JOC The Journal of Organic Chemistry

Article

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

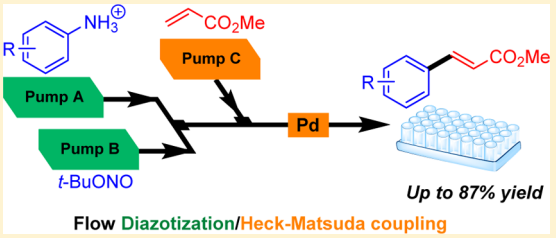
Nicolas Oger,[†] Erwan Le Grognec,[†] and François-Xavier Felpin*[,†,‡]

[†]UFR Sciences et Techniques, UMR CNRS 6230, CEISAM, Université de Nantes, 2 rue de la Houssinière, BP 92208, 44322 Nantes Cedex 3, France

[‡]Institut Universitaire de France, 103 blvd St. Michel, 75005 Paris Cedex 5, France

Supporting Information

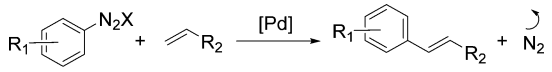
ABSTRACT: This study describes extensive investigations of the Heck–Matsuda reaction carried out by continuous-flow chemistry between aryl diazonium salts generated *in situ* and methyl acrylate. Our optimized procedures enable sequential aniline diazotization/palladium-catalyzed Heck–Matsuda reaction using either $Pd(OAc)_2$ or PdEnCat 30 as respectively a homogeneous or a heterogeneous source of palladium. This safe chemistry that does 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[1] has found a growing interest from the synthetic community these last years.[2] 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.[3] 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,[4] 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.[5] 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_2O, N_2 as byproducts. While this bicatalytic strategy addresses the issue of the diazonium handling in safe conditions, slow kinetics, requiring extensive reaction times (48–65 h), 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,[6] 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.[7] The reaction conditions required the use of AcOH–DMF as a mixture of solvents, $Pd(OAc)_2$ (10 mol %) as catalyst, and alcanes 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,[5a,b] into a flow technology.[8] 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 $MeSO_3H$ as diazotizing agents. These salts were reacted with acrylates and styrene in the presence of $Pd(OAc)_2$ (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 $\mu L \cdot min^{-1}$, corresponding respectively to 6.4 and 1.6 h residence times. These authors essentially studied *ortho*-subtituted anilines, likely because of the positive *ortho*-effect we recently uncovered,[5b] and arylation with less reactive electron-rich anilines were overlooked. Although this study was remarkably conducted, we opted for a significantly different procedure that led to higher throughputs. Ultimately, our procedure was

Received: July 2, 2014
Published: August 4, 2014

   dx.doi.org/10.1021/jo501468z | J. Org. Chem. 2014, 79, 8255–8262

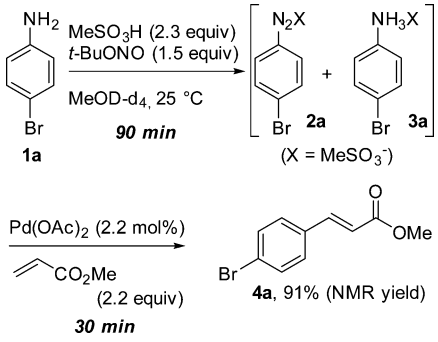
extended with the use of PdEncat30 as an immobilized palladium catalyst.

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 ^{1}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 $Pd(OAc)_2$ as catalyst to carry out the Heck–Matsuda coupling (Scheme 2). Since we

Scheme 2. Two-Step One-Pot Coupling of 4-Bromoaniline 1a with Methyl Acrylate



previously showed that the Heck–Matsuda reaction was best performed in MeOH, with *t*-BuONO and $MeSO_3H$ as diazotizing agents,[5] we followed the formation of the diazonium salt **2a** in MeOD-d_4 by ^{1}H NMR spectroscopy. As expected, the diazotization proceeded smoothly at 25 °C with no formation of degradation product (see Figure S1 in Supporting Information [SI]). Actually, the treatment of aniline with $MeSO_3H$ 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

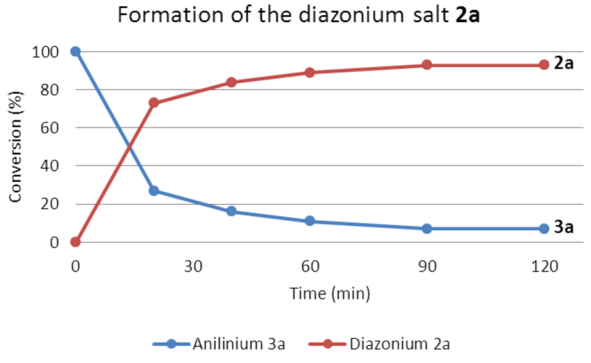
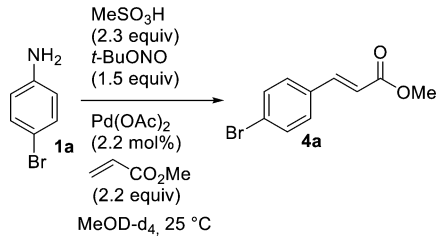


Figure 1. Kinetic of the formation of diazonium salt **2a**.

evolution (Scheme 2). The coupling was achieved in about 30 min, giving >90% NMR yield, and no significant evolution was observed upon further stirring. As a consequence, a maximum of 120 min (90 + 30 min) was required to give >90% NMR yield of **4a**.

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

Scheme 3. Multicomponent Coupling of 4-Bromoaniline 1a with Methyl Acrylate



every hour showed a slower rate since after 90 min 30% of anilinium still remained in solution, while after 120 min of stirring only 75% conversion was observed for **4a** (see Figure S2 in SI). 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.

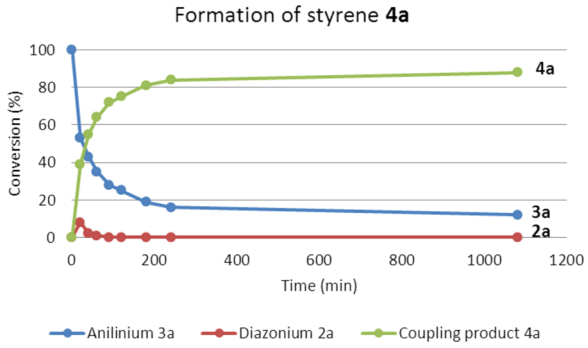


Figure 2. Kinetics for the formation of styrene **4a** in a multicomponent mode.

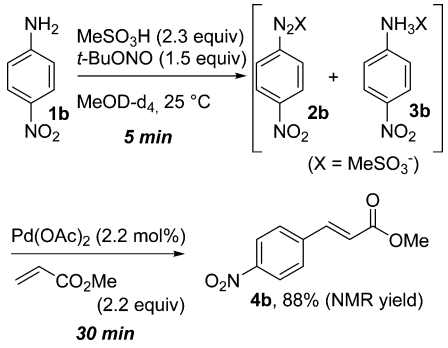
Interestingly, when 4-nitroaniline **1b** was used as an electron-poor aniline, a complete diazonium formation was observed in less than 5 min at room temperature, and the subsequent coupling reaction, leading to styrene **4b**, was achieved in half an hour (Scheme 4).

These particularly informative preliminary studies revealed to 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 on 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 methyl acrylate 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

dx.doi.org/10.1021/jo501468z | J. Org. Chem. 2014, 79, 8255–8262

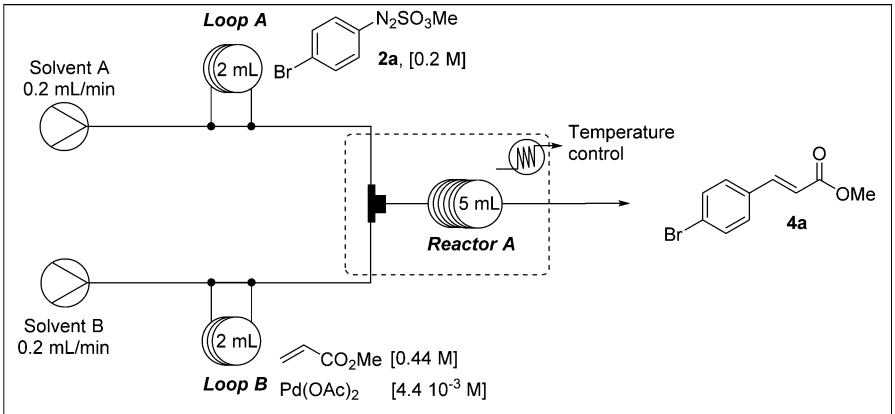
Scheme 4. Two-Step One-Pot Coupling of 4-Nitroaniline 1b with Methyl Acrylate



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 cosolvent 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 H_2O, and *loop B* was filled with a solution of $Pd(OAc)_2$ 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 μL) 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 led to the desired product in 60% NMR yield, but palladium deposits 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 behavior similar to that of 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 the clogging issue (entries 5–6).

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 $MeSO_3H$ 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 μL) and entered into a PEEK tubing *reactor A* (5 mL). Then the catalyst and methyl acrylate in solution in THF were pumped into the system and met the diazonium salt at a second T-mixer (150 μL). The resulting mixture was introduced into a PEEK *reactor B* (5 mL) and finally was collected into a fraction collector. An important slug flow stream was observed at the outlet due to N_2 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 decreased to 0.1 mL/min, an encouraging 40% yield was observed (entry 2). Increasing the temperature of both tubing reactors at 40 and 60

Table 1. Preliminary Solvent Screening with a Two-Stream Flow Device

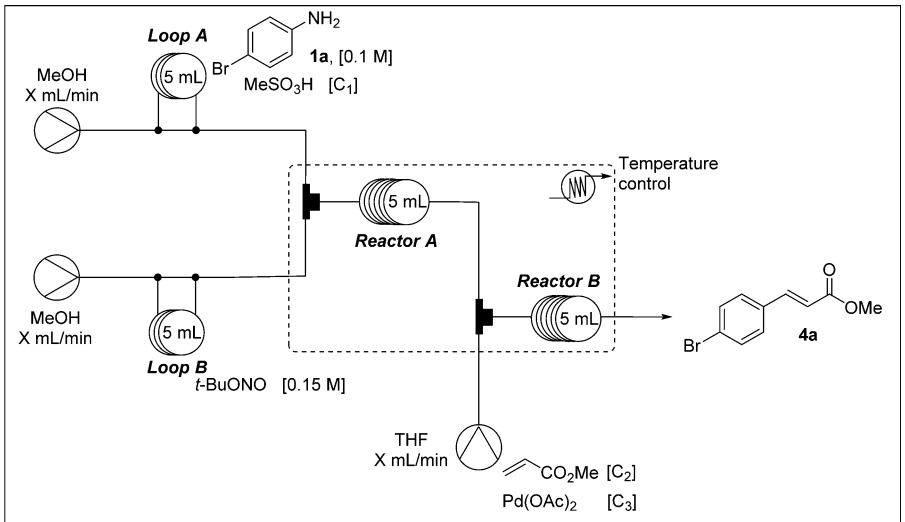


Entry	Solvent A	Solvent B	Temp. (°C)	Yield (%)[a]
1	MeOH	MeOH	25	60
2	MeOH	DMC	25	62
3[b]	H_2O	DMC	25	0
4	MeOH	1,4-dioxane	25	63
5	MeOH	THF	25	78
6	MeOH	THF	40	90

[a]NMR yield. [b]Diazonium salt prepared in water (20 min, 100% conversion).

dx.doi.org/10.1021/jo501468z | J. Org. Chem. 2014, 79, 8255–8262

Table 2. Optimization Studies with a Three-Stream Flow Device



Entry	X (mL/min)[a]	Temp. (°C)	[C_1] (mol/L)[b]	[C_2] (mol/L)[c]	[C_3] (mol/L)[d]	Yield (%)[e]
1	0.2	25	0.23	0.44	$4.4\ 10^{-3}$	22
2	0.1	25	0.23	0.44	$4.4\ 10^{-3}$	40
3	0.1	40	0.23	0.44	$4.4\ 10^{-3}$	65
4	0.1	60	0.23	0.44	$4.4\ 10^{-3}$	90
5	0.1	60	0.23	0.44	$1\ 10^{-3}$	92
6	0.1	60	0.23	0.44	$5\ 10^{-4}$	92
7	0.1	60	0.23	0.44	$1\ 10^{-4}$	85
8	0.1	60	0.23	0.22	$5\ 10^{-4}$	80
9	0.1	60	0.1	0.44	$5\ 10^{-4}$	88

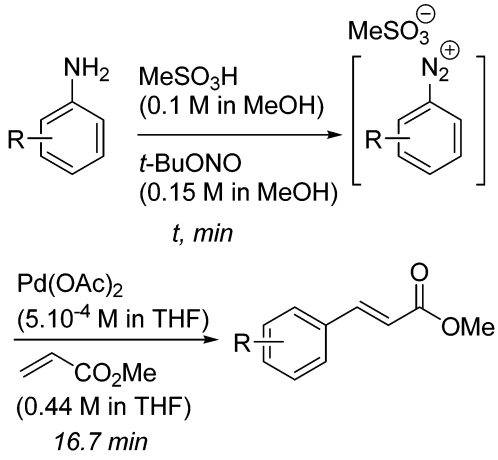
[a]Total flow rate = 3×. [b]Concentration of $MeSO_3H$ in MeOH. [c]Concentration of methyl acrylate in THF. [d]Concentration of $Pd(OAc)_2$ in THF. [e]NMR yield.

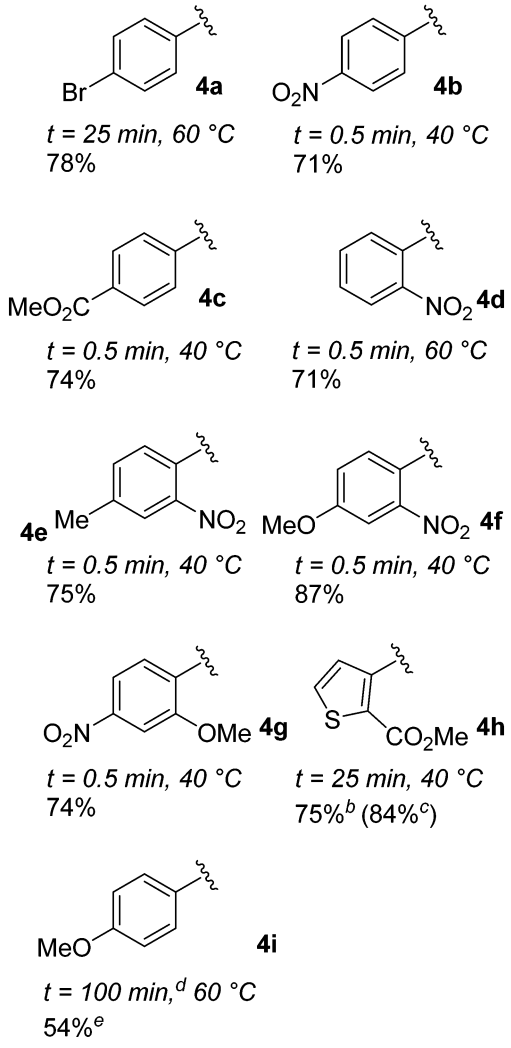
°C improved the yield respectively to 65% (entry 3) and 90% (entry 4) with a total residence time of 41.7 min for the two-step sequence. The optimal concentration of $MeSO_3H$, methyl acrylate and $Pd(OAc)_2$ was also deeply investigated in order to ensure the highest efficiency and sustainability of 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 a concentration as low as 1×10^{-4} M (0.1 mol % Pd) still furnished compound **4a** with a high yield (entry 7). While a lower concentration of the acrylate (0.22 M vs 0.44 M) significantly altered the reaction yield (entry 8), a different trend was observed when lowering the acid concentration from 0.23 to 0.1 M, since it only marginally impacted the reaction efficiency (entry 9). Since an excess of acid might damage pump heads, especially when working on larger scale, we selected these last conditions (entry 9) for our scope studies.

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}H NMR in order to ensure 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 chemoselectivity leave unaffected functionalities that could be further modified using standard chemistry. The good yield obtained for heteroaromatic acrylate **4h** suggests that the scope of the method could be extended to relevant heterocyclic structures. The coupling of anilines bearing electron-withdrawing groups proceed with a total residence time of only ∼17 min, while mildly electron-rich anilines where diazotized and subsequently coupled with a total residence time of ∼42 min. By contrast, the very deactivated 4-methoxy anilines were less efficiently coupled in 54% yield, with a total residence time of ∼117 min. This last result revealed that the coupling of electron-rich anilines proceeded with very slow kinetics, suggesting that continuous flow chemistry might

dx.doi.org/10.1021/jo501468z | J. Org. Chem. 2014, 79, 8255−8262

Table 3. Scope of the Heck–Matsuda Reaction Using a Three-Stream Flow Device[a]





[a]Isolated yield (average of at least two runs). [b]1.10^{-3} M $Pd(OAc)_2$. [c]2.10^{-3} M $Pd(OAc)_2$. [d]Flow rate/stream: 0.025 mL/min. [e]4.10^{-3} M $Pd(OAc)_2$.

not be suitable since the temperature cannot be raised above 60 °C due to the thermal instability of diazonium salts.

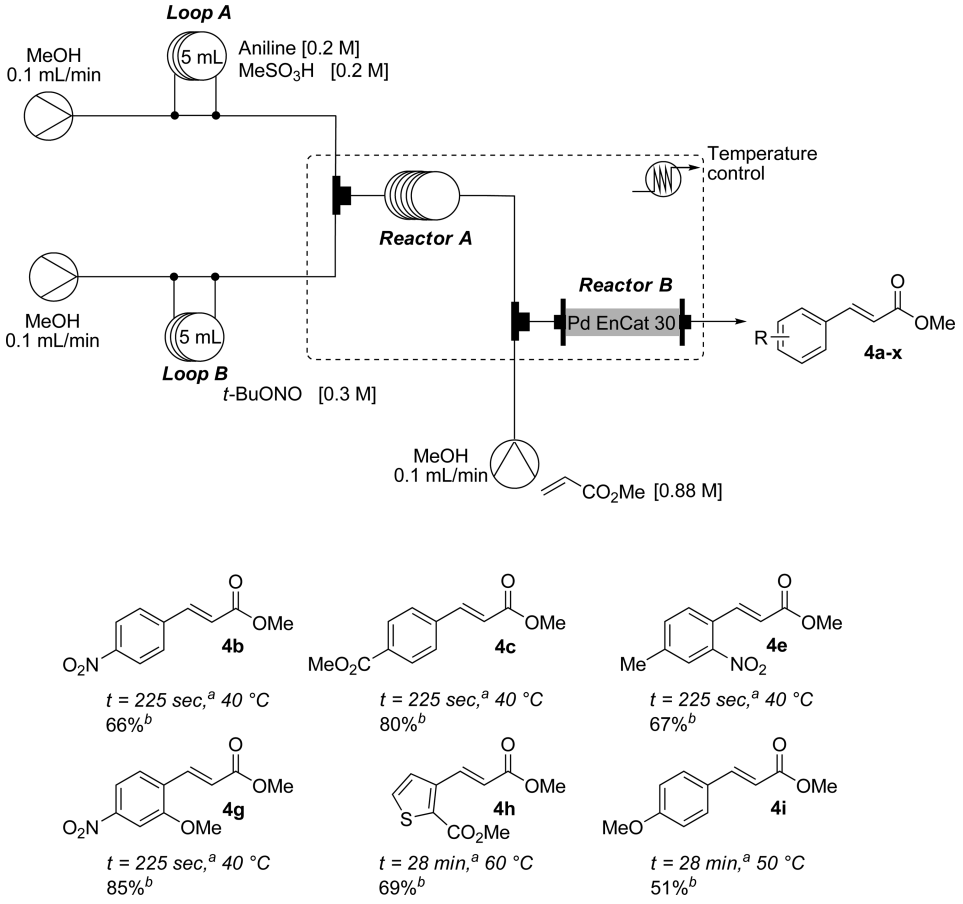
To further explore the scope of the diazotization/Heck coupling sequence in flow and develop a more practical and sustainable procedure, we considered the use of an immobilized palladium catalyst. Since $Pd(OAc)_2$ was arguably the best homogeneous palladium catalyst for conducting Heck–Matsuda coupling in methanol,[2b−d] we opted for the use of commercially available PdEncat 30 which consists of palladium acetate microencapsulated in a polyurea matrix.[9] It should be noted that Heck–Matsuda reaction catalyzed by heterogeneous palladium catalysts has not been described with flow reactors, although it is known in batch.[10] 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 μL) and entered in the coil *reactor A* (0.1 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 μL). 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 was 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 was selected for the evaluation of this unprecedented flow setup. The results showed that the yields for the coupled products were in the same range as those obtained with $Pd(OAc)_2$. 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 s 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 1–7 ppm, representing the acceptable limit for pharmaceutical ingredients. By comparison, under homogeneous conditions, a 100 times higher concentration of palladium was measured for the synthesis of **4i**.

■ CONCLUSION

In summary, we have deeply investigated the two-step diazotization/Heck–Matsuda reaction using a dedicated flow reactor. We provided strong evidence 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 s 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.

dx.doi.org/10.1021/jo501468z | J. Org. Chem. 2014, 79, 8255–8262

Table 4. Scope of the Heck–Matsuda Reaction Using Pd Encat 30 As an Immobilized Catalyst



[a]Total residence time including reactor A and reactor B. [b]Isolated yield.

EXPERIMENTAL SECTION

General Methods. All commercial reagents were used as received. Silica gel (40–63 μm) was used in flash column chromatography. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (TLC silica gel 60 F_{254}), visualized with a UV lamp (254 nm), and stained with a basic solution of $KMnO_4$. Solvent systems and flash column chromatography are reported as percent by volume values. ^1H and ^{13}C NMR were recorded at 300 or 400 and 75 MHz or 100 MHz, respectively. Proton chemical shifts were internally referenced to the residual proton resonance in $CDCl_3$ (δ 7.26 ppm). Carbon chemical shifts were internally referenced to the deuterated solvent signals in $CDCl_3$ (δ 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 μL, 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 MeOD-d_4 (5 mL) were added methanesulfonic acid (2.3 mmol, 150 μL) and *t*-BuONO (1.5 mmol, 180 μL) at 25 °C. The resulting mixture was stirred for 90 min, and then, methyl acrylate (2.2 mmol, 200 μL) and palladium acetate (2.2 mol %, 5 mg) were added, and the reaction was conducted at 25 °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 MeOD-d_4 (3 mL) were added methanesulfonic acid (2.3 mmol, 150 μL) and *t*-BuONO (1.5 mmol, 180 μL) at 25 °C. Then, methyl acrylate (2.2 mmol, 200 μL) and palladium acetate (2.2 mol %, 5 mg) were added with MeOD-d_4 (2 mL). The reaction was conducted at 25 °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_4 (5 mL) were added methanesulfonic acid (2.3 mmol, 150 μL) and *t*-BuONO (1.5 mmol, 180 μL) at 25 °C. The resulting mixture was stirred for 90 min, and then, methyl acrylate (2.2 mmol, 200 μL) 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 μL) and *t*-BuONO (1.5 equiv, 360 μL) in MeOH (10 mL) at 25 °C. In another flask, a solution containing methyl acrylate (0.44 M, 400 μL) and palladium acetate (0.0044 M, 10 mg) was prepared in solvent B (10 mL) at 25 °C. Then, each of the sample loops was filled with the solutions previously prepared, and the reaction was conducted at the corresponding temperature. The collected product **4a** was analyzed by ^1H 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 ($[C_1]$) in MeOH (10 mL) at 25 °C. In another flask, a solution of *t*-BuONO (0.15 M, 180 μL) 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 ($[C_2]$) and palladium acetate ($[C_3]$) 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 ^1H 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 μL) in MeOH (10 mL) at 25

dx.doi.org/10.1021/jo501468z | J. Org. Chem. 2014, 79, 8255–8262

°C was loaded in *loop A* (5 mL). A solution of *t*-BuONO (0.15 M, 180 μL) 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_2CO_3 (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 μL) in MeOH (10 mL) at 25 °C was loaded in *loop A* (5 mL). A solution of *t*-BuONO (0.3 M, 360 μL) in MeOH (10 mL) at 25 °C was loaded in *loop B* (5 mL). A solution of methyl 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 (PdEnCat30, 0.38 mmol). The reaction is conducted at the corresponding temperature. Na_2CO_3 (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.[3h] 88–93 °C]. IR: ν 1490, 1587, 1633, 1710, 2833, 2948, 2997, 3032, 3064 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 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). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.0, 118.7, 124.7, 129.6, 132.3, 133.5, 143.7, 167.4. MS (CI) *m*/*z* 240 (M, ^{79}Br), 242 (M, ^{81}Br), 258 (M + NH_4^+, ^{79}Br), 260 (M + NH_4^+, ^{81}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.[10c] 161 °C]. IR: ν 1638, 1721, 2958, 3041 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 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). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.3, 122.3, 124.4, 128.8, 140.7, 142.1, 148.7, 166.6. HRMS (ESI) calcd for $C_{10}H_9NO_4$ $[M]^+$: 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.[3h] 124 °C]. IR: ν 1641, 1720, 2958 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 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). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.1, 52.5, 120.4, 128.1, 130.3, 131.6, 138.8, 143.6, 166.6, 167.1. HRMS (ESI) calcd for $C_{12}H_{12}O_4Na$ $[M + Na]^+$: 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.[3h] 72 °C]. IR: ν 1637, 1719, 2953, 3024 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 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). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 52.2, 123.0, 125.1, 129.3, 130.5, 130.7, 133.7, 140.3, 148.5, 166.4. HRMS (ESI) calcd for $C_{10}H_9NO_4Na$ $[M + Na]^+$: 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.[5a] 71–72 °C]. IR: ν 1527, 1635, 1716, 2952, 3012, 3070 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 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). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 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 $C_{11}H_{11}NO_4Na$ $[M + Na]^+$: 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.[5a] 90–91 °C]. IR: ν 1639, 1725, 2957, 3005 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 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). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 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 $C_{11}H_{11}O_5NNa$ $[M + Na]^+$: 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.[5a] 108 °C]. IR: ν 1635, 1719, 2957, 3098 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 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). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 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 $C_{11}H_{11}NO_5Na$ $[M + Na]^+$: 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: ν 1525, 1628, 1702, 1726, 2955, 3007, 3103 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 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}C NMR ($CDCl_3$, 75 MHz): δ 52.0, 52.5, 121.8, 126.8, 131.0, 131.3, 136.9, 142.0, 162.4, 167.3. HRMS (ESI) calcd for $C_{10}H_{10}O_4NaS$ $[M + Na]^+$: 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.[5c] 94 °C]. IR: ν 1513, 1603, 1637, 1718, 2843, 2948, 3000, 3031 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ 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}C NMR ($CDCl_3$, 75 MHz): δ 51.8, 55.5, 114.5, 115.4, 127.3, 129.9, 144.7, 161.6, 167.9. HRMS (ESI) calcd for $C_{11}H_{13}O_3$ $[M + H]^+$: 193.0859, found: 193.0860.

■ ASSOCIATED CONTENT

Supporting Information

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

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: fx.felpin@univ-nantes.fr

Notes

The authors declare no competing financial interest.

■ 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)".

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