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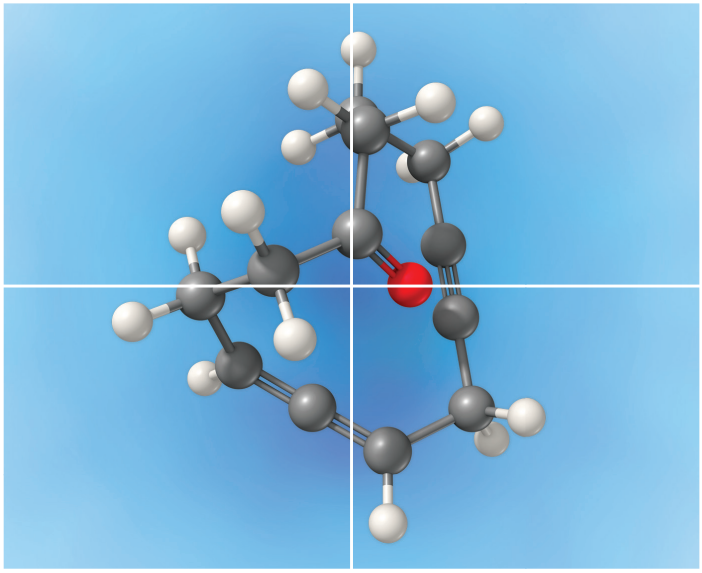

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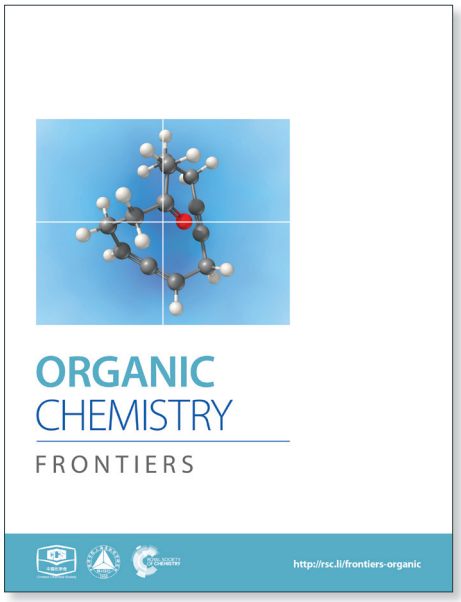


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# Sonogashira Cross-Coupling under Non-Basic Condition. Flow Chemistry as a New Paradigm in Reaction Control.

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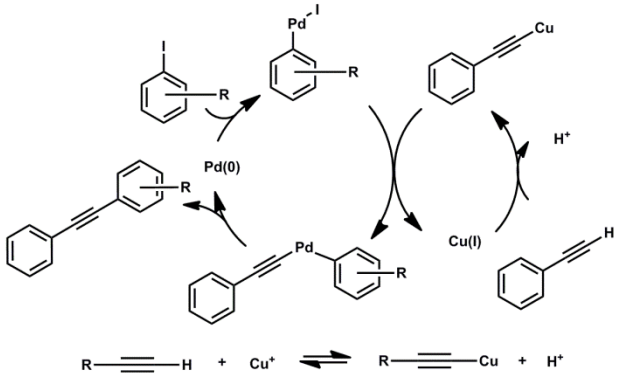
Flow regime was implemented as a non-chemical alternative of the reaction control and detrimental acid byproduct sequestration in transition metal catalyzed cross-coupling reactions. The concept was illustrated on the Sonogashira reaction and resulted into a non-basic version of the cross-coupling protocols.

## Introduction

Ever since the seminal work of Guldberg and Waage, synthetically oriented chemists have used a variety of ways to manipulate chemical equilibrium and thus improve reaction outcomes. Amongst various tactics for driving reactions to completion, the most common and practical approach has been the continual removal of reaction products.[1] In order to attain such a situation, physical (distillation or precipitation of reaction products) and chemical (product sequestration) methods have traditionally been used, leading over the years to their irreplaceable role in organic synthesis. While the conventional control of the reaction equilibrium has been extremely efficient, it is not the only way to affect the balance and tip it in the right direction. Continuous flow processes have recently become a new way to execute traditional chemical reactions.[2-5] Securing their position amongst the valuable synthetic tools for their intrinsically excellent mass and energy transport parameters, the continual flow systems could be, in addition, explored as an avenue for reaching a non-equilibrium state with consequent positive synthetic impact.[6]

Some of the foremost examples of modern synthetic methods are the chemistries that help connect two, often highly functionalized entities, while forming a new bond between two atoms of the respective subunits in the process. In the most common scenario, one of the cross-coupling reaction partners possesses formally electrophilic (organic halides, etc.) properties while the other provides electrons (reactive organometallics, olefines, acetylenes) in the transition metal catalyzed process.[7] A prime example of such chemistry is the Sonogashira protocol, which couples organic halides with terminal acetylenes.

Based on the mechanism, a formal acid byproduct is formed, which obviates the obligatory addition of a stoichiometric base (sequestering thus refractory acid). The way the acid affects the reaction equilibrium is depicted at the bottom of Scheme 1.




**Scheme 1.** Mechanism of Sonogashira cross-coupling reaction

## Results and discussion

A series of experiments was carried out to underscore the key importance of the acid in the reaction mechanism: When the base was omitted from the reaction mixture, no product was detected. When aryl iodide **1a** was treated in the separate Pd catalyzed reaction with Cu phenylacetylide **2a**, likely the reaction intermediate,[8] the reaction proceeded smoothly to completion regardless of the presence of base. In order to support the concept and demonstrate the detrimental role of acid in the system, the reaction setting was supplemented with HI. The HI aliquots were injected into the reaction mixture and

the cross-coupling product formation was monitored by GC and HPLC. For the effects of the acid addition see Figure 1.

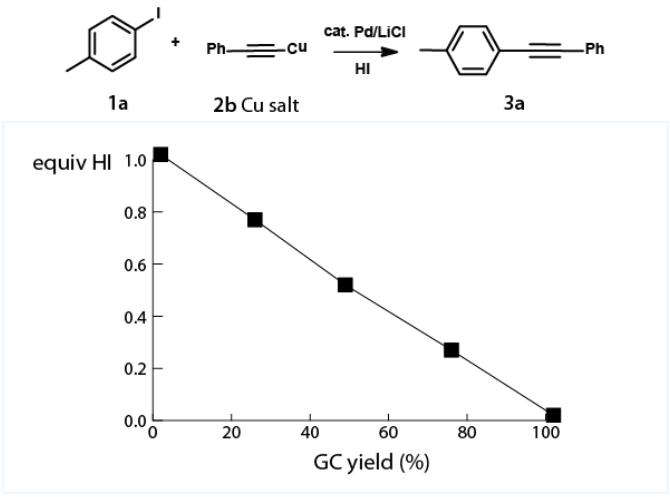


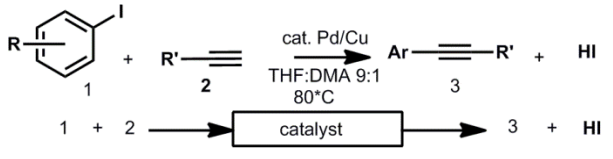

**Figure 1** HI, the formal cross-coupling by-product, was added to the reaction mixture to assess its detrimental role in the reaction system. Conversion to 3a is correlated with the amount of HI added.

The experimental results have clearly identified the importance of the Cu acetylide formation and have pointed to the central role which the acid plays in the cross-coupling scenario.

Encouraged by recent developments in commercially accessible continuous flow systems, we wanted to demonstrate the viability of the non chemical equilibrium manipulation approach by applying flow conditions to non-basic acid sequestration.[9] In analogy with the batch experiments, aryl iodides **1**, known to undergo an efficient oxidative addition to palladium(0), were used as reaction substrates together with terminal acetylenes. In contrast with the common setting, the dissolved substrates, aryl iodides **1** and terminal alkynes **2**, were in the present study driven through a flow apparatus instead.

The central component of the reactor - pair of heated short columns - contained both, Cu and commercially available Pd catalysts on a solid support.[10]

**Table 1.** Sonogashira reaction in continuous flow regime under non-basic conditions.



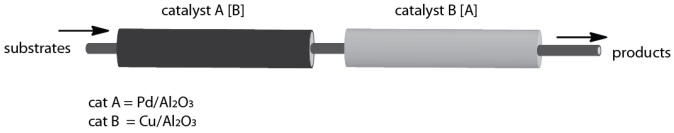

| Entry | R | R‘ | Yield GC (%) | Yield isol. (%) |
|---|---|---|---|---|
| **3a** | 4-$CH_3$ | phenyl | 74 | 60 |
| **3b** | H | phenyl | 76 | 74 |
| **3c** | 4- $CH_3$ | 2-hydroxypropane-2-yl | 64 | 58 |
| **3d** | 2-$CH_3$-4-$NO_2$ | phenyl | 80 | dec. |
| **3e** | H | cyclopropyl | 94 | 72 |
| **3f** | 4-$CH_3$ | pyridine-3-yl | 80 | 73 |
| **3g** | H | 2-bromophenyl | 63 | 50 |
| **3h** | 4-$CH_3$ | 4-acetylphenyl | 83 | 61 |
| **3i** | H | 4-fluorophenyl | 91 | 73 |
| **3j** | 4- $CH_3$ | 4-fluorophenyl | 73 | 62 |
| **3k** | 4-CH=O | pyridine-3-yl | 56 | 45 |
| **3l** | 4- $CH_3$ | 2-bromophenyl | 74 | 58 |
| **3m** | H | pyridine-3-yl | 79 | 65 |
| **3n** | 4- $CH_3$ | cyclopropyl | 98 | 85 |
| **3o** | H | 2-hydroxypropane-2-yl | 80 | 63 |
| **3p** | 4-CH=O | phenyl | 92 | 75 |

**General procedure for Sonogashira coupling in flow regime**: Substituted iodobenzene **1** (0.5 mmol) and aryl acetylene **2** (0.6 mmol) were dissolved in dried THF-DMA 9:1 (10 mL) and passed through the cartridges packed with Escat™ 1241 (5% Pd on alumina powder): (0.1% $Cu_2O$ on alumina powder) = 17:1 at 80 °C in the same solvent composition**.**

A smooth product formation was conveniently followed by UPLC and GC chromatography. The anticipated dramatic decrease of the reaction mixture pH, monitored in real time, complemented the mass balance. No products were observed and the starting material remained unchanged when either of the catalytic components was omitted from the setup.

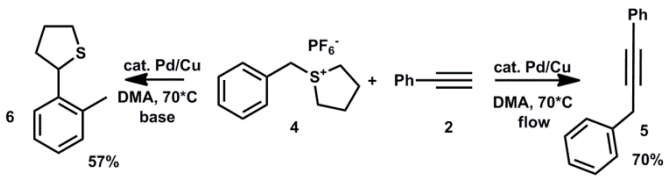
In an attempt to glean some extra insight into the process, the solid supported catalysts, Cu and Pd, were separated into two different cartridges. Both cartridges were subsequently placed in the flow instrument in a serial fashion.

**Figure 2**. Effect of the catalyst placement. In the first of the two possible




situations the cartridge **A** containing Pd catalyst was preceding the cartridge **B** containing Cu. Taking in account the mechanistic scenario of the Sonogashira protocol it was not surprising there was no product detected.‡ In the complementary situation - the cartridge **B** preceding the cartridge **A** - no product was observed either. While this observation is somehow unexpected it can be rationalized by a limited motility of Cu acetylide likely formed in the cartridge **B**

While the primary goal of the study is not a synthetic exploitation of non basic conditions in a cross-coupling reaction, the practical potential can be illustrated by the Sonogashira cross-coupling of intrinsically base sensitive benzylsulfonium salt **4**, which was treated under flow regime conditions.[13]




**Scheme 2. .** Cross-coupling of base sensitive substrate

Again, the reaction proceeded smoothly leading to the desired coupling product **5** in very good yield. The concurrent control batch experiment only yielded the rearrangement product **6**.[14]

Numerous control experiments were carried out in traditional batch settings with *no base present* under the otherwise identical conditions (catalyst, solvent, temperature). As expected, the batch experiments produced no trace of the desired products, supporting thus the notion of the fundamental differences between flow and batch systems on one side and the importance of the acid sequestration on the other.[15]

## Experimental section

General procedure for Sonogashira coupling in flow regime: Continuous-flow reactions were performed on reactor X-Cube™ (ThalesNano Inc., Hungary; two CatCarts™ of 64 mm size, 4 mm i.d. in series connection, residence volume of the system was 6 mL). Substituted iodobenzene **1** (0.5 mmol) and aryl acetylene **2** (0.6 mmol) were dissolved in dried THF-DMA 9:1 (10 mL) and passed through the cartridges packed with commercially available Pd catalyst on a solid support[10] and 0.1% $Cu_2O$ (Sigma-Aldrich) on alumina powder (Sigma-Aldrich) in the weight ratio of 17:1 (total amount of the catalyst was 1.9 g, average TON 120-150) at 80 °C in the same solvent composition with the flow rate 0.1-0.2 mL/min.

*Continuous-Flow Preparation of Compounds* **3a-3p**:

4-(Phenylethynyl)toluene (**3a**): synthesized from 4-iodotoluene (**1a**, 0.109 g, 0.5 mmol) and phenylacetylene (**2a**, 0.062 g, 0.6 mmol), yield 0.0576 g (74%), m.p. 72.5-74.5 °C (ref.[16] 72.5-74 °C). $^1$H NMR spectrum ($CDCl_3$): δ 7.55 – 7.50 (m, 2H), 7.43 (d, *J* = 8.1, 2H), 7.37 – 7.30 (m, 3H), 7.18 – 7.12 (m, 2H), 2.36 (s, 3H).

1,2-Diphenylethyne (**3b**): synthesized from iodobenzene (**1b**, 0.102 g, 0.5 mmol) and **2a** (0.062 g, 0.6 mmol), yield 0.0659 g (60%), m.p. 58.5-60.5 °C (ref.[17] 58-60 °C). $^1$H NMR spectrum ($CDCl_3$): δ 7.55 – 7.50 (m, 4H), 7.37 – 7.30 (m, 6H).

2-Methyl-4-*p*-tolylbut-3-yn-2-ol (**3c**): synthesized from **1a** (0.109 g, 0.5 mmol) and 2-methylbut-3-yn-2-ol (**2b**, 0.050 g, 0.6 mmol), yield 0.0505 g (58%), m.p. 48.9-49.1 °C (ref.[18] 50-52 °C). $^1$H NMR spectrum (cf. ref.[19]) ($CDCl_3$): δ 7.30 (d, *J* = 8.1, 2H), 7.11 (d, *J* = 7.8, 2H), 2.34 (s, 3H), 1.95 (br s, 1H), 1.61 (s, 6H). $^{13}$C NMR spectrum ($(CD_3)_2CO$): δ 139.8 (C), 133.1 (2xCH), 130.9 (2xCH), 122.3 (C), 96.4 (C), 82.6 (C), 66.1 (C), 33.1 (2x$CH_3$), 22.3 ($CH_3$).

2-Methyl-4-nitro-1-(phenylethynyl)benzene (**3d**): synthesized from 1-iodo-2-methyl-4-nitrobenzene (**1c,** 0.132 g, 0.5 mmol) and **2a** (0.062 g, 0.6 mmol), LRMS (EI): m/z 237 ($M^+$). The product could not be obtained pure after column chromatography.

(Cyclopropylethynyl)benzene (**3e**): synthesized from **1b** (0.102 g, 0.5 mmol) and ethynylcyclopropane (**2c**, 0.040 g, 0.6 mmol), yield 0.0512 g (72%), oil. $^1$H NMR spectrum (cf. ref.[20]) ($(CD_3)_2CO$): δ 7.35 (m, 2H), 7.30 (m, 3H), 1.48 (m, 1H), 0.89 (m, 2H), 0.73 (m, 2H). $^{13}$C NMR spectrum ($(CD_3)_2CO$): δ 133.2 (2xCH), 130.1 (2xCH), 129.4 (CH), 125.9 (C), 95.2 (C), 77.3 (C), 9.8 (2x$CH_2$), 1.5 (CH).

3-(*p*-Tolylethynyl)pyridine (**3f**): synthesized from **1a** (0.109 g, 0.5 mmol) and 3-ethynylpyridine (**2d**, 0.062 g, 0.6 mmol), yield 0.0705 g (73%), colorless oil. $^1$H NMR spectrum (cf. ref.[21]) ($CDCl_3$): δ 8.75 (d, 1H, *J* = 1.5 Hz), 8.53 (dd, 1H, *J* = 5.0, 1.5 Hz), 7.79 (dt, 1H, *J* = 1.75, 8.0 Hz), 7.44 (d, *J* = 8.1, 2H), 7.29-7.26 (m, 1H), 7.17 (d, *J* = 8.1, 2H).

1-Bromo-2-(phenylethynyl)benzene (**3g**): synthesized from **1b** (0.102 g, 0.5 mmol) and 1-bromo-2-ethynylbenzene (**2e**, 0.108 g, 0.6 mmol), catalyst: (5% Pd on alumina powder) : (0.1% $Cu_2O$ on alumina powder) = 50:1; yield 0.0642 g (50%), isolated as colorless oil. $^1$H NMR spectrum (cf. ref.[22]) ($(CD_3)_2CO$): δ 7.72 (m, 1H), 7.64 (m, 1H), 7.59 (m, 2H), 7.44 (m, 4H), 7.34 (m, 1H). $^{13}$C NMR spectrum ($(CD_3)_2CO$): δ 135.2 (CH), 134.4 (CH), 133.3 (2xCH), 131.9 (2xCH), 130.8 (CH), 130.5 (CH), 129.5 (CH), 126.9 (C), 126.8 (C), 124.6 (C), 95.6 (C), 89.6 (C).

1-(4-(*p*-Tolylethynyl)phenyl)ethanone (**3h**): synthesized from **1a** (0.109 g, 0.5 mmol) and 1-(4-ethynylphenyl)ethanone (**2f**, 0.087 g, 0.6 mmol), yield 0.0714 g (61%), m.p. 122.7-123.0 °C (ref.[23] 126-127 °C). $^1$H NMR spectrum (cf. ref.[23]) ($(CD_3)_2CO$): δ 8.09 (d, *J* = 8.8, 2H), 7.67 (d, *J* = 8.6, 2H), 7.47 (d, *J* = 8.1, 2H), 7.27 (d, *J* = 7.8, 2H), 2.61 (s, 3H), 2.37 (s, 3H).

1-Fluoro-4-(phenylethynyl)benzene (**3i**): synthesized from **1b** (0.102 g, 0.5 mmol) and 1-ethynyl- 4-fluorobenzene (**2g**, 0.072 g, 0.6 mmol), yield 0.0716 g (73%), m.p. 107.8-109.7 °C (ref.[24] 108-111 °C). $^1$H NMR spectrum (cf. ref.[24]) ($CDCl_3$): δ 7.53 (m, 4H), 7.35 (m, 3H), 7.05 (m, 2H). $^{13}$C NMR spectrum ($(CD_3)_2CO$): δ 165.7 (C), 135.5 (2xCH), 133.3 (2xCH), 130.4 (2xCH), 125.5 (C), 121.4 (C), 117.7 (2xCH), 117.5 (CH), 90.7 (C), 89.9 (C).

1-Fluoro-4-(*p*-tolylethynyl)benzene (**3j**): synthesized from **1a** (0.109 g, 0.5 mmol) and **2g** (0.072 g, 0.6 mmol), yield 0.0651 g (62%), m.p. 97.6-98.2 °C (ref.[25] 91-92 °C). $^1$H NMR spectrum (cf. ref.[25]) ($(CD_3)_2CO$): δ 7.58 (m, 2H), 7.42 (m, 2H), 7.19 (m, 4H), 2.90 (s, 3H). $^{13}$C NMR spectrum ($(CD_3)_2CO$): δ 165.6 (C), 140.6 (C), 135.4 (2xCH), 133.2 (2xCH), 131.1 (2xCH), 121.8 (C), 121.6 (C), 117.6 (2xCH), 90.9 (C), 89.2 (C), 22.4 ($CH_3$).

4-(Pyridin-3-ylethynyl)benzaldehyde (**3k**): synthesized from 4-iodobenzaldehyde (**1d**, 0.116 g, 0.5 mmol) and **2d** (0.062 g, 0.6 mmol), yield 0.0466 g (45%), m.p. 96.5-98.0 °C (ref.[26] 98.5-99.3 °C). $^1$H NMR spectrum (cf. ref.[27]) ($CDCl_3$): δ 10.09 (s, 1H), 8.83 (br s, 1H), 8.66 (br s, 1H), 7.99 (d, *J* = 8.1, 2H), 7.95 (d, *J* = 6.1, 1H), 7.80 (d, *J* = 8.1, 2H), 7.49 (br m, 1H).

1-Bromo-2-(*p*-tolylethynyl)benzene (**3l**): synthesized from **1a** (0.109 g, 0.5 mmol) and **2e** (0.108 g, 0.6 mmol), catalyst: (5% Pd on alumina powder) : (0.1% $Cu_2O$ on alumina powder) = 50:1; yield 0.0786 g (58%), isolated as colorless oil. $^1$H NMR spectrum (cf. ref.[28]) ($(CD_3)_2$)CO): δ 7.70 (d, *J* = 8.1, 1H), 7.62 (d, *J* = 7.6, 1H), 7.48 (d, *J* = 8.1, 2H), 7.41 (m, 1H), 7.31 (m, 1H), 7.25 (d, *J* = 7.8, 2H), 2.36 (s, 3H). $^{13}$C NMR spectrum ($(CD_3)_2$)CO): δ 141.1 (C), 135.1 (CH), 134.4 (CH), 133.3 (2xCH), 131.7 (2xCH), 131.2 (CH), 129.4 (CH), 127.2 (C), 126.8 (C), 121.6 (C), 95.9 (C), 89.0 (C), 22.5 ($CH_3$).

3-(Phenylethynyl)pyridine (**3m**): synthesized from **1b** (0.102 g, 0.5 mmol) and **2d** (0.062 g, 0.6 mmol), yield 0.0582 g (65%), m.p. 50.5-52 °C (ref.[29] 50-51 °C). $^1$H NMR spectrum ($CDCl_3$): δ 8.77 (d, 1H, *J* = 1.5 Hz), 8.55 (dd, 1H, *J* = 5.0, 1.5 Hz), 7.81 (dt, 1H, *J* = 1.75, 8.0 Hz), 7.56-7.53 (m, 2H), 7.38-7.36 (m, 3H), 7.30-7.27 (m, 1H).

4-(Cyclopropylethynyl)toluene (**3n**): synthesized from **1a** (0.109 g, 0.5 mmol) and **2c** (0.040 g, 0.6 mmol), yield 0.0663 g (85%), oil. $^1$H NMR spectrum (cf. ref.[20]) ($(CD_3)_2$)CO): δ 7.23 (d, *J* = 8.1, 2H), 7.11 (d, *J* = 7.8, 2H), 2.30 (s, 3H), 1.46 (m, 1H), 0.87 (m, 2H), 0.70 (m, 2H). $^{13}$C NMR spectrum ($(CD_3)_2$)CO): δ 139.2 (C), 133.2 (2xCH), 130.8 (2xCH), 122.9 (C), 94.3 (C), 77.4 (C), 22.3 ($CH_3$), 9.8 ($2xCH_2$), 1.6 (CH).

2-Methyl-4-phenylbut-3-yn-2-ol (**3o**): synthesized from **1b** (0.102 g, 0.5 mmol) and **2b** (0.050 g, 0.6 mmol), yield 0.0504 g (63%), m.p. 53.5-53.8 °C (ref.[30] 52-54 °C). $^1$H NMR spectrum (cf. ref.[32]) ($(CD_3)_2$)CO): δ 7.41 (m, 2H), 2.03 (br s, 1H), 1.62 (s, 6H). $^{13}$C NMR spectrum ($(CD_3)_2$)CO): δ 133.2 (2xCH), 130.2 (2xCH), 129.9 (CH), 125.3 (C), 97.1 (C), 82.6 (C), 66.1 (C), 33.0 ($2xCH_3$).

4-(Phenylethynyl)benzaldehyde (**3p**): synthesized from **1d** (0.123 g, 0.5 mmol) and **2a** (0.062 g, 0.6 mmol), yield 0.0773 g (75%), m.p. 95.5-98 °C (ref.[31] 96.5-98 °C). $^1$H NMR spectrum ($CDCl_3$): δ 10.02 (s, 1H), 7.87 (ddd, *J* = 0.4, 1.6, 8.1, 2H), 7.68 (ddd, *J* = 0.4, 1.6, 8.1, 2H), 7.58-7.54 (m, 2H), 7.36 – 7.40 (m, 3H).

*Sonogashira cross-coupling of base-sensitive substrate (batch reaction)*: 1-Benzyltetrahydro-1*H*-thiophenium hexafluorophosphate[32] (**4**, 0.128 g, 0.4 mmol), phenylacetylene (**2a**, 0.042 g, 0.4 mmol) and potassium carbonate (0.5 g) were suspended in DMA (5 mL). The catalyst (5% Pd on alumina powder) : (0.1% $Cu_2O$ on alumina powder) = 17:1; 0.040 g was added and the reaction mixture heated to 80 °C with stirring under Ar atmosphere. After 16 h, the UPLC analysis showed complete conversion of the starting sulfonium salt. The reaction mixture was poured to 5% HCl (30 mL) and shaken with ether (5x30 mL). The collected ether portion was washed with brine and dried by $MgSO_4$. After evaporation, the residue was purified by column chromatography on silica gel (hexane:ether:acetone (30:1:2). The obtained colorless oil (0.040 g) was identified as 2-*o*-tolyltetrahydrothiophene (**6**, Scheme 2), which is the usual product of the Sommelet-Hauser rearrangement of the starting sulfonium salt in the presence of bases[13]. Yield 57%, *m/z* (EI) 178, $^1$H NMR spectrum ($CDCl_3$) (cf. ref.[13]): *δ* 7.61 (d, *J* = 7.0, 1H), 7.12-7.24 (m, 3H), 4.76 (dd, *J* = 8.0, 5.9, 1H), 3.12-3.18 (m, 1H), 3.00-3.08 (m, 1H), 2.40 (s, 3H), 2.25-2.39 (m, 2H), 1.93-2.09 (m, 2H).

*Continuous flow reaction*: 1-Benzyltetrahydro-1*H*-thiophenium hexafluorophosphate[32] (**4**, 0.128 g, 0.4 mmol) and phenylacetylene (**2a**, 0.042 g, 0.4 mmol) were dissolved in DMA (10 mL) and passed through the cartridges packed with (5% Pd on alumina powder) : (0.1% $Cu_2O$ on alumina powder) = 17:1 at 80 °C at flow 0.3 mL/min. To the solution was then added water (30 mL) and the mixture shaken with hexane (3x30 mL). The collected hexane portion was washed with brine and dried by $MgSO_4$. After evaporation, the residue was purified by column chromatography on silica gel (hexane:ether:acetone 30:1:2). The obtained colorless oil (0.052 g) was identified as the Sonogashira product, 1,3-diphenylpropyne (**5**). Yield 70%, *m/z* (EI) 192, $^1$H NMR spectrum ($CDCl_3$) (cf. ref.[33]): *δ* 7.39-7.44 (m, 4H), 7.18-7.36 (m, 6H), 3.81 (s, 2H).

*Reaction of copper acetylide with HI in batch regime:* Copper(I) phenylacetylide (0.033 g, 0.2 mmol), lithium chloride (0.0084 g, 0.2 mmol), 4-iodotoluene (**1a**, 0.044 g, 0.2 mmol), degassed dried DMA (4 mL), and $Pd(PPh_3)_4$ (0.002 g, cat.) were stirred at 90 °C for 3 h in the presence of 0.00, 0.25, 0.50, 0.75 and 1.00 equivalents of 48% hydriodic acid. The course of the reaction was monitored with GC-MS (Fig. 1).

*Control experiments in batch regime:* **Sonogashira protocol:** a) Representative example: With catalytic amount (4.4%) of Pd: 4-Iodotoluene (**1a**, 0.109 g, 0.5 mmol) and phenylacetylene (**2a**, 0.062 g, 0.6 mmol) were dissolved in degassed dried THF-DMA 9:1 (10 mL). The catalyst (5% Pd on alumina powder) : (0.1% $Cu_2O$ on alumina powder) = 17:1; 0.050 g was added and the reaction mixture heated to 75 °C with stirring under Ar atmosphere. After 72 h, less than 2 % of the Sonogashira product **3a** was formed in the reaction mixture (detection: UPLC-MS, GC-MS). When under the same conditions $K_2CO_3$ (0.276 g, 2 mmol) was added, the reaction proceeded smoothly with the GC yield 86%.

b) With more than stoichiometric amount of Pd (equivalent amount of catalyst present in the cartridge): 4-Iodotoluene (**1a**, 0.109 g, 0.5 mmol) and phenylacetylene (**2a**, 0.062 g, 0.6 mmol) were dissolved in THF-DMA 9:1 (10 mL). The catalyst (5% Pd on alumina powder) : (0.1% $Cu_2O$ on alumina powder) = 17:1; 1.90 g was added and the reaction mixture heated to 80 °C with stirring under Ar atmosphere. After 72 h, less than 2 % of the Sonogashira product **3a** was formed in the reaction mixture (detection: UPLC-MS, GC-MS). The same conditions were used for reactions of iodobenzene (**1b**, 0.102 g, 0.5 mmol) and phenylacetylene (**2a**, 0.062 g, 0.6 mmol), with the results giving less than 2-3 % of the Sonogashira product **3b** (GC-MS).

## Conclusions

Overall, the present study describes the role of a flow regime in the development of traditional cross-coupling reactions under non-basic conditions. Even though a certain synthetic advantage of the protocol was illustrated by the transformation of the sensitive substrate, the main value of the

present study should not be seen solely in the synthetic exploitation of the reaction conditions for the construction of base sensitive molecules. Rather, its major forte may be found in exposing a less traditional facet of a flow regime as an alternative strategy for reaction mixture composition control.

## Acknowledgements

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## Notes and references

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† Electronic Supplementary Information (ESI) available: Copies of the $^{1}H$ and $^{13}C$ NMR spectra of prepared compounds. See DOI: 10.1039/b000000x/

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