

Article

## Continuous-Flow Heck-Matsuda Reaction: Homogeneous versus Heterogeneous Palladium-Catalysts

Nicolas Oger, Erwan Le Grogne, and Francois-Xavier Felpin

*J. Org. Chem.*, **Just Accepted Manuscript** • DOI: 10.1021/jo501468z • Publication Date (Web): 04 Aug 2014

Downloaded from <http://pubs.acs.org> on August 10, 2014

### Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



**ACS Publications**  
High quality. High impact.

The Journal of Organic Chemistry is published by the American Chemical Society, 1155 Sixteenth Street N.W., Washington, DC 20036  
Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

# Continuous-Flow Heck-Matsuda Reaction: Homogeneous *versus* Heterogeneous Palladium-Catalysts

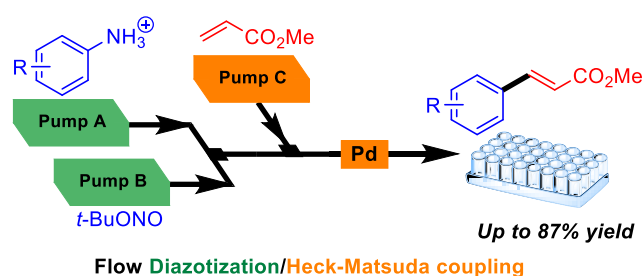
Nicolas Oger,<sup>a</sup> Erwan Le Grogneq,<sup>a</sup> François-Xavier Felpin<sup>\*,a,b</sup>

<sup>a</sup> Université de Nantes, UFR Sciences et Techniques, UMR CNRS 6230, CEISAM, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France.

Email: fx.felpin@univ-nantes.fr

<sup>b</sup> Institut Universitaire de France, 103 blvd St Michel, 75005 Paris Cedex 5, France

## Graphical Abstract

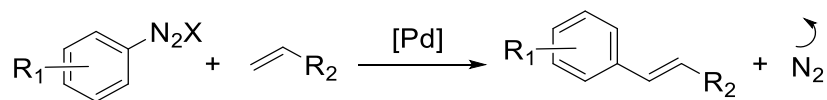


## Abstract

This study describes extensive investigations of the Heck-Matsuda reaction carried out by continuous-flow chemistry between aryl diazonium salts generated *in situ* and methyl acrylate. Our optimized procedures enable sequential aniline diazotization/palladium-catalyzed Heck-Matsuda reaction using either Pd(OAc)<sub>2</sub> or PdEnCat® 30 as respectively a homogeneous or a heterogeneous source of palladium. This safe chemistry that do not require the handling of hazardous aryl diazonium salts, involves inexpensive reagents and solvents, under ligand- and base-free conditions.

## Introduction

The Heck-Matsuda reaction<sup>1</sup> has found a growing interest from the synthetic community these last years.<sup>2</sup> This variant of the Heck-Mizoroki reaction, involves the use of aryl diazonium salts as “super electrophiles” instead of traditional aryl halides or aryl sulfonates (Scheme 1).



**Scheme 1.** General equation of the Heck-Matsuda reaction

The high reactivity of aryl diazonium salts, easily accessed from diazotization of readily available anilines, has been exploited for the development of transformations in mild conditions, with hydrophilic solvents such as alcohols or water, and under ligand- and base-free conditions.<sup>3</sup> The major drawback associated with this high reactivity is the hazardous character of some diazonium salts. Indeed, although it has been reported that aryl diazonium salts suitably functionalized can be stable up to 600 °C,<sup>4</sup> their stability rules are more or less a black box. In order to increase the synthetic potential of these salts in palladium-catalysis, we recently uncovered an innovative strategy based on the *in-situ* catalytic activation of anilines into the corresponding diazonium salts.<sup>5</sup> This approach, using catalytic amounts of both palladium and acid (required for the diazonium formation), proceeds under mild conditions at room temperature in methanol, and only produces *t*-BuOH, H<sub>2</sub>O, N<sub>2</sub> as by-products. While this bicatalytic strategy addresses the issue of the diazonium handling in safe conditions, slow kinetics, requiring extensive reaction times (48-65 hours), still limit its use to a laboratory scale. We reasoned that an approach significantly decreasing the reaction times should be decisive for improving the synthetic potential of these transformations.

In this event, we felt that flow technology could considerably enhance kinetics due to improved heat and mass transfer,<sup>6</sup> while keeping the advantage of a safe handling of diazonium salts. Such an approach has been pioneered by Wirth *et al.* with the development of segmented flow conditions for the coupling of aryl diazonium salts, either prepared *in-situ* or preformed, with methyl acrylate and styrenes.<sup>7</sup> The reaction conditions required the use of AcOH-DMF as mixture of solvents, Pd(OAc)<sub>2</sub> (10 mol%) as catalyst, and alkanes as segmenting phase, giving products in yields ranging from 18 to 90%. Improved mixing by internal circulation was expected into segmented flow compared to laminar flow.

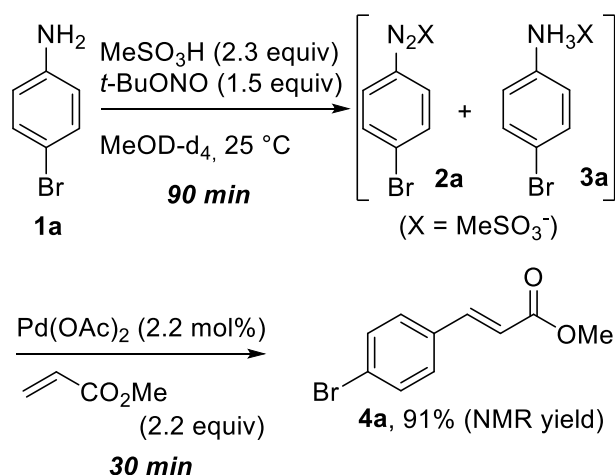
More recently, while we were achieving our studies described in this paper, McGuire, Organ *et al.* adapted reaction conditions we recently reported in batch,<sup>5a,5b</sup> into a flow technology.<sup>8</sup> They developed a multicomponent process whereby diazotization and cross-coupling occurred in one single reactor. Diazonium salts were generated *in situ* from the corresponding anilines with *t*-BuONO and MeSO<sub>3</sub>H as diazotizing agents. These salts were reacted with acrylates and styrene in the presence of Pd(OAc)<sub>2</sub> (2 mol%) as catalyst in a mixture of MeOH and DMF. With such reaction conditions they were able to efficiently couple electron-deficient and neutral anilines in excellent yields with flow rate ranging from 3 to 12  $\mu\text{L}\cdot\text{min}^{-1}$ , corresponding respectively to 6.4 and 1.6 hours residence times. These authors essentially studied *ortho*-substituted anilines, likely because of the positive *ortho*-effect we recently uncovered,<sup>5b</sup> and arylation with less reactive electron-rich anilines were overlooked. Although this study was remarkably conducted, we opted for a significant different procedure that led to higher throughputs. Ultimately, our procedure was extended with the use of PdEncat®30 as an immobilized palladium catalyst.

## Results and Discussion

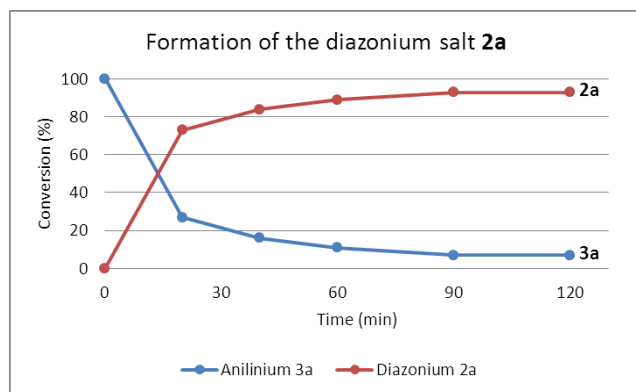
The first stage of our studies was to determine whatever a two-step flow sequence involving sequential diazotation-coupling or a multicomponent process whereby diazotization and coupling occur in a concomitant fashion (as described by Organ *et al.*) was the most efficient way, considering reaction rates. To address this point, we initially studied these two approaches in batch and monitored the reaction by <sup>1</sup>H NMR.

The two-step one-pot coupling of 4-bromoaniline **1a** with methyl acrylate requires, in a first stage, the formation of 4-bromobenzene diazonium salt **2a**, followed, in a second stage, by the addition of methyl acrylate and Pd(OAc)<sub>2</sub> as catalyst to carry out the Heck-Matsuda coupling (Scheme 2). Since we previously showed that the Heck-Matsuda reaction was best performed in MeOH, with *t*-BuONO and MeSO<sub>3</sub>H as diazotizing agents,<sup>5</sup> we followed the formation of the diazonium salt **2a** in MeOD-d<sub>4</sub> by <sup>1</sup>H NMR spectroscopy. As expected, the diazotization proceeded smoothly at 25 °C with no formation of degradation product (see Figure S1 in supporting information). Actually, the treatment of aniline with MeSO<sub>3</sub>H led quickly and quantitatively to the formation of the corresponding anilinium **3a**. As soon as *t*-BuONO was added to the reaction mixture, the diazonium salt formation started (Figure 1). A maximum conversion of 93% was reached after 90 min and no evolution was observed upon

further stirring. At this time (90 min), the palladium catalyst and methyl acrylate was added to the reaction mixture and the cross-coupling started immediately, as observed with the vigorous nitrogen evolution (Scheme 2). The coupling was achieved in about 30 minutes, giving >90% NMR yield and no significant evolution was observed upon further stirring. As a consequence, a maximum of 120 minutes (90 + 30 min) were required to give >90% NMR yield of **4a**.



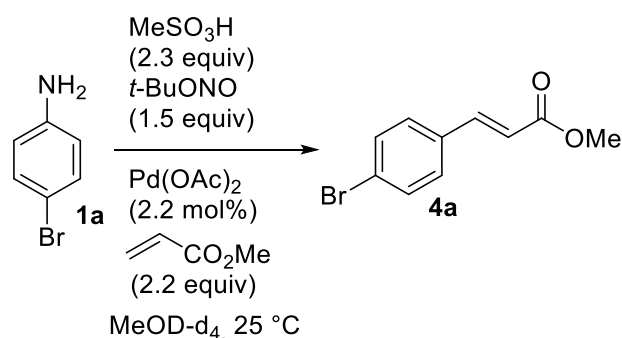
**SCHEME 2.** Two-step one-pot coupling of 4-bromoaniline **1a** with methyl acrylate



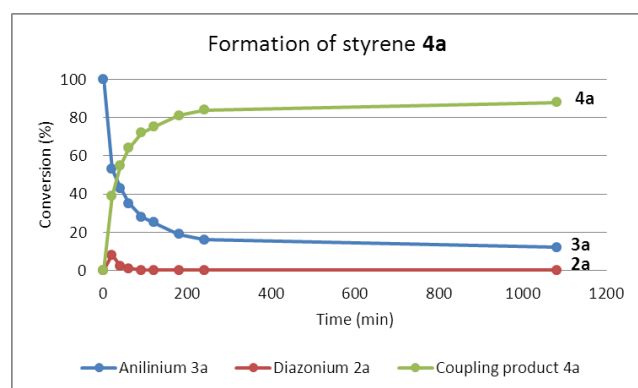
**FIGURE 1.** Kinetic of the formation of diazonium salt **2a**

On the other hand the same coupling was studied with a procedure whereby all reactants were introduced at one time (Scheme 3). The NMR recording of the crude reaction mixture every hours showed a slower rate since after 90 min 30% of anilinium still remains in solution while after 120 min of stirring only 75% conversion was observed for **4a** (see Figure S2 in supporting information). Actually, a total of 1080 min (18 h) was required to achieve the

reaction in >90% NMR yield (Figure 2). Only trace amounts of diazonium salts can be observed at any time of the NMR recording, suggesting that the coupling reaction is not the rate limiting step of the process.

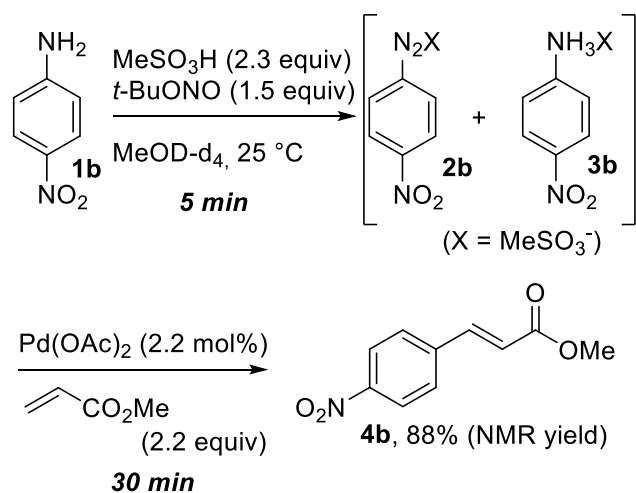


**SCHEME 3.** Multicomponent coupling of 4-bromoaniline **1a** with methyl acrylate



**FIGURE 2.** Kinetics for the formation of styrene **4a** in a multicomponent mode

Interestingly, when 4-nitroaniline **1b** was used as an electron-poor aniline, a complete diazonium formation was observed in less than 5 minutes at room temperature, and the subsequent coupling reaction, leading to styrene **4b**, was achieved in half an hour (Scheme 4).



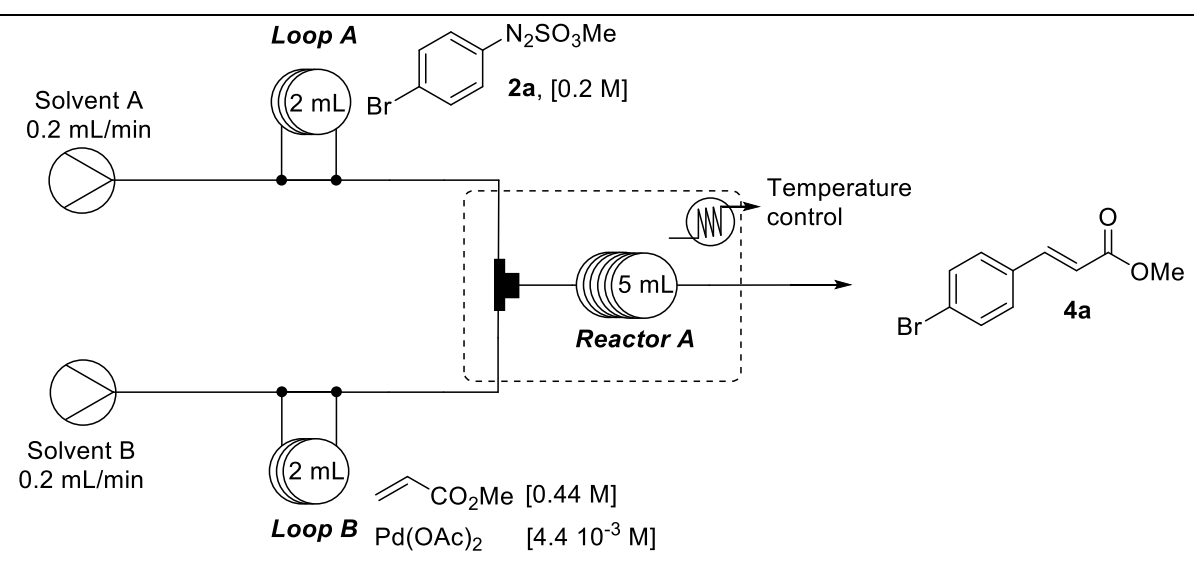
**SCHEME 4.** Two-step one-pot coupling of 4-nitroaniline **1b** with methyl acrylate

These particularly informative preliminary studies revealed us three important features: (1) for unclear reasons, the diazonium formation is significantly slowed down in the multicomponent process, compared to the two-step sequence; (2) the kinetics of the diazotization-coupling sequence are highly dependent of the electronic nature of the anilines; and (3) the diazotization is likely the rate determining step with neutral and electron-rich anilines.

With these results in hand, we looked for implementing this chemistry into a flow device using aniline **1a** and methylacrylate as starting materials. Before developing a two-step procedure in flow, a preliminary screening of solvents was required since we observed in batch the rapid precipitation of insoluble palladium black in MeOH. This behavior likely resulted from the instability of ligand-free palladium species in methanol. A more coordinating solvent should be more suitable to address this issue. Indeed, we anticipated that precipitation of palladium into the reaction coil of the flow device could lead to clogging issues and severely compromise the flow efficiency. Since the diazonium salt has to be prepared in MeOH, or eventually in water, a co-solvent was required for the Pd catalyst and the olefin. Our initial reaction setup employed two ways equipped with 2 mL injection loops (Table 1). *Loop A* was loaded with the diazonium salt, preformed in a flask in either MeOH or  $\text{H}_2\text{O}$ , and *loop B* was filled with a solution of  $\text{Pd}(\text{OAc})_2$  and methyl acrylate. Pumping of each way was initiated at 0.2 mL/min with two independent pumps. The flow streams met at a T-shaped mixer (150  $\mu\text{L}$ ) before entering into the reaction coil (*reactor A*, 5 mL), these latter being placed in an oven for an accurate control of the temperature. The use of MeOH as solvent carrier effectively lead to the desired product in 60% NMR yield, but palladium

deposit were observed on the side of the PFA tubing and the T-mixer clogged after a few runs (entry 1). The use of environmentally friendly dimethyl carbonate marginally improved the reaction yield but, most importantly, palladium deposit and clogging issues were not observed (entry 2). The use of water as solvent for the diazonium stream, completely inhibited the coupling, likely due to the immiscibility of water and DMC (entry 3). While 1,4-dioxane displayed a similar behavior than DMC (entry 4), the use of THF significantly improved the yield to 78% at 25 °C and even 90% at 40 °C, while keeping the flow device away from clogging issue (entries 5-6).

**TABLE 1.** Preliminary solvent screening with a two-stream flow device



Entry	Solvent A	Solvent B	Temp. (°C)	Yield (%) <sup>a</sup>
1	MeOH	MeOH	25	60
2	MeOH	DMC	25	62
3 <sup>b</sup>	H <sub>2</sub> O	DMC	25	0
4	MeOH	1,4-dioxane	25	63
5	MeOH	THF	25	78
6	MeOH	THF	40	90

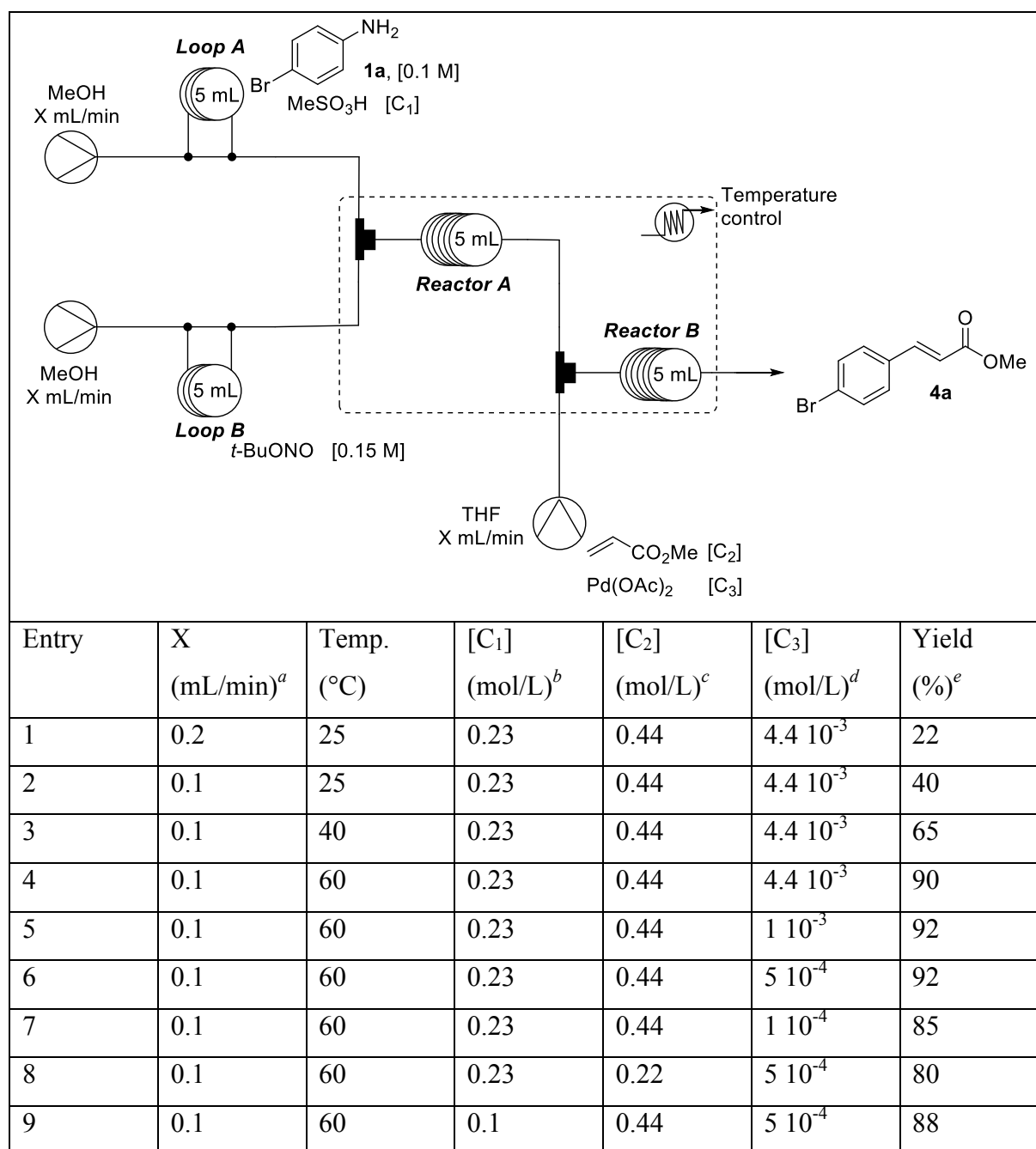
<sup>a</sup> NMR yield. <sup>b</sup> Diazonium salt prepared in water (20 min, 100% conversion).

Having determined a suitable solvent combination, we further explored the two-step flow diazotization-coupling sequence. In this event, a three-stream flow reactor was constructed as depicted in Table 2. In the flow setup, 4-bromoaniline **1a** and MeSO<sub>3</sub>H were loaded in *loop A*



while *t*-BuONO was independently charged in *loop B*; these 5 mL loops being pumped with MeOH as solvent. The two streams met at a T-mixer (150  $\mu$ L) and entered into a PEEK tubing *reactor A* (5 mL). Then the catalyst and methyl acrylate in solution in THF was pumped into the system and met the diazonium salt at a second T-mixer (150  $\mu$ L). The resulting mixture was introduced into a PEEK *reactor B* (5 mL) and finally collected into a fraction collector. An important slug flow stream was observed at the outlet due to N<sub>2</sub> release. All the tubing, including T-mixers and reaction coils were placed in an oven for an accurate control of the reaction temperature. Initially, the flow rate was fixed at 0.2 mL/min, corresponding to 12.5 and 8.3 min residence time for respectively the first and second tubing reactor. At 25 °C a modest 22% NMR yield was obtained for the expected coupling product **4a** (table 2, entry 1). When the flow rate of each pump was decrease to 0.1 mL/min, an encouraging 40% yield was observed (entry 2). Increasing the temperature of both tubing reactors at 40 °C and 60 °C improved the yield respectively to 65% (entry 3) and 90% (entry 4) with a total residence time of 41.7 min for the two-step sequence. The optimal concentration of MeSO<sub>3</sub>H, methyl acrylate and Pd(OAc)<sub>2</sub> was also deeply investigated in order to ensure the highest efficiency and sustainability of our flow process. Interestingly, the Pd concentration could be considerably lowered, up to 5  $10^{-4}$  M (corresponding to a 0.5 mol% loading) while keeping the same NMR yield (entry 6), and even concentration as low as 1  $10^{-4}$  M (0.1 mol% Pd) still furnished compound **4a** with a high yield (entry 7). While lower concentration of the acrylate (0.22 M vs 0.44 M) significantly alter the reaction yield (entry 8), a different trend was observed when lowering the acid concentration from 0.23 M to 0.1 M, since it only marginally impacted the reaction efficiency (entry 9). Since excess of acid might damage pump heads, especially when working on larger scale, we selected these last conditions (entry 9) for our scope studies.

**TABLE 2.** Optimization studies with a three-stream flow device

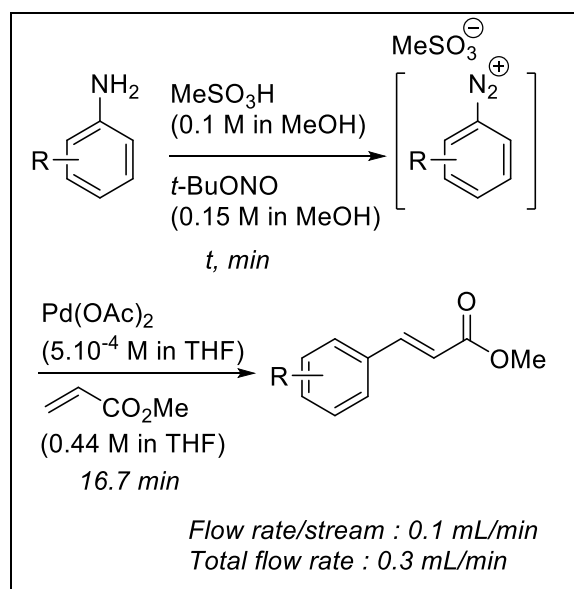


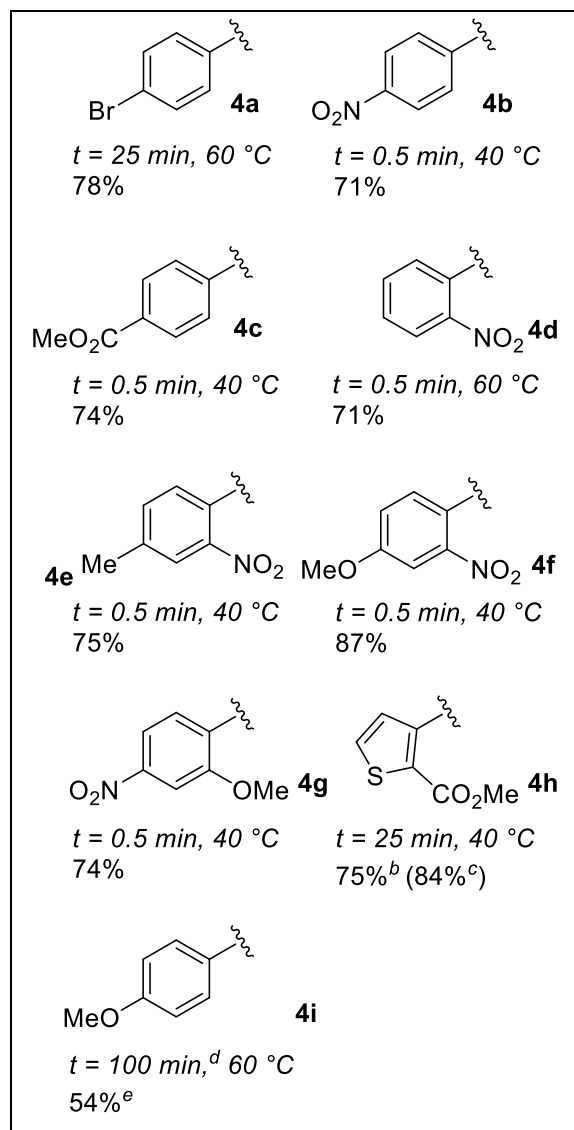
<sup>a</sup> Total flow rate = 3X. <sup>b</sup> Concentration of MeSO<sub>3</sub>H in MeOH. <sup>c</sup> Concentration of methyl acrylate in THF. <sup>d</sup> Concentration of Pd(OAc)<sub>2</sub> in THF. <sup>e</sup> NMR yield.

The flow setup was then evaluated on a collection of both electron-poor and electron-rich anilines (Table 3). Since electron-deficient anilines were converted into the corresponding diazonium salt in a few seconds at 40 °C, *reactor A* was dimensioned according to the electronic nature of the anilines. Thereby, while a 5 mL *reactor A* was used with electron-rich and neutral anilines, it was downsized at 100 µL for the formation of electron-poor diazonium salts. We observed that anilines bearing both electron-withdrawing and mildly electron-

releasing groups underwent the diazotization-coupling sequence in good to high yields. The reaction advancement was monitored by  $^1\text{H}$  NMR in order to assure the complete consumption of the diazonium salt. Remarkably, the mild experimental conditions tolerated a variety of functional groups on the aniline, including bromo (**4a**), nitro (**4b**, **4d-g**), ester (**4c**, **4h**), and methoxy (**4i**). The conditions used in this transformation do not affect the bromo-reactive functionality since no trace of coupling at the bromine atom was observed. Such high regio- and chemoselective leave unaffected functionalities that could be further modified using standard chemistry. The good yield obtained for heteroaromatic acrylate **4h** suggest that the scope of the method could be extended to relevant heterocyclic structures. The coupling of aniline bearing electron-withdrawing groups proceed with a total residence time of only c.a. 17 min while mildly electron-rich anilines were diazotized and subsequently coupled with a total residence time of c.a. 42 min. By contrast, the very deactivated 4-methoxy aniline were less efficiently coupled in 54% yield, with a total residence time of c.a. 117 min. This last result, revealed that the coupling of electron rich anilines proceeded with very slow kinetics suggesting that continuous flow chemistry might be not suitable since temperature cannot be raised above 60 °C due to the thermal instability of diazonium salts.

**TABLE 3.** Scope of the Heck-Matsuda reaction using a three-stream flow device<sup>a</sup>





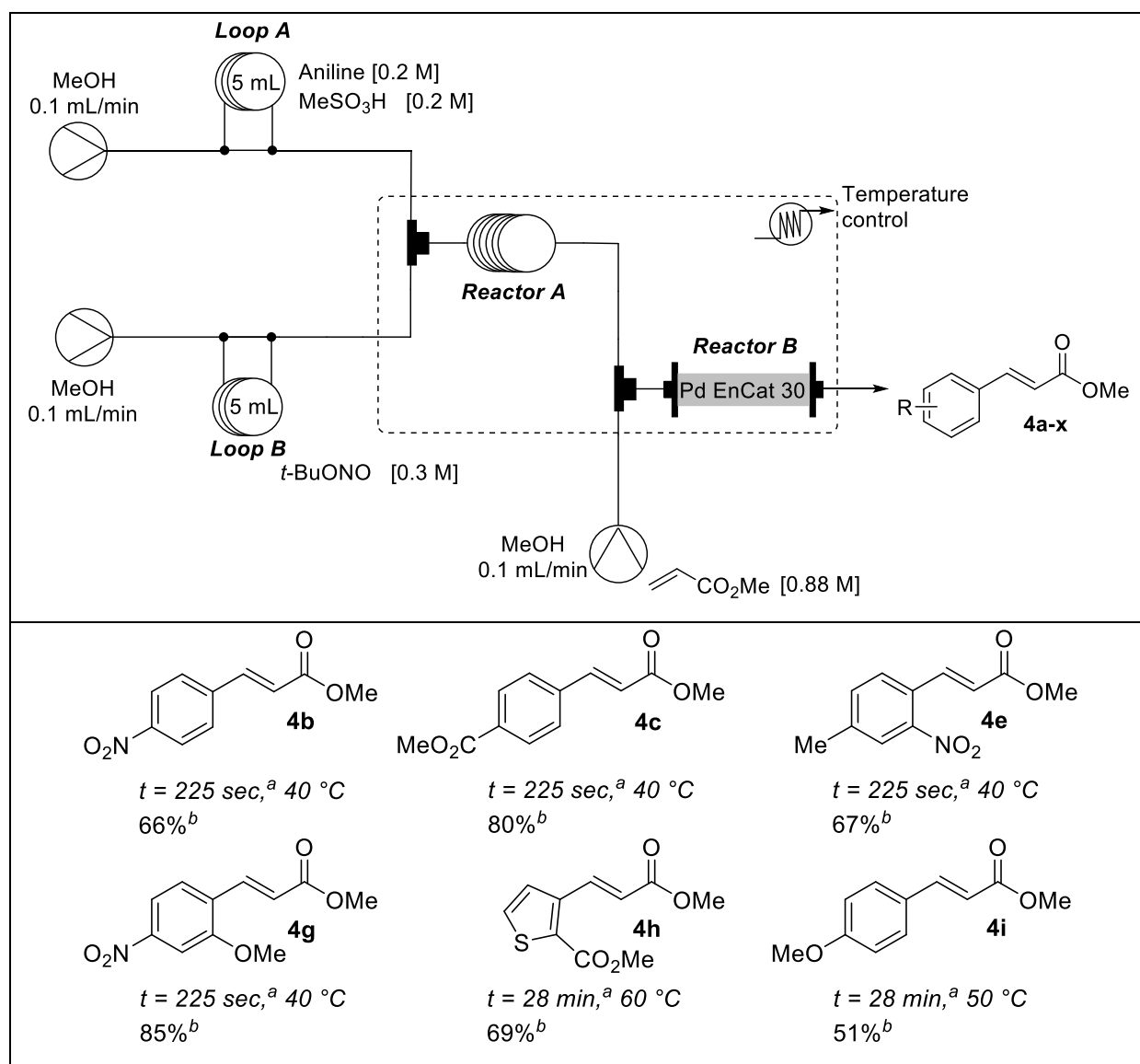
<sup>a</sup> Isolated yield (average of at least two runs). <sup>b</sup> 1.10<sup>-3</sup> M Pd(OAc)<sub>2</sub>. <sup>c</sup> 2.10<sup>-3</sup> M Pd(OAc)<sub>2</sub>. <sup>d</sup> Flow rate/stream : 0.025 mL/min. <sup>e</sup> 4.10<sup>-3</sup> M Pd(OAc)<sub>2</sub>.

To further explore the scope of the diazotization/Heck coupling sequence in flow and develop a more practical and sustainable procedure, we considered the use of an immobilized palladium-catalyst. Since Pd(OAc)<sub>2</sub> was arguably the best homogeneous palladium-catalyst for conducting Heck-Matsuda coupling in methanol,<sup>2b-d</sup> we opted for the use of commercially available PdEncat® 30 which consist of palladium acetate microencapsulated in a polyurea matrix.<sup>9</sup> It should be noted that Heck-Matsuda reaction catalyzed by heterogeneous palladium catalysts has neither been described with flow reactors, though it is known in batch.<sup>10</sup> Accordingly, a three-stream flow reactor was elaborated as depicted in Table 4. The reaction setup consisted of two injection loops containing the material required for the diazonium

formation that met at a T-shaped mixer (150  $\mu$ L) and enter in the coil *reactor A* (0.1 mL or 5 mL). Then, the flow stream containing the diazonium salt in MeOH met a solution of methyl acrylate in MeOH at a second T-mixer (150  $\mu$ L). The mixture was then transferred to an Omnifit-type glass column loaded with PdEncat® 30 at a flow rate of 0.3 mL/min (0.1 mL/min per pump) and maintained in an oven at the specified temperature (see Table 4). Since the palladium catalyst was immobilized in a polyurea matrix, the use of THF was not required anymore and the whole process was carried out in MeOH. A selection of representative anilines were selected for the evaluation of this unprecedented flow setup. The results showed that the yields for the coupled products were in the same range than those obtained with Pd(OAc)<sub>2</sub>. As previously observed, electron-rich 4-methoxyaniline gave a modest yield of the corresponding coupled product **4i** (51%), and slowing down the flow rate to 0.05 mL/min per pump did not affect the result. However, this approach features three decisive advantages compared to the homogeneous conditions: (1) the total residence time is significantly lowered up to only 225 seconds with electron-poor anilines; (2) the use of THF as solvent is not required anymore; (3) the concentration of palladium, leached from the PdEncat® 30 catalyst and measured by ICP-MS in the crude product solution, is in the range 1 to 7 ppm, representing the acceptable limit for pharmaceutical ingredients. By comparison, under homogeneous conditions, a one hundred times higher concentration of palladium was measured for the synthesis of **4i**.

**TABLE 4.** Scope of the Heck-Matsuda reaction using Pd Encat® 30 as an immobilized catalyst.

--



<sup>a</sup> Total residence time including reactor A and reactor B. <sup>b</sup> Isolated yield.

## Conclusion

In summary, we have deeply investigated the two-step diazotization/Heck-Matsuda reaction using a dedicated flow reactor. We provided strong evidences for preferentially conducting the diazotization/Heck-Matsuda reaction sequentially rather than as a multicomponent process whereby diazotization and coupling occur in a concomitant fashion. The experimental simplicity and the mild conditions render this flow approach highly competitive and safer compared to traditional batch approaches. This work allows a better understanding of the scope and limitation of the Heck-Matsuda reaction conducted in a flow reactor. For instance, the uncovered use of an immobilized catalyst considerably increase the throughput of the

process with residence time as low as 225 seconds for the sequential two-step diazotization/Heck-Matsuda reaction while limiting to low ppm levels the contamination of the crude products by palladium residues. From a larger perspective, we provided important advances for considering in a safer environment the rich chemistry of aryl diazonium salts in palladium-catalyzed transformations under continuous-flow conditions.

## Experimental section

**General methods.** All commercial reagents were used as received. Silica gel (40-63  $\mu\text{m}$ ) was used in flash column chromatography. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (TLC silica gel 60 F<sub>254</sub>), visualized with a UV lamp (254 nm), and stained with a basic solution of  $\text{KMnO}_4$ . Solvent systems and flash column chromatography are reported as percent by volume values.  $^1\text{H}$  and  $^{13}\text{C}$  NMR were recorded at 300 MHz or 400 MHz and 75 MHz or 100 MHz respectively. Proton chemical shifts were internally referenced to the residual proton resonance in  $\text{CDCl}_3$  ( $\delta$  7.26 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in  $\text{CDCl}_3$  ( $\delta$  77.2 ppm). FT-IR spectra were recorded with samples loaded as KBr plates. Low resolution mass spectroscopy (LRMS) was performed using chemical ionization (CI). High resolution mass spectroscopy (HRMS) was recorded on an orbitrap spectrometer. Sample loops and reactors were made out of PEEK with a 0.75 mm internal diameter. T-mixers were made out of PEEK with an internal volume of 150  $\mu\text{L}$  and connecting tubing was made out of PFA with a 0.75 mm internal diameter.

**General procedure for the two-step one-pot coupling of 4-bromoaniline with methyl acrylate in batch.** To a solution of aniline (1.0 mmol, 172 mg) in  $\text{MeOD-d}_4$  (5 mL) were added methanesulfonic acid (2.3 mmol, 150  $\mu\text{L}$ ) and *t*-BuONO (1.5 mmol, 180  $\mu\text{L}$ ) at 25  $^\circ\text{C}$ . The resulting mixture was stirred for 90 minutes and then, methyl acrylate (2.2 mmol, 200  $\mu\text{L}$ ) and palladium acetate (2.2 mol%, 5 mg) were added and the reaction was conducted at 25  $^\circ\text{C}$ .

**General procedure for the multicomponent coupling of 4-bromoaniline with methyl acrylate in batch.** To a solution of aniline (1.0 mmol, 172 mg) in  $\text{MeOD-d}_4$  (3 mL) were added methanesulfonic acid (2.3 mmol, 150  $\mu\text{L}$ ) and *t*-BuONO (1.5 mmol, 180  $\mu\text{L}$ ) at 25  $^\circ\text{C}$ . Then, methyl acrylate (2.2 mmol, 200  $\mu\text{L}$ ) and palladium acetate (2.2 mol%, 5 mg) were added with  $\text{MeOD-d}_4$  (2 mL). The reaction was conducted at 25  $^\circ\text{C}$ .

**General procedure for the two-step one-pot coupling of 4-nitroaniline with methyl acrylate in batch.** To a solution of aniline (1.0 mmol, 138 mg) in MeOD-d<sub>4</sub> (5 mL) were added methanesulfonic acid (2.3 mmol, 150  $\mu$ L) and *t*-BuONO (1.5 mmol, 180  $\mu$ L) at 25 °C. The resulting mixture was stirred for 90 minutes and then, methyl acrylate (2.2 mmol, 200  $\mu$ L) and palladium acetate (2.2 mol%, 5 mg) were added and the reaction was conducted at 25 °C.

**General procedure for the solvent screening using a two-stream flow device.** A solution of *p*-bromobenzene diazonium salt (0.2 M) was prepared using *p*-bromoaniline (2.0 mmol, 344 mg) with methanesulfonic acid (2.3 equiv., 300  $\mu$ L) and *t*-BuONO (1.5 equiv., 360  $\mu$ L) in MeOH (10 mL) at 25 °C. In another flask, a solution containing methyl acrylate (0.44 M, 400  $\mu$ L) and palladium acetate (0.0044 M, 10 mg) was prepared in solvent B (10 mL) at 25 °C. Then, each sample loops were filled with the solutions previously prepared and the reaction was conducted at the corresponding temperature. The collected product **4a** was analyzed by <sup>1</sup>H NMR.

**General procedure for the optimization studies with a three-stream flow device.** To a solution of *p*-bromoaniline (0.1 M, 172 mg) was added methanesulfonic acid ([C<sub>1</sub>]) in MeOH (10 mL) at 25 °C. In another flask, a solution of *t*-BuONO (0.15 M, 180  $\mu$ L) was prepared in MeOH (10 mL) at 25 °C. Both of them were injected into two different sample loops (5 mL). A solution of methyl acrylate ([C<sub>2</sub>]) and palladium acetate ([C<sub>3</sub>]) prepared in THF at 25 °C was continuously added on a third pump. The reaction was conducted at the corresponding temperature. The collected product **4a** was analyzed by <sup>1</sup>H NMR.

**General procedure for the homogeneous Heck-Matsuda cross-coupling using a flow device.** A solution of aniline (0.1 M) and methanesulfonic acid (0.1 M, 65  $\mu$ L) in MeOH (10 mL) at 25 °C was loaded in *loop A* (5 mL). A solution of *t*-BuONO (0.15 M, 180  $\mu$ L) in MeOH (10 mL) at 25 °C was loaded in *loop B* (5 mL). A solution of methyl acrylate (0.44 M) and palladium acetate (0.0005 M, 0.5 mol%) prepared in THF at 25 °C was continuously added on a third pump. The reaction is conducted at the corresponding temperature. Na<sub>2</sub>CO<sub>3</sub> (0.5 mmol) was added to the collected product and then, the solvent was removed. The crude product was purified by flash chromatography to give the corresponding coupling product.

**General procedure for the heterogeneous Heck-Matsuda cross-coupling using a flow device.** A solution of aniline (0.2 M) and methanesulfonic acid (0.2 M, 130  $\mu$ L) in MeOH (10 mL) at 25 °C was loaded in *loop A* (5 mL). A solution of *t*-BuONO (0.3 M, 360  $\mu$ L) in MeOH



(10 mL) at 25 °C was loaded in *loop B* (5 mL). A solution of methyle acrylate (0.44 M) prepared in MeOH at 25 °C was continuously added on a third pump. The resulting flow stream went through the packed bed containing the heterogeneous catalyst (PdEnCat®30, 0.38 mmol). The reaction is conducted at the corresponding temperature. Na<sub>2</sub>CO<sub>3</sub> (1.0 mmol) was added to the collected product and then, the solvent was removed. The crude product was purified by flash chromatography to give the corresponding coupling product.

**(E)-Methyl-4-bromocinnamate (4a).** This compound was prepared according to the general cross-coupling procedures. Purification by flash chromatography (5% AcOEt-petroleum ether) gave a white solid (*homogeneous procedure*: 94 mg, 78%). mp 89 °C [Lit.<sup>3h</sup> 88-93 °C]. IR:  $\nu$  1490, 1587, 1633, 1710, 2833, 2948, 2997, 3032, 3064 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  3.81 (s, 3H), 6.43 (d, 1H, J = 16.0 Hz), 7.39 (d, 2H, J = 8.4 Hz), 7.52 (d, 2H, J = 8.5 Hz), 7.62 (d, 1H, J = 16.0 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  52.0, 118.7, 124.7, 129.6, 132.3, 133.5, 143.7, 167.4. MS (CI) *m/z* 240 (M, <sup>79</sup>Br), 242 (M, <sup>81</sup>Br), 258 (M+NH<sub>4</sub><sup>+</sup>, <sup>79</sup>Br), 260 (M+NH<sub>4</sub><sup>+</sup>, <sup>81</sup>Br).

**(E)-Methyl 4-nitrocinnamate (4b).** This compound was prepared according to the general cross-coupling procedures. Purification by flash chromatography (20% AcOEt-petroleum ether) gave a white solid (*homogeneous procedure*: 73 mg, 71%; *heterogeneous procedure*: 137 mg, 66%). mp 161 °C [Lit.<sup>10c</sup> 161 °C]. IR:  $\nu$  1638, 1721, 2958, 3041 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  3.84 (s, 3H), 6.57 (d, 1H, J = 16.1 Hz), 7.68 (d, 2H, J = 8.7 Hz), 7.71 (s, 1H, J = 16.1 Hz), 8.25 (d, 2H, J = 8.8 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  52.3, 122.3, 124.4, 128.8, 140.7, 142.1, 148.7, 166.6. HRMS (ESI) calcd for C<sub>10</sub>H<sub>9</sub>NO<sub>4</sub> [M]<sup>+</sup>: 207.0532, found: 207.0533.

**(E)-Methyl 4-methoxycarbonylcinnamate (4c).** This compound was prepared according to the general cross-coupling procedures. Purification by flash chromatography (15% AcOEt-petroleum ether) gave a white solid (*homogeneous procedure*: 81 mg, 74%; *heterogeneous procedure*: 176 mg, 80%). mp 124 °C [Lit.<sup>3h</sup> 124 °C]. IR:  $\nu$  1641, 1720, 2958 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  3.82 (s, 3H), 3.93 (s, 3H), 6.52 (d, 1H, J = 16.1 Hz), 7.58 (d, 2H, J = 8.3 Hz), 7.70 (d, 1H, J = 16.1 Hz), 8.04 (d, 2H, J = 8.4 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  52.1, 52.5, 120.4, 128.1, 130.3, 131.6, 138.8, 143.6, 166.6, 167.1. HRMS (ESI) calcd for C<sub>12</sub>H<sub>12</sub>O<sub>4</sub>Na [M+Na]<sup>+</sup>: 243.0633, found: 243.0629.

**(E)-Methyl 2-nitrocinnamate (4d).** This compound was prepared according to the general cross-coupling procedures. Purification by flash chromatography (20% AcOEt-petroleum

ether) gave a yellow solid (*homogeneous procedure*: 73 mg, 71%). mp 71-72 °C [Lit.<sup>3h</sup> 72 °C]. IR:  $\nu$  1637, 1719, 2953, 3024 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  3.83 (s, 3H), 6.37 (d, 1H, J = 15.8 Hz), 7.51-7.57 (m, 1H), 7.61-7.68 (m, 2H), 8.03 (d, 1H, J = 7.8 Hz), 8.11 (d, 1H, J = 15.8 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  52.2, 123.0, 125.1, 129.3, 130.5, 130.7, 133.7, 140.3, 148.5, 166.4. HRMS (ESI) calcd for C<sub>10</sub>H<sub>9</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 230.0429, found: 230.0429.

**(E)-Methyl 4-methyl-2-nitrocinnamate (4e).** This compound was prepared according to the general cross-coupling procedures. Purification by flash chromatography (20% AcOEt-petroleum ether) gave a yellow solid (*homogeneous procedure*: 83 mg, 75%; *heterogeneous procedure*: 147 mg, 67%). mp 73-75 °C [Lit.<sup>5a</sup> 71-72 °C]. IR:  $\nu$  1527, 1635, 1716, 2952, 3012, 3070 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  2.47 (s, 3H), 3.82 (s, 3H), 6.35 (d, 1H, J = 15.8 Hz), 7.45 (app. d, 1H, J = 8.0 Hz), 7.53 (d, 1H, J = 8.0 Hz), 7.84 (s, 1H), 8.07 (d, 1H, J = 15.8 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  21.3, 52.1, 122.3, 125.4, 127.8, 129.0, 134.4, 140.2, 141.6, 148.6, 166.6. HRMS (ESI) calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>4</sub>Na [M+Na]<sup>+</sup>: 244.0586, found: 244.0584.

**(E)-Methyl 4-methoxy-2-nitrocinnamate (4f).** This compound was prepared according to the general cross-coupling procedures. Purification by flash chromatography (15% AcOEt-petroleum ether) gave a yellow solid (*homogeneous procedure*: 103 mg, 87%). mp 90-91 °C [Lit.<sup>5a</sup> 90-91 °C]. IR:  $\nu$  1639, 1725, 2957, 3005 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  3.82 (s, 3H), 3.91 (s, 3H), 6.32 (d, 1H, J = 15.8 Hz), 7.17 (dd, 1H, J = 2.7 Hz, J = 8.7 Hz), 7.50 (d, 1H, J = 2.6 Hz), 7.58 (d, 1H, J = 8.7 Hz), 8.04 (d, 1H, J = 15.8 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  52.1, 56.2, 109.6, 120.2, 121.2, 122.7, 130.2, 139.7, 149.6, 161.1, 166.7. HRMS (ESI) calcd for C<sub>11</sub>H<sub>11</sub>O<sub>5</sub>NNa [M+Na]<sup>+</sup>: 260.0529, found: 260.0525.

**(E)-Methyl 2-methoxy-4-nitrocinnamate (4g).** This compound was prepared according to the general cross-coupling procedures. Purification by flash chromatography (15% AcOEt-petroleum ether) gave a yellow solid (*homogeneous procedure*: 88 mg, 74%; *heterogeneous procedure*: 201 mg, 85%). mp 108 °C [Lit.<sup>5a</sup> 108 °C]. IR:  $\nu$  1635, 1719, 2957, 3098 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300 MHz):  $\delta$  3.83 (s, 3H), 4.00 (s, 3H), 6.64 (d, 1H, J = 16.2 Hz), 7.64 (d, 1H, J = 8.5 Hz), 7.76 (d, 1H, J = 2.1 Hz), 7.84 (dd, 1H, J = 2.1 Hz, J = 8.5 Hz), 7.95 (d, 1H, J = 16.2 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75 MHz):  $\delta$  52.1, 56.4, 106.4, 116.0, 122.5, 129.2, 129.9, 138.0, 149.6, 158.5, 167.2. HRMS (ESI) calcd for C<sub>11</sub>H<sub>11</sub>NO<sub>5</sub>Na [M+Na]<sup>+</sup>: 260.0535, found: 260.0540.

**(E)-Methyl (2-methoxycarbonyl-3thienyl)acrylate (4h).** This compound was prepared according to the general cross-coupling procedures. Purification by flash chromatography (20% AcOEt-petroleum ether) gave a white solid (*homogeneous procedure*: 85 mg, 75% and 95 mg, 84%; *heterogeneous procedure*: 157 mg, 69%). mp 89-91 °C. IR:  $\nu$  1525, 1628, 1702, 1726, 2955, 3007, 3103  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  3.80 (s, 3H), 3.90 (s, 3H), 6.37 (d, 1H,  $J = 16.2$  Hz), 7.34 (dd, 1H,  $J = 0.3$  Hz,  $J = 5.3$  Hz), 7.46 (dd, 1H,  $J = 0.6$  Hz,  $J = 5.3$  Hz), 8.50 (d, 1H,  $J = 16.2$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  52.0, 52.5, 121.8, 126.8, 131.0, 131.3, 136.9, 142.0, 162.4, 167.3. HRMS (ESI) calcd for  $\text{C}_{10}\text{H}_{10}\text{O}_4\text{NaS} [\text{M}+\text{Na}]^+$ : 249.0197, found: 249.0198.

**(E)-Methyl-4-methoxycinnamate (4i).** This compound was prepared according to the general cross-coupling procedure. Purification by flash chromatography (20% AcOEt-petroleum ether) gave a white solid (*homogeneous procedure*: 52 mg, 54%; *heterogeneous procedure*: 98 mg, 51%). mp 86 °C [Lit.<sup>5c</sup> 94 °C]. IR:  $\nu$  1513, 1603, 1637, 1718, 2843, 2948, 3000, 3031  $\text{cm}^{-1}$ .  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300 MHz):  $\delta$  3.79 (s, 3H), 3.83 (s, 3H), 6.32 (d, 1H,  $J = 16.0$  Hz), 6.91 (d, 2H,  $J = 8.8$  Hz), 7.47 (d, 2H,  $J = 8.7$  Hz), 7.64 (d, 1H,  $J = 16.0$  Hz).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75 MHz):  $\delta$  51.8, 55.5, 114.5, 115.4, 127.3, 129.9, 144.7, 161.6, 167.9. HRMS (ESI) calcd for  $\text{C}_{11}\text{H}_{13}\text{O}_3 [\text{M}+\text{H}]^+$ : 193.0859, found: 193.0860.

## Acknowledgments

We gratefully acknowledge the “Université de Nantes”, the “Centre National de la Recherche Scientifique (CNRS)”, and the “Région Pays de la Loire” in the framework of a “Recrutement sur poste stratégique” for the financial support to this project and C. Douchet (Université Montpellier) for ICPMS analyses. F.-X. Felpin is member of the “Institut Universitaire de France (IUF)”.

## Supporting Information

Figure S1, Figure S2,  $^1\text{H}$ ,  $^{13}\text{C}$  NMR and HRMS spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## References

- (1) Kikukawa, K.; Matsuda, T. *Chem. Lett.* **1977**, 159.
- (2) (a) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622. (b) Felpin, F.-X.; Nassar-Hardy, L.; Le Callonnec, F.; Fouquet, E. *Tetrahedron* **2011**, *67*, 2815. (c) Taylor, J. G.; Moro, A. V.; Correia, C. R. D. *Eur. J. Org. Chem.* **2011**, 1403. (d) Mo, F.; Dong, G.; Zhang, Y.; Wang, J. *Org. Biomol. Chem.* **2013**, *11*, 1582.
- (3) (a) Darses, S.; Pucheault, M.; Genêt, J.-P. *Eur. J. Org. Chem.* **2001**, 2001, 1121. (b) Masllorens, J.; Bouquillon, S.; Roglans, A.; Hénin, F.; Muzart, J. *J. Organomet. Chem.* **2005**, *690*, 3822. (c) Artuso, E.; Barbero, M.; Degani, I.; Dughera, S.; Fochi, R. *Tetrahedron* **2006**, *62*, 3146. (d) Pastre, J. C.; Correia, C. R. D. *Adv. Synth. Catal.* **2009**, *351*, 1217. (e) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Sferrazza, A. *Synlett* **2009**, 2009, 1277. (f) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Sferrazza, A. *Synlett* **2009**, 2009, 973. (g) Stern, T.; Rückbrod, S.; Czekelius, C.; Donner, C.; Brunner, H. *Adv. Synth. Catal.* **2010**, *352*, 1983. (h) Felpin, F.-X.; Miqueu, K.; Sotiropoulos, J.-M.; Fouquet, E.; Ibarguren, O.; Laudien, J. *Chem. Eur. J.* **2010**, *16*, 5191. (i) Siqueira, F. A.; Taylor, J. G.; Correia, C. R. D. *Tetrahedron Lett.* **2010**, *51*, 2102. (j) Raduán, M.; Padrosa, J.; Pla-Quintana, A.; Parella, T.; Roglans, A. *Adv. Synth. Catal.* **2011**, *353*, 2003. (k) Taylor, J. G.; Ribeiro, R. d. S.; Correia, C. R. D. *Tetrahedron Lett.* **2011**, *52*, 3861. (l) da Penha, E. T.; Forni, J. A.; Biajoli, A. F. P.; Correia, C. R. D. *Tetrahedron Lett.* **2011**, *52*, 6342. (m) Gaikwad, D. S.; Pore, D. M. *Synlett* **2012**, *23*, 2631. (n) Schwalm, C. S.; Correia, C. R. D. *Tetrahedron Lett.* **2012**, *53*, 4836. (o) Schmidt, B.; Elizarov, N. *Chem. Commun.* **2012**, *48*, 4350. (p) Barancelli, D. A.; Salles, A. G.; Taylor, J. G.; Correia, C. R. D. *Org. Lett.* **2012**, *14*, 6036. (q) Schmidt, B.; Elizarov, N.; Berger, R.; Holter, F. *Org. Biomol. Chem.* **2013**, *11*, 3674. (r) Salabert, J.; Sebastián, R. M.; Vallribera, A.; Cívicos, J. F.; Nájera, C. *Tetrahedron* **2013**, *69*, 2655.
- (4) Filimonov, V. D.; Trusova, M.; Postnikov, P.; Krasnokutskaya, E. A.; Lee, Y. M.; Hwang, H. Y.; Kim, H.; Chi, K.-W. *Org. Lett.* **2008**, *10*, 3961.
- (5) (a) Le Callonnec, F.; Fouquet, E.; Felpin, F.-X. *Org. Lett.* **2011**, *13*, 2646. (b) Susperregui, N.; Miqueu, K.; Sotiropoulos, J.-M.; Le Callonnec, F.; Fouquet, E.; Felpin, F.-X. *Chem. Eur. J.* **2012**, *18*, 7210. (c) Oger, N.; Le Callonnec, F.; Jacquemin, D.; Fouquet, E.; Le Grogne, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2014**, *356*, 1065.
- (6) (a) Jas, G.; Kirschning, A. *Chem. Eur. J.* **2003**, *9*, 5708. (b) Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. *Synlett* **2008**, 2008, 151. (c) Wegner, J.; Ceylan, S.; Kirschning, A. *Chem. Commun.* **2011**, *47*, 4583. (d) Ley, S. V. *Chem. Rec.* **2012**, *12*, 378.
- (7) Ahmed-Omer, B.; Barrow, D. A.; Wirth, T. *Tetrahedron Lett.* **2009**, *50*, 3352.
- (8) Nalivela, K. S.; Tilley, M.; McGuire, M. A.; Organ, M. G. *Chem. Eur. J.* **2014**, *20*, 6603.

- (9) (a) Lee, C. K. Y.; Holmes, A. B.; Ley, S. V.; McConvey, I. F.; Al-Duri, B.; Leeke, G. A.; Santos, R. C. D.; Seville, J. P. K. *Chem. Commun.* **2005**, 2175. (b) Baxendale, I. R.; Griffiths-Jones, C. M.; Ley, S. V.; Tranmer, G. K. *Chem.-Eur. J.* **2006**, *12*, 4407.
- (10) (a) Beller, M.; Kühlein, K. *Synlett* **1995**, 1995, 441. (b) Brunner, H.; de Courcy, N. L. C.; Genêt, J.-P. *Tetrahedron Lett.* **1999**, *40*, 4815. (c) Felpin, F.-X.; Fouquet, E.; Zakri, C. *Adv. Synth. Catal.* **2008**, *350*, 2559. (d) Felpin, F. X.; Ibarguren, O.; Nassar-Hardy, L.; Fouquet, E. *J. Org. Chem.* **2009**, *74*, 1349. (e) Felpin, F. X.; Coste, J.; Zakri, C.; Fouquet, E. *Chem.-Eur. J.* **2009**, *15*, 7238. (f) Ibarguren, O.; Zakri, C.; Fouquet, E.; Felpin, F. X. *Tetrahedron Lett.* **2009**, *50*, 5071. (g) Gholinejad, M. *Appl. Organomet. Chem.* **2013**, *27*, 19. (h) Li, X.; Wang, L.-C.; Chang, H.-H.; Zhang, C.-X.; Wei, W.-L. *Appl. Catal. A: Gen.* **2013**, 462–463, 15. (i) Singh, A. S.; Shendage, S. S.; Nagarkar, J. M. *Tetrahedron Lett.* **2013**, *54*, 6319.