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Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides: Synthesis of 2-arylbenzoate derivatives.

Aya Ismael,^a Troels A. Skrydstrup^b and Annette Bayer^{*a}

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We have developed a carbonylative approach to the synthesis of diversely substituted 2-arylbenzoate esters featuring a new protocol for the carbonylative coupling of aryl bromides with boronic acids and a new strategy to favour carbonylative over non-carbonylative reactions. Two different synthetic pathways – (i) the alkoxycarbonylation of 2-bromo benzophenones and (ii) the carbonylative Suzuki-Miyaura coupling of 2-bromobenzoate esters - were evaluated. The latter approach provided a broader substrate tolerance, and thus was the preferred pathway. We observed that 2-substituted aryl bromides were challenging substrates for carbonylative chemistry favouring the non-carbonylative pathway. However, we found that carbonylative Suzuki-Miyaura couplings can be improved by slow addition of the boronic acid, suppressing the unwanted direct Suzuki coupling and, thus increasing the yield of the carbonylative reaction.

Introduction

Through our program on fragment-based design of metallo- β -lactamase inhibitors, we became interested in the development of efficient strategies for the synthesis of functionalized 2-arylbenzoic acids **1** (Scheme 1).¹ Among other, 2-arylbenzoic acids have gained keen interest as synthetic intermediates for accessing bioactive compounds,²⁻⁷ as subunits of natural products and pharmaceuticals e.g. (-)-balanol⁸ and pitfenone, and as fragment-sized inhibitors of the human aldo-keto reductase AKR1C3⁹ and the hepatitis C virus NS3 protease.¹⁰ Most commonly, 2-arylbenzoic acids are prepared from phthalic anhydride by treatment with organometallic reagents^{2, 7, 11} or by a Friedel-Craft acylation^{3, 5, 12} with aromatic nucleophiles. However, these methods are incompatible with

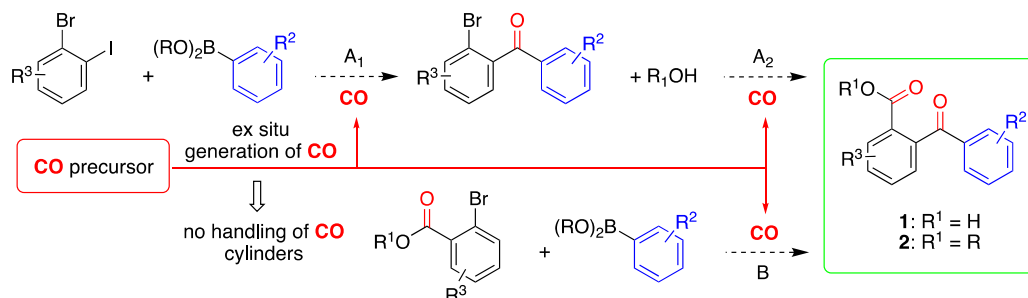
many functional groups, requiring excess Lewis acid and harsh reaction conditions, and often provide poor regioselective control. On the other hand, the biaryl ketone subscaffold of 2-arylbenzoic acids has been synthesized by transition metal-catalyzed carbonylative cross-couplings of organometallic reagents and aryl electrophiles,¹³⁻¹⁵ or the non-decarbonylative coupling of acyl electrophiles, e.g. carboxylic acids,¹⁶⁻¹⁸ esters¹⁹⁻²¹ or amides.^{19, 22} Despite the advances in the synthesis of biaryl ketones, only few methods have been demonstrated to be applicable for the formation of 2-aryl benzoic acid derivatives. Such methods comprise of the Pd-catalyzed *ortho*-C–H activation of benzoic acids followed by decarboxylative coupling with α -oxocarboxylic acids,²³ Pd-catalyzed *ortho*-C–H activation of aryl amides followed by coupling with aryl aldehydes,²⁴ and the Pd-catalyzed coupling of 2-iodobenzoates with aldehydes.²⁵ However, the available protocols have limited regiocontrol and/or substrate scope especially with regard to electron-deficient aryl groups.

In this study, we investigated two alternative routes towards 2-arylbenzoate esters **2** featuring carbonylative couplings using safe and easy to handle *ex situ* generated CO as a key step (Scheme 1). In the first approach (route A), we examined the Pd-catalyzed alkoxycarbonylation of 2-bromo functionalized biaryl

^a Department of Chemistry, Faculty of Science and Technology, UiT The Arctic University of Norway, N-9037 Tromsø, Norway.

^b Carbon Dioxide Activation Center (CADIAC), Interdisciplinary Nanoscience Center (iNANO) and Department of Chemistry, Aarhus University, Gustav Wiedes Vej 14, 8000 Aarhus C, Denmark.

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Scheme 1 Routes towards 2-arylbenzoic acid derivatives explored in this work.

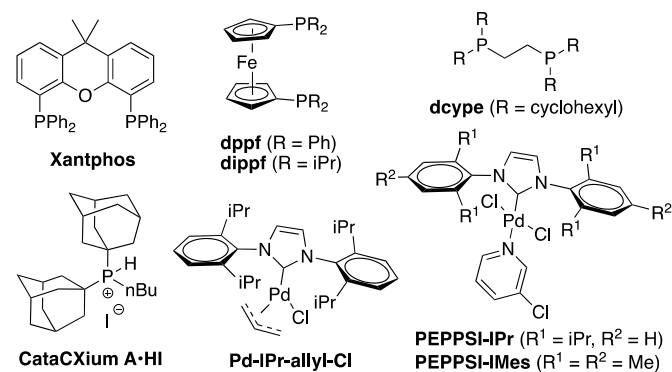
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ketones, which in turn could be prepared by carbonylative Suzuki-Miyaura couplings of 2-bromiodobenzene. In the second approach (route B), we investigated the carbonylative Suzuki-Miyaura coupling of 2-bromo substituted benzoate esters. A new protocol for the carbonylative coupling of aryl bromides and simple boronic acids preventing the use of iodide salts as additives or high-pressure CO gas was developed. Moreover, we demonstrate that slow addition of the nucleophilic coupling reagent is an uninvestigated strategy to enhance formation of the carbonylative product over the non-carbonylative side-product. The latter discovery was essential for sterically-demanding *ortho*-substituted aryl bromides in order to provide useful yields of the carbonylative coupling products.

Results and discussion

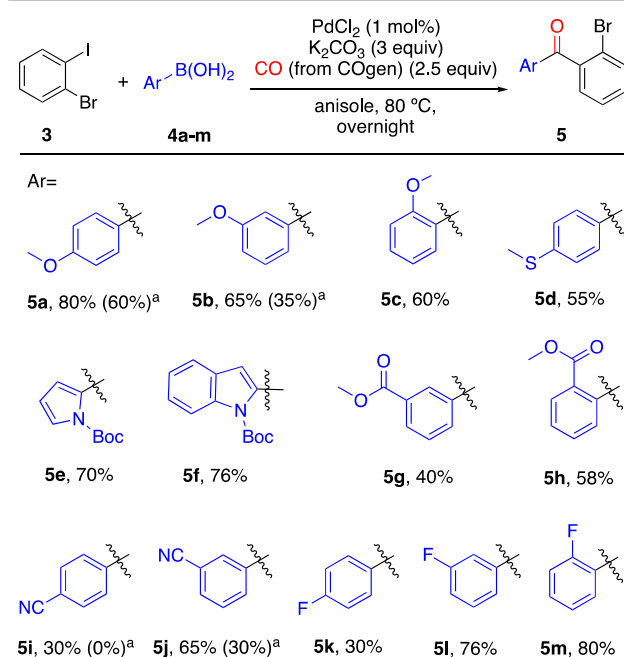
Carbonylative Suzuki-Miyaura of 2-bromiodobenzene (step A₁).

Initially, we focused on the Pd-catalyzed carbonylative Suzuki-Miyaura coupling of 2-bromiodobenzene **3** with aryl boronic acids **4** in order to prepare substituted 2-bromobenzophenone derivatives **5** as starting materials for further alkoxyacylation reactions (Scheme 2). A range of catalysts derived from a variety of Pd sources including Pd(OAc)₂,²⁶ Pd(dba)₂,²⁷ Pd(PPh₃)₂Cl₂,²⁸ PdCl₂, PEPPSI-IPr²⁹ were evaluated for the carbonylative coupling of the aryl iodide in presence of a bromide using 2-bromiodobenzene **3** and 4-methoxyphenyl boronic acid **4a** (Table ESI-1). The yields varied from 10% to 65% of the furnished benzophenone (Table ESI-1, entries 1-5), and competitive formation of the direct coupling product (biphenyl) was a major limitation. The most promising catalytic system identified from the screening used PdCl₂ as catalyst precursor, K₂CO₃ as base, and anisole as solvent (Table ESI-1, entry 5).



In addition, several methods for the ex situ generation of carbon monoxide from formic acid,³⁰ oxalyl chloride,³¹ COgen,³² and electrochemical reduction of CO₂ to CO³³ were screened to

prevent the risk of handling toxic carbon monoxide from a cylinder (Table ESI-2). The most promising and convenient CO source turned out to be 9-methylfluorene-9-carbonyl chloride (COgen) (Table ESI-2, entry 3). Oxalyl chloride as CO source provided comparable results if the CO gas was generated outside the reaction chamber making the handling more inconvenient (Table ESI-2, entry 5), while both formic acid and electrochemical reduction of CO₂ resulted in substantially reduced yields (Table ESI-2, entries 1 and 7).



Scheme 2. Carbonylative Suzuki-Miyaura coupling of 2-bromiodobenzene with boronic acids. Reaction conditions: Chamber A: **3** (0.18 mmol), PdCl₂ (1 mol%) and K₂CO₃ (0.55 mmol) in anisole (3 ml). Chamber B: COgen (0.45 mmol), Pd(dba)₂ (5 mol%) and TTBP•HBF₄ (5 mol%) in anisole (3 ml). DIPEA (3 equiv) was added to chamber B to start CO formation, before **4** (1.2 equiv) in anisole (3 ml) was added slowly to chamber A (general procedure A, ESI). ^a Yield obtained when **4** (1.2 equiv) was added to chamber A before CO release (general procedure B, ESI).

The catalytic system employing PdCl₂ as precatalyst was further optimized with regard to different reaction times, temperatures, and slow addition of the boronic acid. Yields up to 65% of the carbonylated product were obtained with PdCl₂ (3 mol%) at 80 °C for 20 h (Table ESI-1, entry 5). Reduction of the catalyst loading to 1 mol% led to a slight decrease in yield to 60% (Table ESI-1, entry 6) and 1 mol% of precatalyst was used in the following reactions. A lower reaction temperature led to incomplete conversion and lower yields (Table ESI-1, entries 7 and 8). Addition of KI to favor carbonylative over direct coupling²⁸ did not improve the yield (Table ESI-1, entry 11). However, when the aryl boronic acid was added slowly over 2

h, direct coupling was suppressed and the yield improved up to 80% (Table ESI-1, entry 13). Similarly, the yield of the carbonylated product was improved from 30% to 60% by slow addition of the aryl boronic acid for reactions with PEPPSI-IPr as the precatalyst (Table ESI-1, entries 4 and 15).

Then, we explored the scope of the Pd-catalyzed reaction using PdCl₂ with respect to different aryl and heteroaromatic boronic acids **4** (Scheme 2). In all cases, slow addition of the aryl boronic acid increased the yield by 20–35 percentage points. Both electron-rich and electron-deficient aryl boronic acids (**4a–c**, **e**, **f**, **j**, **l**, **m**) gave moderate to high yields (60–80%) of the products. However, some electron-deficient boronic acids **4g**, **i** and **k** provided lower yields in the range of 30–40%. *Ortho*-substituents on the boronic acid (**4c**, **h** and **m**) and some electron-rich heterocycles (**4e** and **f**) were well tolerated to the reaction conditions. However, hydroxy and *N*-acyl substituted aryl boronic acids and 2-furyl boronic acid only provided products from the direct coupling instead of carbonylative coupling.

Hydroxy- or alkoxy-carbonylation of 2-bromo-substituted biaryl ketones (step A₂).

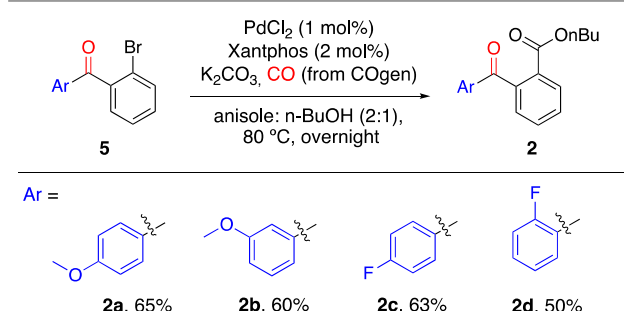
With a set of 2-bromobenzophenone derivatives **5a–m** in hand, we investigated the Pd-catalyzed hydroxy- and alkoxy-carbonylation to transform the aryl bromide into the carboxylic acid or ester, respectively.³⁴ Previous reports on Pd-catalyzed hydroxycarbonylation^{30, 34–36} or alkoxy-carbonylation^{26, 34, 37, 38} have had little focus on *ortho*-substituted aryl bromides. Unfortunately, all attempts to transform 2-bromo-4'-methoxybenzophenone **5a** directly to 2-(4-methoxybenzoyl)benzoic acid via a hydroxycarboxylation using MePh₂SiCO₂H³⁵ were unsuccessful (Table ESI-3).

Next, we turned our attention to the alkoxy-carbonylation of 2-bromobenzophenones **5** (Scheme 3).³⁷ Using **5a** as the test substrate, a range of precatalysts and ligands (Pd(OAc)₂, PdCl₂ or Pd(dba)₂ with Xantphos, dppf or PPh₃, Pd(PPh₃)₂Cl₂/IMes,³⁹ dppf(PdCl₂), PEPPSI-IPr or PEPPSIIMes), nucleophiles (MeOH, iPrOH, *n*-BuOH, *t*-BuONa, EtONa), bases and solvents were screened (Table ESI-4). Only few systems were able to provide the corresponding alkyl 2-(4-methoxybenzoyl)benzoate **2**. Comparison of the catalyst performance for 2-bromo-substituted **5a** and the corresponding 4-bromo-substituted analog showed that the yields were highly influenced by the substitution pattern. For example, for catalyst systems based on dppf(PdCl₂) or Pd(OAc)₂/Xantphos, the yields dropped from >95% for the 4-bromo-substituted analog to an 11% yield for 2-bromo-substituted **5a** under otherwise identical conditions (Table ESI-5). The best results for the latter were obtained with PdCl₂ and Xantphos as catalytic system, *n*-butanol as the nucleophile, K₂CO₃ as the base and anisole as solvent furnishing the ester **2a** in acceptable yield (65%) (Table ESI-4, entry 12). We applied these conditions to our library of 2-bromobenzophenone derivatives **5a–m** (Scheme 2). While the substrates **5a**, **b**, **k** and **m** gave alkoxy-carbonylation products **2a–d** in acceptable yields (65%, 60%, 63% and 55%, respectively), compounds **5c–h** and **5l** gave low yields to no product. Over all, we conclude that while the carbonylative

Suzuki-Miyaura coupling was tolerant to a variety of aryl boronic acids, the alkoxy-carbonylation of 2-bromo-biaryl ketones displayed a high dependence on the substrate structure rendering the approach unsuitable for the synthesis of a larger library of compounds.

Carbonylative Suzuki-Miyaura coupling with 2-bromobenzoates (Route B₁).

Due to the limited substrate scope of the alkoxy-carbonylation of 2-bromobenzophenone derivatives, we decided to study the carbonylative Suzuki-Miyaura coupling of methyl 2-bromobenzoates **6** (Table 1). Few examples of carbonylative couplings with aryl bromides^{28,40–43} have been reported and those rely on the use of iodide salts as additives (3 equiv.),²⁸ high



Scheme 3 Palladium-catalyzed alkoxy-carbonylation of 2-bromo biaryl ketones. Reaction conditions: Chamber A: **5** (1.0 equiv, 0.18 mmol), PdCl₂ (2 mol%), Xantphos (3 mol%), K₂CO₃ (3 equiv, 0.55 mmol) in anisole:*n*-BuOH (2: 1, 3 ml). Chamber B: COgen (107 mg, 2.5 equiv, 0.45 mmol), Pd(dba)₂ (12 mg, 5 mol%) and TTBP•HBF₄ (6.3 mg, 5 mol%) in anisole (3 ml). DIPEA (240 mg, 3 equiv) was added to chamber B to start CO release.

Table 1 Boronate derivatives in carbonylative Suzuki-Miyaura couplings.

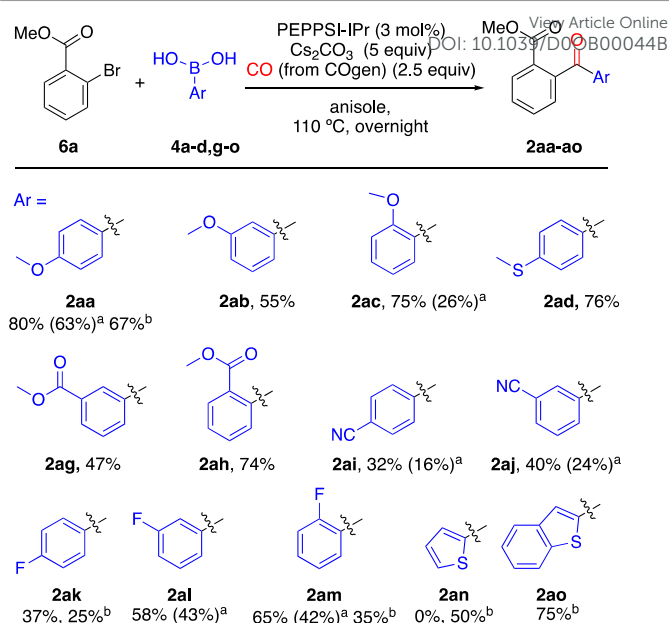
Boronic acid derivatives	Catalyst system	Yield
7a	Pd(acac) ₂ /cataXCium A-HI	67%
8	Pd(acac) ₂ /cataXCium A-HI	65%
4a	Pd(acac) ₂ /CataXCium A-HI	30%
	PEPPSI-IPr	63%
	PEPPSI-IPr / slow addition of 4a	80%

pressure of CO gas (5 bar)^{41–43} or the use of less accessible boronate esters⁴⁰ like DABO boronates⁴⁴ or aryl trihydroxyborates⁴⁵ instead of boronic acids. Only two examples of successful couplings with *ortho*-substituted substrates were reported.⁴¹ While carbonylative couplings of sterically hindered,

electron-rich aryl iodides have been achieved with PEPPSI-IPr as the precatalyst,²⁹ electron-poor aryl bromides like **6** have been shown to be challenging substrates favoring non-carbonylative direct couplings providing biaryl derivatives.^{28,41} In this perspective, general methods for carbonylative Suzuki-Miyaura couplings of aryl bromides with boronic acids are still needed. With methyl 2-bromobenzoate **6a** as the test substrate, the protocol reported by Skrydstrup and Molander⁴⁰ using Pd(acac)₂/CataCXium A·HI (5/10 mol%) afforded acceptable yields of **2aa** with 65–67% when the DABO boronate⁴⁴ **7a** or aryl trihydroxyborate⁴⁵ **8** were used as the nucleophilic coupling reagent (Table 1). However, the yield decreased to 30% with the boronic acid **4a**. Attempts to increase the yield by slow addition of the DABO boronate **6** or the trihydroxyborate **7** were not successful due to low solubility of these boronic acid derivatives in the reaction medium (toluene/water). The use of other solvent systems dramatically reduced the yields (Table ESI-6, entries 4–8).

Therefore, we proceeded to identify reaction conditions for the coupling of 2-bromobenzoate **6a** with aryl boronic acids **4a** using COgen as the carbon monoxide source. A range of experimental conditions including different palladium sources and ligands (Pd(acac)₂ or Pd(OAc)₂/CataCXium A or A·HI,⁴⁰ Pd(OAc)₂ or PdCl₂/Xantphos, Xantphos-G2, PEPPSI-IPr, [Pd(IPr)(allyl)Cl], Pd(PPh₃)₂Cl₂^{28,43} and Ni(COD)/dcype) and solvents were screened (Table ESI-6, entries 9–20). In most of the systems, the undesired non-carbonylative coupling was the dominant reaction pathway (Table ESI-6, entries 9–15). Only the Pd(IPr)-based catalytic systems were able to accomplish the carbonylative Suzuki-Miyaura coupling (Table ESI-6, entries 16–19). The best system using PEPPSI-IPr (3 mol%) as catalyst precursor, Cs₂CO₃ as base in chlorobenzene or anisole as solvent provided the product **2aa** in 63% yield (Table 1 and Table ESI-6, entry 16). The yield could be further increased to 80% by slow addition of the boronic acid (Table 1 and Table ESI-6, entry 17). A range of aryl boronic acids **4** were tested to examine the scope of the reaction as depicted in Scheme 4. Most of the electron rich boronic acids (**4a**, **c** and **d**) provided good yields (**2aa**: 80%; **2ac**: 75%; **2ad**: 76%), while electron-deficient boronic acids (**4g**, **i**, **j**, **k** and **l**) generally led to lower yields (**2ag**: 47%; **2ai**: 32%; **2aj**: 40%; **2ak**: 37%; **2al**: 58%). Yields obtained with slow addition of the aryl boronic acid were consistently higher (**2aa**: 80%; **2ac**: 75%; **2ai**: 32%; **2aj**: 40%; **2al**: 58%; **2am**: 65%), when compared with yields obtained by instantaneous addition (**2aa**: 63%; **2ac**: 26%; **2ai**: 16%; **2aj**: 24%; **2al**: 43%; **2am**: 42%). Slow addition of the boronic acid under reaction conditions favors the CO insertion step by slowing down the faster transmetalation^{28, 41} by limiting access to the organometallic nucleophile.

Aryl boronic acids containing acidic protons and the heteroaromatic boronic acid **4n** only underwent direct coupling instead of carbonylative coupling using PEPPSI-IPr. Couplings with heteroaromatic organometallic reagents could be achieved using the corresponding DABO boronates providing **2an** and **2ao** with Pd(acac)₂/CataCXium A·HI as the catalytic system.



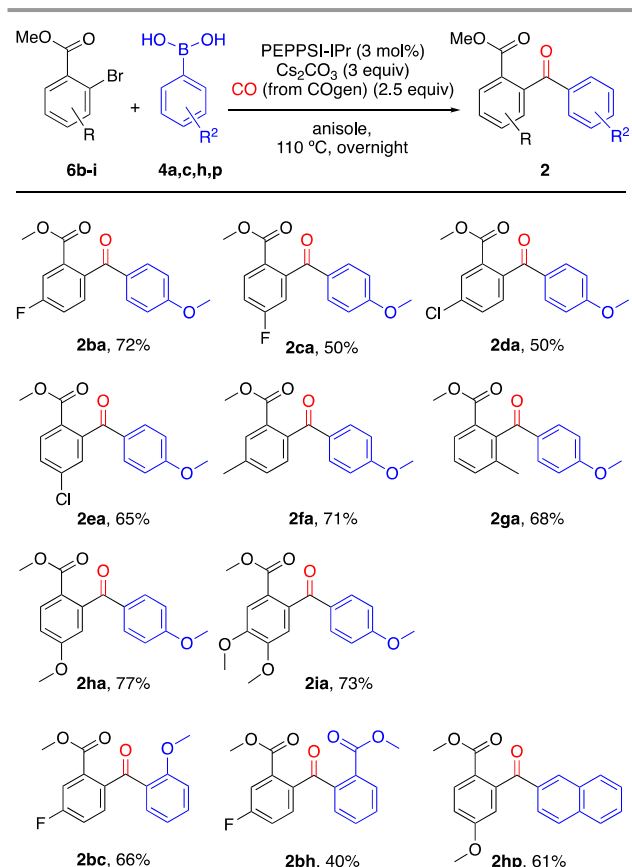
Scheme 4 Suzuki-Miyaura coupling of methyl 2-bromobenzoate **6a** with boronic acids **4**. Reaction conditions: Chamber A: **6a** (1.0 equiv, 0.47 mmol), PEPPSI-IPr (3 mol%) and Cs₂CO₃ (3 equiv, 1.4 mmol) in anisole (3 ml). Chamber B: COgen (282 mg, 2.5 equiv, 1.2 mmol), Pd(dba)₂ (30 mg, 5 mol%) and TTBP·HBF₄ (10 mg, 5 mol%) in anisole (3 ml). DIPEA (450 mg, 3 equiv) was added to chamber B, before **4** (1.5 equiv) was added slowly to chamber A (general procedure C, ESI). ^a Yield obtained when **4** (1.5 equiv) was added to chamber A before CO release (general procedure D, ESI). ^b Yield obtained by reaction with DABO boronate **7** (1.5 equiv) using Pd(acac)₂/CataCXium A·HI (5 mol%) as catalyst (general procedure E, ESI).

We further investigated the scope of the reaction with regard to a range of substituted methyl 2-bromobenzoates **6b–i** (Scheme 5). Aryl bromide **6** with both electron-withdrawing **6b–e** and donating substituents **6f–i** gave acceptable yields (50–72%). Surprisingly, also the coupling of *ortho* disubstituted **6g** provided good yields (**2ga**: 68%). The lowest yield (**2bh**: 40%) was obtained for the coupling of the electron-deficient **6b** with the electron-deficient boronic acid **4p**.

Conclusions

In summary, two routes for accessing 2-aryloxybenzoate esters have been evaluated. In the first strategy, the key step was the alkoxy-carbonylation of 2-bromo-diarylketones, which unfortunately appeared sensitive to the substitution pattern of the aryl bromide. The second strategy employed a carbonylative Suzuki-Miyaura coupling of 2-bromobenzoate esters, which was more robust with regard to the structure of aryl bromide and the aryl boronic acid. The latter approach was exploited to prepare a range of diversely substituted 2-aryloxybenzoate esters.

Moreover, we found that slow addition of the boronic acid is a strategy to favour carbonylative over non-carbonylative processes in Suzuki-Miyaura couplings – a finding that should be of general value.



Conflicts of interest

The authors declare the following competing financial interest(s): T.S. is co-owner of SyTracks A/S, which commercializes the two-chamber system (COware) and COgen.

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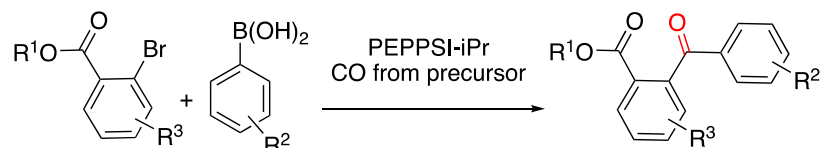
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Carbonylative Suzuki-Miyaura couplings of sterically hindered aryl halides: Synthesis of 2-arylbenzoate derivatives

Aya Ismael,^a Troels A. Skrydstrup^b and Annette Bayer*^a

A carbonylative approach to the synthesis of diversely substituted 2-arylbenzoate esters featuring a new protocol for carbonylative coupling of aryl bromides with boronic acids and slow addition of the boronic acid as a strategy to suppress unwanted non-carbonylative couplings for sterically hindered aryl bromides.



- new protocol for carbonylative coupling of aryl bromides with boronic acids
 - slow addition of boronic acids improve yields
- access to diversely substituted 2-arylbenzoate esters