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Homogeneous and Gas-Liquid Catellani-type Reaction Enabled by Continuous-Flow Chemistry

Alessandra Casnati⁺, Hannes P. L. Gemoets⁺, Elena Motti, Nicola Della Ca'*, Timothy Noël*

Abstract: Herein, we describe a practical homogeneous and gasliquid palladium-catalyzed Catellani-type reaction using a continuous-flow platform. The implementation of continuous-flow technology allowed us to accelerate the transformation and to expand the chemical space for the first time to gaseous olefins (i.e. ethylene, propylene and 3,3,3-trifluoropropene), while providing a safe and practical approach to sterically hindered ortho-disubstituted styrenes and vinyl arenes. The complete control over the stoichiometry of gaseous reagents through flow technology proved essential in directing the selectivity of the Catellani reaction to the desired products.

From an atom economy perspective, the ultimate goal in modern organic chemistry is to develop efficient and regioselective methodologies by employing readily available hydrocarbon building blocks.^[1] Site-selective functionalization of the ubiquitous C-H bond via transition metal catalysis (i.e. C-H activation) has transformed the way we currently address synthetic challenges, opening new horizons beyond the restriction of conventional synthetic approaches.^[2] In particular, metal-organic cooperative catalytic systems have emerged as a powerful tool for the development of mild and selective C-H functionalization strategies.^[3] In this respect, the Pd/norbornenecatalyzed Catellani reaction represents a unique example of a Pd^{0/II/IV} catalytic cycle, combining the effectiveness of crosscoupling with the neatness of C-H functionalization.^[4] Therefore, Catellani reactions result in the simultaneous functionalization of both ortho and ipso position of an aryl halide, while circumventing the need for a pre-installed directing group (Scheme 1).

Historically, Catellani reactions have been limited to liquid or solid reagents. This can be ascribed to the fact that the use of gaseous olefins has long been avoided due to safety concerns (*i.e.* pressurized headspace and leakages) and process constraints (*i.e.* gas-liquid mass-transfer limitations). We anticipated that the translation of Catellani-like reactions to a continuous-flow platform would be highly beneficial in terms of safety,^[5] reproducibility,^[6] scalability,^[7] and time-gain,^[8] and,

[*]	A. Casnati, Dr. ing. H. P. L. Gemoets and Dr. T. Noël Department of Chemical Engineering and Chemistry Micro Flow Chemistry & Process Technology Eindhoven University of Technology Den Dolech 2, 5612 AZ Eindhoven, The Netherlands E-mail: t.noel@tue.nl Website: www.noelresearchgroup.com A. Casnati, Prof. E. Motti and Dr. Nicola Della Ca' Department of Chemistry, Life Sciences and Environmental Sustainability (SCVSA) University of Parma Parco Area delle Scienze, 17/A, 43124 Parma, Italy E-mail: nicola.dellaca@unipr.it
[*]	These authors contributed equally.

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Scheme 1. A) An example of the Catellani reaction using an aryl halide and an olefin as terminal reagent. B) Enabling gas-liquid Catellani reactions via a continuous-flow platform..

ultimately, cost efficiency.^[9] Furthermore, the use of gaseous reagents,^[10] *i.e.* olefins would expand the scope of Catellani-like reactions, providing direct access to a series of relevant, but otherwise difficult to synthesize, sterically-congested *ortho*-disubstituted styrenes and vinyl arenes in an atom-efficient fashion.

With this goal in mind, we commenced our investigations by converting the classical Catellani reaction conditions, which utilize a heterogeneous base, to a homogeneous solution to avoid microreactor clogging.^[11] The homo-coupling of methyl 2iodobenzoate (1a) with methyl acrylate (2a) was chosen as benchmark reaction. An initial batch screening revealed that tetrabutylammonium acetate (TBAA) could successfully replace potassium carbonate as a base, while providing complete solubility. Given recent developments, we reasoned that a phosphine ligand could have a significant effect on the reactivity of the Catellani reaction.^[12] It was found that the presence of XPhos^[13] significantly improved the selectivity of the reaction (see ESI Table S1-3 for further information). Next, a continuousflow reactor was constructed, comprising a 20 mL PFA capillary reactor (1.65 mm i.d.) which was submerged in a heating bath. Interestingly, the target compound was obtained within 2 hours residence time in excellent isolated yield (3a, 91%) (see ESI Table S4). Subsequently, we set out to explore the reaction scope of the homogeneous Catellani reaction in flow (see Table 1). High reactivity was observed when using activated olefins, such as methyl acrylate (3a), α,β -unsaturated ketones/aldehyde (3d-e), N,N-dimethylacrylamide (3f) and acrylonitrile (3l)

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[a] Reaction conditions: 2.5 mol % Pd(OAc)₂, 5.0 mol % XPhos, 0.6 equiv norbornene (NB), 1 equiv 1 (1.0 mmol), 0.6 equiv 2, 1.1 equiv TBAA, 4 mL DMF, performed under Argon atmosphere, flow rate at 0.166 mL/min, added to the reactor via syringe pump. [b] Ratio given as (vinyl : allyl olefin). [c] 0.1 M. [d] 0.5 mmol of 1-ethyl-2-iodobenzene (1t) and 0.5 mmol of methyl 2-bromobenzoate (4a).

obtaining good to excellent isolated yields (77-91%). Sterically hindered methyl methacrylate was well tolerated and resulted in a yield of 54% of the most favored isomerization product (**3c**). We then explored the possibility to expand the existing scope of olefins to a fluorine-containing acrylate (**3b**), styrenes (**3g-i**) and a vinyl pyridine (**3j**). To our delight, all styrene reagents could be readily coupled, irrespective of their substitution pattern. Notably, when using 1-octene as terminating reagent, a mixture of compounds (**3k** and **3k'**) was obtained with a ratio of 1:3 favored to the allylic product. This phenomena was attributed to the fact that two β -hydride elimination pathways are possible.^[14]

Next, we varied the aryl iodide substrate using methyl acrylate (2a) as benchmark olefin. When employing aryl iodides bearing *ortho*-alkylated substituents (3m-n), poor reactivity was observed, with no full conversion obtained within 2 hours residence time. In the case of 1-iodonaphthalene (3o) a slight

improved yield was observed (43 to 51%) using more diluted conditions. 2-iodoanisole gave some product (**3p**, 32%), while only traces of product were detected for compounds **3q** and **3r**.^[4h] Interestingly, the heteroaromatic substrate **1s**, displayed good reactivity obtaining the desired product **3s** in 54% yield. Aware of the difficulties in undertaking non-symmetrical coupling,^[4h] further experiments were then performed in order to ascertain whether the combination of an electron-rich aryl iodide with an electron-deficient aryl bromide would positively impact the reactivity of the Catellani reaction under flow conditions, thus affording relevant hetero-coupled moieties within a reasonable time frame. To our delight, 1-ethyl-2-iodobenzene was readily coupled with methyl 2-bromobenzoate and methyl acrylate to obtain product **3t** in a good isolated yield of 76%. This promising result demonstrates the efficacy of our continuous platform to

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Table 2. Substrate scope for the gas-liquid Catellani-type reaction in continuous flow.[a]

[a] Reaction conditions: 5 mol % Pd(OAc)₂, 10 mol % XPhos, 1.2 equiv norbornene (NB), 1 equiv **1** (0.5 mmol), 1 equiv **4**, 2 equiv **5** (dosed via a MFC), 2.2 equiv TBAA, 4 mL DMF, performed under Argon atmosphere, liquid flow rate at 0.04 mL/min and gas flow rate at 0.4 mL/min, 100 psi back pressure regulator. [b] Analogous batch experiment with an ethylene balloon. [c] 6 mmol scale experiment. [d] 3 h residence time. [e] ratio given as (styrene : terminal olefin).

enable multi-component reactions yielding complex heterocoupled biaryl motives.

Having determined a suitable protocol for homogeneous Catellani reactions in flow, we set out to develop a gas-liquid variant utilizing gaseous olefins as coupling partners (see Table 2). By employing ethylene, propylene and 3,3,3-trifluoropropene gas, we intended to prepare sterically-hindered *ortho*disubstituted styrenes building blocks, which are not easily synthesized via traditional methods. In order to accommodate gaseous reagents, the flow reactor was equipped with a mass flow controller (MFC) and a back pressure regulator (BPR) (Scheme 1B).^[15] The liquid stream was merged with the olefin gas resulting in a stable Taylor flow regime, which provides an excellent interfacial area between the two phases. Within the liquid segments, toroidal vortices are established which ensure optimal mixing and reduces gas-liquid mass transfer limitations.^[16]

To our delight, when subjecting ethylene gas and the benchmark substrate **1a** to our reaction conditions, we obtained the desired styrene **6a** within 2 hours of residence time in good yield (79%). It should be noted that the formation of undesired Heck-like or norbornene containing by-products is a known complication of the Catellani transformation, which is normally circumvented by carefully balancing the amount of olefin and norbornene.^[4a, 4f] However, regulating the stoichiometry of the gaseous olefin is extremely challenging in batch due a poor control over the interfacial area and diffusion limitations. Indeed, when the same gas-liquid reaction was carried out in batch, uncontrolled and inefficient use of the gaseous olefin and the evaporation of norbornene into the headspace resulted in a lower yield for the desired product **6a** (64% batch vs 79% flow)

along with the formation of several by-products. The difference between batch and flow was even more pronounced in more challenging hetero-coupling reactions: e.g. 6b was obtained in 66% yield in flow, while in batch a complex mixture was observed with only 12% of the desired product (see ESI Scheme S1). The latter example highlights the need for a high degree of control over the stoichiometry of gaseous reagents to obtain optimal results. Moreover, this observation demonstrates the key role of flow technology to enable efficient gas-liquid transformations. Furthermore, the use of flow also allows to readily scale the reaction conditions (72% yield, 1.26 g of product 6a). Next, the scope was determined for the ethylene coupling partner. Aryl iodides bearing ortho electron-donating substituents (6b-c, 6e) as well as 1-iodonapthalene (6d) all reacted well with methyl 2-bromobenzoate and ethylene, resulting in moderate to good yields (61-70%). A modest yield of 37% was obtained for 1-iodo-2-(trifluoromethyl)benzene (6f). More complex ortho/meta- and ortho/para-disubstituted aryl iodides proved compatible with our method, thus yielding compounds 6g-j in synthetically useful yields (53-74%). Next, aryl bromides were shown to be competent substrates requiring longer residence times to reach full conversion (3 h, 6k-m).

Finally, we turned our attention towards two more gaseous reagents, *i.e.* propylene and 3,3,3-trifluoropropene. When performing the reaction with **1a** and propylene gas, a mixture of **6n:6n'** was obtained in high yield (83%) in a 1:2.3 ratio in favour of the terminal olefin. Hetero-coupling of 1-ethyl-2-iodobenzene or 2,4-dimethyl-1-iodobenzene with methyl 2-bromobenzoate and propylene, gave the product mixtures **6o:6o'** and **6p:6p'** in moderate yields. When 3,3,3-trifluoropropene gas was introduced into the reactor, a set of *ortho*-disubstituted trifluoromethylated styrenes (**6q-t**) could be obtained in good yield.

In conclusion, we have developed for the first time a highly practical and efficient continuous-flow platform for homogeneous and gas-liquid Catellani-type reactions. The application of flow reactors resulted in reduced reaction times and enabled the use of gaseous olefin reagents (*i.e.* ethylene, propylene and 3,3,3-trifluoropropene) in a safe and scalable manner. This continuous platform provided direct access to valuable *ortho*-disubstituted styrenes and vinyl arenes within 2 hours of residence time. For these reasons, we believe that the developed flow protocol will be of interest to both academia and industry and will be implemented as a powerful strategy to accommodate not only gas-liquid Catellani-like reactions but also other C–H activation transformations.

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Entry for the Table of Contents

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Homogeneous and Gas-liquid Catellani Reactions in Continuous-flow



Alessandra Casnati, Hannes P. L. Gemoets, Elena Motti, Nicola Della Ca', Timothy Noël*

Page No. – Page No.

Homogeneous and Gas-Liquid Catellani-type Reaction Enabled by Continuous-flow Chemistry

Herein, we describe a practical continuous-flow platform enabling both homogeneous and gas-liquid Catellani-type reactions. The implementation of continuous-flow technology allowed us to accelerate the transformation and to expand the chemical space to gaseous olefins. The complete control over the stoichiometry of gaseous reagents was deemed essential to direct selectivity, while providing a practical approach to sterically hindered ortho-disubstituted styrenes and vinyl arenes.