

## Flow Chemistry

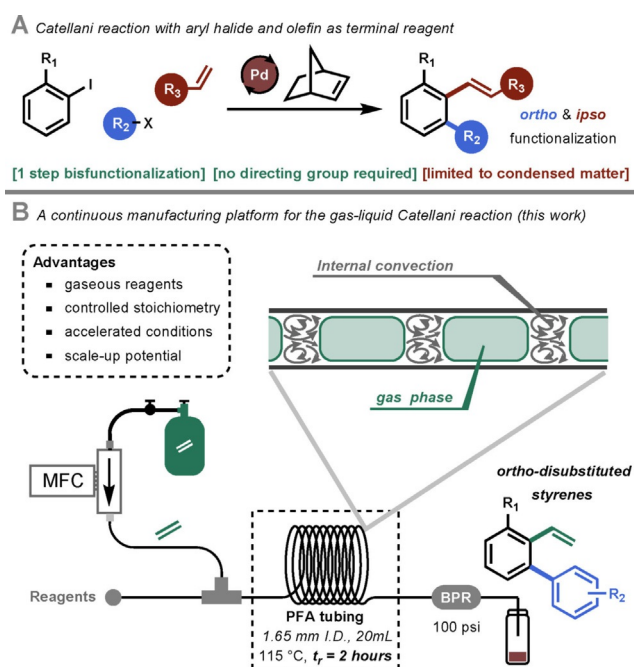
## Homogeneous and Gas–Liquid Catellani-Type Reaction Enabled by Continuous-Flow Chemistry

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**Abstract:** A practical homogeneous and gas-liquid palladium-catalyzed Catellani-type reaction using a continuous-flow platform is described. The implementation of continuous-flow technology allowed the acceleration of the transformation and, for the first time, expansion of the chemical space to gaseous olefins (i.e., ethylene, propylene and 3,3,3-trifluoropropene), thus 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 for directing the selectivity of the Catellani reaction to the desired products.

From an atom-economic perspective, the ultimate goal in modern organic chemistry is to develop efficient and regioselective methodologies by employing readily available hydrocarbon building blocks.<sup>[1]</sup> Site-selective functionalization of the ubiquitous C–H bond through 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.<sup>[2]</sup> In particular, metal–organic cooperative catalytic systems have emerged as a powerful tool for the development of mild and selective C–H functionalization strategies.<sup>[3]</sup> In this respect, the Pd/norbornene-catalyzed Catellani reaction represents a unique example

of a Pd<sup>0/II/IV</sup> catalytic cycle, combining the effectiveness of cross-coupling with the neatness of C–H functionalization.<sup>[4]</sup> Therefore, Catellani reactions result in the simultaneous functionalization of both the *ortho* and *ipso* positions of an aryl halide, while circumventing the need for a preinstalled directing group (Scheme 1).



**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 through a continuous-flow platform.

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,<sup>[5]</sup> reproducibility,<sup>[6]</sup> scalability,<sup>[7]</sup> time-gain,<sup>[8]</sup> and, ultimately, cost efficiency.<sup>[9]</sup> Furthermore, the use of gaseous reagents,<sup>[10]</sup> that is, olefins, would expand the scope of Catellani-like reactions to provide direct access to a series of relevant, but otherwise difficult to synthesize, sterically congested *ortho*-

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Table 1. Substrate scope for the liquid-phase Catellani-type reaction in continuous flow.<sup>[a]</sup>

3a, 91%	3b, 89%	3c, 54% (X = 85%)	3d, 84%	3e, 86%
3f, 77%	3g, 66%	3h, 65%	3i, 76%	3j, 72%
3k:3k', 67% (ratio: 1:3) <sup>[b]</sup>	3l, 89%	3m, 29% (X = 65%)	3n, 37% (X = 74%)	3o, 43%, 51% <sup>[c]</sup>
3p, 32% (X = 63%)	3q, traces	3r, traces	3s, 54%	3t, 76% <sup>[d]</sup>

[a] Reaction conditions: 2.5 mol% Pd(OAc)<sub>2</sub>, 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<sup>-1</sup>, added to the reactor by syringe pump; t<sub>r</sub> = residence time; X = conversion determined from amount of recovered starting material. [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**).

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.<sup>[11]</sup> The homo-coupling of methyl 2-iodobenzoate (**1a**) with methyl acrylate (**2a**) was chosen as a benchmark reaction. An initial batch screening revealed that tetrabutylammonium acetate (TBAA) could successfully replace potassium carbonate as a base, and this provided complete solubility. Given recent developments, we reasoned that a phosphine ligand could have a significant effect on the reactivity of the Catellani reaction.<sup>[12]</sup> It was found that the presence of XPhos<sup>[13]</sup> significantly improved the selectivity of the reaction (see Tables S1–S3 in the Supporting Information for further details). Next, a continuous-flow reactor was constructed,

comprising a 20 mL PFA (perfluoroalkoxy) capillary reactor [1.65 mm inner diameter (I.D.)], which was submerged into a heating bath. Interestingly, the target compound was obtained within 2 hours residence time in excellent isolated yield (**3a**, 91%) (see Table S4, Supporting Information). 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, an  $\alpha,\beta$ -unsaturated ketone or aldehyde, *N,N*-dimethylacrylamide and acrylonitrile, which provided the corresponding products **3a**, **3d–f**, and **3l**, respectively, in 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, substituted styrenes and a vinyl pyridine

to give the corresponding products **3b** and **3g–j**, respectively. To our delight, all styrene reagents could be readily coupled, irrespective of their substitution pattern. Notably, when 1-octene was used as a terminating reagent, a mixture of compounds, **3k** and **3k'**, was obtained with a ratio of 1:3 in favor of the allylic product. This phenomenon was attributed to the fact that two  $\beta$ -hydride elimination pathways are possible.<sup>[14]</sup>

Next, we varied the aryl iodide substrate using methyl acrylate (**2a**) as benchmark olefin. When aryl iodides bearing *ortho*-alkyl substituents were subjected to the reaction conditions, poor reactivity was observed, with no full conversion to the corresponding products **3m,n** within 2 hours residence time. In the case of 1-iodonaphthalene, a slightly improved yield (ranging from 43 to 51%) of the corresponding product **3o** was observed using more dilute conditions. The use of 2-iodoanisole gave product **3p** in 32% yield, whereas only traces of product were detected for compounds **3q** and **3r**, in which amide- and trifluoromethyl-substituted aryl iodides were used.<sup>[4h]</sup> Interestingly, a thiophene-derived substrate displayed good reactivity giving the desired product **3s** in 54% yield. Aware of the difficulties in undertaking non-symmetrical coupling,<sup>[4h]</sup> further experiments were then performed 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 enable multicomponent reactions yielding complex hetero-coupled 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 by traditional methods. To accommodate gaseous reagents, the flow reactor was equipped with a mass flow controller (MFC) and a backpressure regulator (BPR) (Scheme 1B).<sup>[15]</sup> 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 that ensure optimal mixing and reduce gas–liquid mass transfer limitations.<sup>[16]</sup>

To our delight, when ethylene gas and the benchmark substrate methyl 2-iodobenzoate (**1a**) were subjected 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 byproducts is a known complication of the Catellani transformation, which is normally circumvented by carefully balancing the amount of olefin and norbornene.<sup>[4a,i]</sup> However, regulating the stoichiometry of the gaseous olefin is extremely challenging in batch due to 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 byproducts. The difference between batch and flow was even more pronounced in more challenging hetero-coupling reactions; for example, **6b** was obtained in 66% yield in flow, whereas in batch, a complex mixture was observed with only 12% of the desired product (see Scheme S1 in the Supporting Information). 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 one 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 as well as 1-iodonaphthalene all reacted well with methyl 2-bromobenzoate and ethylene, resulting in moderate to good yields of the corresponding products **6b–e**, respectively (61–70% yield). A modest yield of 37% was obtained for **6f** starting from 1-iodo-2-(trifluoromethyl)benzene. 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 (**4**) were shown to be competent substrates, but required longer residence times (3 h) to reach full conversion to the corresponding products **6k–m**.

Finally, we turned our attention towards two more gaseous reagents, that is, propylene and 3,3,3-trifluoropropene. When the reaction of **1a** with propylene gas was performed, a mixture of **6n/6n'** was obtained in high yield (83%) in a 1:2.3 ratio in favor 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 yields.

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.

**Table 2.** Substrate scope for the gas–liquid Catellani-type reaction in continuous flow.<sup>[a]</sup>

<p><b>6a</b>, 79%, 64%<sup>[b]</sup>, (1.26 g, 72%)<sup>[c]</sup></p>	<p><b>6b</b>, 66%, 12%<sup>[b]</sup></p>	<p><b>6c</b>, 64%</p>	<p><b>6d</b>, 61%</p>	<p><b>6e</b>, 70%</p>
<p><b>6f</b>, 37% (X = 84%)</p>	<p><b>6g</b>, 66%</p>	<p><b>6h</b>, 53%</p>	<p><b>6i</b>, 69%</p>	<p><b>6j</b>, 74%</p>
<p><b>6k</b>, 58%<sup>[d]</sup></p>	<p><b>6l</b>, 51%<sup>[d]</sup></p>	<p><b>6m</b>, 70%<sup>[d]</sup></p>	<p><b>6n:6n'</b>, 83% (ratio 1:2.3)<sup>[e]</sup></p>	<p><b>6o:6o'</b>, 52% (ratio 1:3.3)<sup>[e]</sup></p>
<p><b>6p:6p'</b>, 47% (ratio 1:2)<sup>[e]</sup></p>	<p><b>6q</b>, 86%</p>	<p><b>6r</b>, 61%</p>	<p><b>6s</b>, 62%</p>	<p><b>6t</b>, 66%</p>

[a] Reaction conditions: 5 mol% Pd(OAc)<sub>2</sub>, 10 mol% XPhos, 1.2 equiv norbornene (NB), 1 equiv **1** (0.5 mmol), 1 equiv **4**, 2 equiv **5** (dosed using a MFC), 2.2 equiv tetrabutylammonium acetate (TBAAC), 4 mL DMF, performed under argon atmosphere, liquid flow rate at 0.04 mL min<sup>-1</sup> and gas flow rate at 0.4 mL min<sup>-1</sup>, 100 psi back pressure regulator; conversion determined from amount of recovered starting material. [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).

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## Conflict of interest

The authors declare no conflict of interest.

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