goossen, C. Linder, N. Rodriguez, P. P. Lange, A. Fromm, *Chem. Commun.* **2009**, 7173; d) L. J. Goossen, N. Rodriguez, C. Linder, P. P. Lange, A. Fromm, *ChemCatChem* **2010**, *2*, 430.
- [9] a) R. Giri, N. L. Maugel, J.-J. Li, D.-H. Wang, S. P. Breazzano, L. B. Saunders, J.-Q. Yu, *J. Am. Chem. Soc.* **2007**, *129*, 3510; b) H. A. Chiong, Q.-N. Pham, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 9879.
- [10] One should be cautious when employing “aged” Ag₂CO₃ as we have found that lower yields can be obtained in this case. We attribute this effect to the presence of variable amounts of water in the silver salt; this water seems to enhance the protodecarboxylation rate in the benzoic acid starting material. No acid starting material **1a** was recovered when a standard reaction in the presence of 10 equiv of H₂O was carried out (Table 1, Entry 6).
- [11] a) T. Satoh, M. Miura, *Synthesis* **2010**, 3395; b) L. J. Goossen, F. Collet, K. Goossen, *Isr. J. Chem.* **2010**, *50*, 617.
- [12] For selected recent examples of Pd/Ag-mediated decarboxylative functionalizations of benzoic acids, see a) C. Wang, I. Piel, F. Glorius, *J. Am. Chem. Soc.* **2009**, *131*, 4194; b) J. Cornella, P. Lu, I. Larrosa, *Org. Lett.* **2009**, *11*, 5506; c) L. J. Goossen, P. P. Lange, N. Rodriguez, C. Linder, *Chem. Eur. J.* **2010**, *16*, 3906; d) F. Zhang, M. F. Greaney, *Angew. Chem.* **2010**, *122*, 2828; *Angew. Chem. Int. Ed.* **2010**, *49*, 2768; e) J. Zhou, P. Hu, M. Zhang, S. Huang, M. Wang, W. Su, *Chem. Eur. J.* **2010**, *16*, 5876; f) K. Xie, Z. Yang, X. Zhou, X. Li, S. Wang, Z. Tan, X. An, C.-C. Guo, *Org. Lett.* **2010**, *12*, 1564; g) M. Zhang, J. Zhou, J. Kan, M. Wang, W. Su, M. Hong, *Chem. Commun.* **2010**, *46*, 5455; h) C. Wang, S. Rakshit, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 14006; i) J. Cornella, H. Lahlali, I. Larrosa, *Chem. Commun.* **2010**, *46*, 8276; j) F. Zhang, M. F. Greaney, *Org. Lett.* **2010**, *12*, 4745; k) Y. Luo, J. Wu, *Chem. Commun.* **2010**, *46*, 3785; l) J. Wang, Z. Cui, Y. Zhang, H. Li, L.-M. Wu, Z. Liu, *Org. Biomol. Chem.* **2011**, *9*, 663.
- [13] The direct arylation of naphthalene usually leads to mixtures of the two regioisomers, with 1-arylnaphthoic being the most favored, see: a) O. Kobayashi, D. Uruguchi, T. Yamakawa, *Org. Lett.* **2009**, *11*, 2679; b) C. Qin, W. Lu, *J. Org. Chem.* **2008**, *73*, 7424.
- [14] In these examples, the product of the protodecarboxylation of the starting benzoic acid was found to be the main side product.
- [15] For example, 3-methoxyphenylboronic acid costs ca. £2,310 per mol, compared to £24 for the equivalent 2-methoxybenzoic acid (Aldrich) used to synthesize compound **4l**.
- [16] The same selectivity was observed when **1a** and **3n** were treated with 2 mol % of Pd(OAc)₂ and 1 equiv of Ag₂CO₃ in AcOH for 16 h, however, there was a remarkable decrease in the decarboxylation rate. This decrease in rate is most likely caused by the fast formation of a palladacycle with the silver salt of **1a**, thus trapping the Pd catalyst in an unproductive route.
- [17] L. Xue, W. Su, Z. Lin, *Dalton Trans.* **2010**, *39*, 9815.
- [18] a) S. J. Dickstein, C. A. Mulrooney, E. M. O'Brien, B. J. Morgan, M. C. Kozlowski, *Org. Lett.* **2007**, *9*, 2441; b) A. A. Núñez Magro, G. R. Eastham, D. J. Cole-Hamilton, *Dalton Trans.* **2009**, 4683.