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# Sustainable and selective Ni-catalyzed allylation of 2-oxindoles and 2-coumaranones in batch and flow chemistry†

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2-Oxindoles and 2-coumaranones could be selectively allylated in the presence of low cost catalysts based on nickel, leading selectively to different polysubstituted derivatives. Allyl alcohol was used as an allylating reagent and allowed the synthesis of compounds under neutral conditions with water produced as the sole by-product. Experiments have been performed in batch and in flow chemistry. The latter protocol in flow led to a very efficient and straightforward allylic alkylation of 2-oxindoles in only a few minutes with high chemoselectivities towards either the *C,C*-bisallylated product or the *C,C,N*-trisallylated one.



## Introduction

The development of greener synthetic methods is a major challenge for chemists in order to reduce the negative impacts of chemical products and processes on human health and the environment. The use of catalysts using earth-abundant metals and the prevention of waste are important to develop economic and sustainable reactions and processes. The development of flow chemistry also presents a real opportunity for more selective and, hence, greener chemical productions.[1] As a powerful tool in organic chemistry, flow chemistry has now become common in a wide range of chemical industries.[2,3] This technology aims to enhance a researcher's ability to perform chemical reactions with unique control over key reaction parameters.[4–8]

2-Oxindoles and 2-coumaranones belong to an important class of molecules with a privileged aromatic heterocyclic scaffold. 2-Oxindoles are for example found in a wide range of bioactive natural products and pharmaceuticals.[9–15] The introduction of substituents on the nucleophilic positions (N1 or C3) of 2-oxindoles allows the synthesis of a large panel of valuable molecules with unique biological activities such as anti-cancer, anti-microbial or anti-bacterial properties.[16–19] In this context, the introduction of an allyl functionality on oxindole or coumaranone frameworks is interesting because of further possible reactions on the terminal double bond such as oxidation, hydroformylation or metathesis and the possibility of producing new valuable building blocks. The allylic alkylation reaction is one of the most relevant and efficient reactions for the construction of C–C and C–heteroatom (N/O/S) bonds.[20,21] Despite the abundant studies in this field, allylation of 2-oxindoles has been poorly explored. This reaction has been performed in the presence of transition metals as palladium,[22–26] molybdenum[27] and iridium/copper[28] as catalysts. 2-Coumaranone allylation has only been performed by stoichiometric means, typically with allyl bromide in the presence of $K_2CO_3$/$Bu_4NHSO_4$ or NaH, thus generating large amounts of salts.[29,30] To the best of our knowledge, the use of nickel in the catalytic allylation of 2-oxindoles and 2-coumaranones has never been reported.[31–34]

Herein, we report the allylic alkylation of 2-oxindoles and 2-coumaranones with a particular focus on the sustainability of the process. The *N*-unprotected 2-oxindole skeleton bears two nucleophilic sites (N1 and C3) which are in competition for the allylation reaction (Scheme 1). For the first time, catalytic oxindole allylation is performed in the presence of a nickel based catalyst as a non-critical material and low cost metal. In order to prevent waste, allyl alcohol is used as an allylation reagent leading to water as the sole reaction by-product.[35–39] It is also noteworthy that allyl alcohol is industrially produced[40] and is also accessible from vegetal feedstock as glycerol.[41–44]

Depending on the sites that are allylated and the substitution degree, several products are accessible. Diallylated products are particularly interesting as precursors of pharmaceutically active

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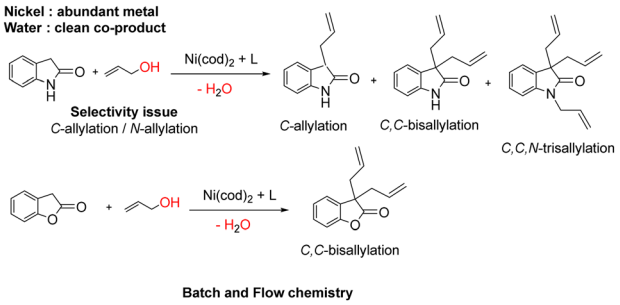



**Scheme 1** The nickel-catalyzed allylation of 2-oxindole and 2-coumaranone with allyl alcohol: sustainability of the reaction/selectivity issue.

compounds.[16] Herein, we wish to report that nickel-based catalytic systems are able to promote the *C*,*C*-bisallylation and *C*,*C*,*N*-trisallylation of 2-oxindoles with allyl alcohol under additive-free conditions. This protocol also proved to be suitable for the *C*,*C*-bisallylation of 2-coumaranones. As part of our interest in developing efficient continuous flow protocols,[45,46] this reaction was implemented under flow conditions, thus allowing better activities and a highly improved selectivity control toward the products of *C*,*C*-bisallylation or *C*,*C*,*N*-trisallylation of 2-oxindoles.

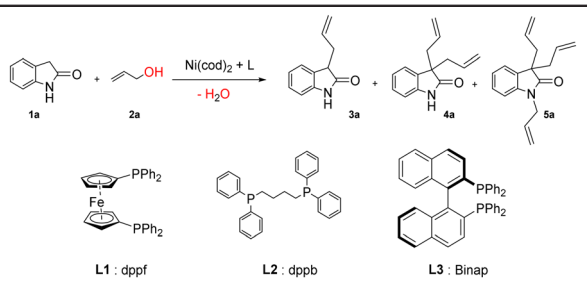
## Results and discussion

### Allylation reaction of 2-oxindoles

In order to determine critical reaction parameters, the study was first focused on the allylation of 2-oxindole **1a** as a model substrate with allyl alcohol **2a** (2 equiv.) in MeOH at 80 °C. The catalyst was *in situ* generated by combining 1.5 mol% $Ni(cod)_2$ and 3 mol% of ligand **L1**, **L2** or **L3** (Table 1, entries 1–3) which proved to be the most efficient during allylation of various substrates.[35,36] The reactions with the three bidentate ligands gave a mixture of products of *C*,*C*-bisallylation and *C*,*C*,*N*-trisallylation, **4a** and **5a**, respectively. No formation of the monoallylated 2-oxindole **3a** could be detected. In these cases, modest selectivities were obtained with 27–60% of the bisallylated product **4a** and 33–50% of the trisallylated product **5a**.

The **1a** conversions were not complete (77 to 85%) because of the total consumption of allyl alcohol to produce the polysubstituted products **4a** and **5a**. The ratio of allyl alcohol **2a**/2-oxindole **1a** and the catalyst amount were then increased (3 equiv. of **2a** and 3 mol% Ni) resulting in a total 2-oxindole conversion (entry 4). This also led to the formation of **4a** as the major product of reaction (yield = 70%) in the mixture with the trisallylated derivative **5a** (yield = 30%). An increase of reaction temperature to 100 °C allowed the selective formation of the trisallylated product **5a** with 100% 2-oxindole conversion (entry 5). In this case, EtOH was chosen instead of MeOH due to its higher boiling point. In order to evaluate the possibility of synthesizing the monosubstituted product **3a**, the quantity of allyl alcohol was then decreased (entries 6 and 7). The bisallylated derivative **4a** was always the major product of reaction even with only 1 equiv. of allyl alcohol. In the latter case, **3a** was obtained with a low yield of 18% and the conversion of the starting material

**Table 1** Optimization of the nickel catalyzed allylation of 2-oxindole **1a** with allyl alcohol **2a**[a]



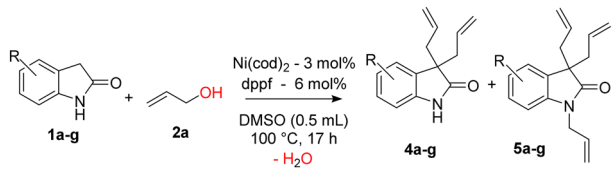

| Entry | [Ni] (mol%) | L | *T* (°C) | Solvent (0.5 mL) | Equiv. **2a** | Conv. **1a** (%) | Yield[b] (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **3a** | **4a** | **5a** |
| 1 | 1.5 | **L1** | 80 | MeOH | 2 | 83 | — | 50 | 33 |
| 2 | 1.5 | **L2** | 80 | MeOH | 2 | 85 | — | 60 | 25 |
| 3 | 1.5 | **L3** | 80 | MeOH | 2 | 77 | — | 27 | 50 |
| 4 | 3 | **L1** | 80 | MeOH | 3 | 100 | — | 70 | 30 |
| 5 | 3 | **L1** | 100 | EtOH | 3 | 100 | — | — | >99 |
| 6 | 3 | **L1** | 100 | EtOH | 2 | 81 | — | 56 | 25 |
| 7 | 3 | **L1** | 100 | EtOH | 1 | 61 | 18 | 43 | — |
| 8 | 3 | **L1** | 100 | Toluene | 3 | 100 | — | — | 97 |
| 9 | 3 | **L1** | 100 | Dioxane | 3 | 100 | — | — | >99 |
| 10 | 3 | **L1** | 100 | THF | 3 | 100 | — | — | >99 |
| 11 | 3 | **L1** | 100 | Neat | 3 | 100 | — | — | 98 |
| 12 | 3 | **L1** | 100 | DMSO | 3 | 100 | — | 75 | 25 |

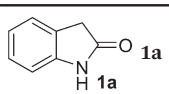
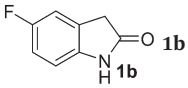
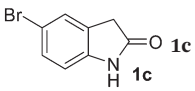
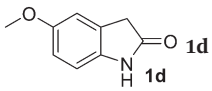
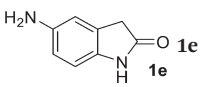
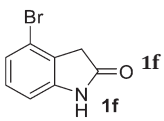
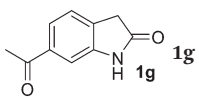
[a] Conditions: **1a** (1.8 mmol), $Ni(cod)_2$/ligand (1 : 2), 17 h in a sealed Schlenk tube. [b] Determined by GC of the crude product using anisole as an internal standard.

was not complete, thus showing rapid bisallylation shortly after the first allylation of 2-oxindole (entry 7). For further investigation, various solvents were also evaluated. The reaction yielded more than 97% of the trisallylated product in most solvents such as toluene, dioxane and THF as well as under solvent-less conditions (entries 8–11). However, DMSO as a polar aprotic solvent proved to be the convenient choice for the allylation of indoles[38] and allowed a more selective synthesis of the *C*,*C*-bisallylated 2-oxindole **4a** which was obtained with 75% yield (entry 12).

In summary, the *C*,*C*,*N*-trisallylated 2-oxindole could be easily produced in different solvents with 3 equiv. of allyl alcohol and 3 mol% Ni catalyst at 100 °C. The use of DMSO clearly improves the selectivity of the reaction toward the *C*,*C*-bisallylated derivative. At this point, we decided to study the scope of the reaction for the synthesis of more challenging compounds. Various 2-oxindoles have then been scrutinized as substrates under the optimized conditions for the synthesis of *C*,*C*-bisallylated derivatives ($Ni(cod)_2$/dppf/DMSO/100 °C) (Table 2). The *C*,*C*-bisallylated **4a–g** and *C*,*C*,*N*-trisallylated **5a–g** derivatives were separated and purified by silica gel column chromatography, thus allowing access to isolated yields for both families of compounds. 2-Oxindole **1a** was transformed into the **4a** and **5a** derivatives and the products were isolated with yields of 60% and 20% respectively (entry 1). No clear tendency corresponding to electronic effects of the oxindole 5-substitution could be highlighted. 5-Fluorooxindole **1b** led to the formation of both bis and trisallylated derivatives with respectively 67% and 29% yields (entry 2). The *C*,*C*-bisallylated product **4c** was isolated as the sole product with a yield of 70% from the reaction with 5-bromooxindole **1c** (entry 3) and the *C*,*C*-bisallylated product **4d** was also selectively obtained from 5-methoxyoxindole **1d** with a yield of 95% (entry 4). The bis and trisallylated products were respectively obtained with 63% and 32% yields from the reaction with 5-aminooxindole **1e**. It is very noteworthy that no allylation occurred on the amino group of the aniline moiety, very likely because of the lower acidity of this group in comparison to the amide group of the 2-oxindole (entry 5). The introduction of substituents at positions 4 and 6 of 2-oxindole led to very similar results. For example, only 36%

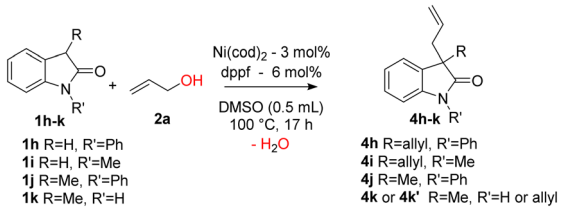
**Table 2** Substrate scope for the nickel catalyzed allylation of 2-oxindoles **1a–g** with allyl alcohol **2a**[a]

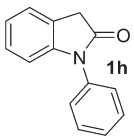
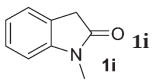
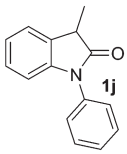
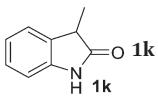



| Entry | 2-Oxindole **1a–g** | Conv.[b] (%) | Isolated yield (%) **4a–g** | **5a–g** |
|---|---|---|---|---|
| 1 |  **1a** | 100 | 60 | 20 |
| 2 |  **1b** | 100 | 67 | 29 |
| 3 |  **1c** | 82 | 70 | — |
| 4 |  **1d** | 100 | 95 | — |
| 5 |  **1e** | 100 | 63 | 32 |
| 6 |  **1f** | 95 | 36 | 30 |
| 7 |  **1g** | 100 | 73 | 17 |

[a] Reaction conditions: **1a–g** (1.8 mmol), **2a** (5.4 mmol), $Ni(cod)_2$ (0.054 mmol), dppf (0.108 mmol), DMSO (0.5 mL), 17 h, $T$ = 100 °C in a sealed Schlenk tube. [b] Conversions determined by GC using anisole as an internal standard.

**Table 3** Substrate scope for the nickel catalyzed allylation of *N*-substituted 2-oxindoles **1h–k** with allyl alcohol **2a**[a]




| Entry | 2-Oxindole **1h–k** | Conv.[b] (%) | Isolated yield (%) **4h–k** |
|---|---|---|---|
| 1 |  **1h** | 85 | 82 |
| 2 |  **1i** | 56 | 51 |
| 3 |  **1j** | 100 | 98 |
| 4 |  **1k** | 100 | **4k**: 85%<br>**4k′**: 10% |

[a] Reaction conditions: **1h–k** (1.8 mmol), **2a** (5.4 mmol), $Ni(cod)_2$ (0.054 mmol), dppf (0.108 mmol), DMSO (0.5 mL), 17 h, $T$ = 100 °C in a sealed Schlenk tube. [b] Conversions determined by GC using anisole as an internal standard.

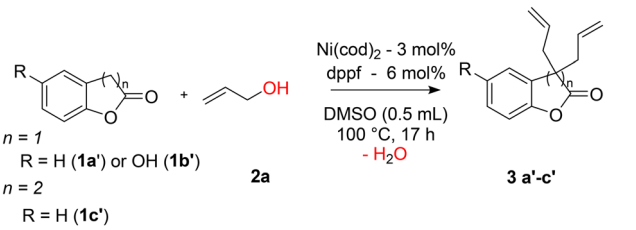
of the *C*,*C*-bisallylated product **4f** was isolated from 4-bromooxindole derivative **1f** along with 30% **5f** (entry 6). **4g** and **5g** were obtained with respectively 73% and 17% yields from 6-acyloxindole **1g** (entry 7).

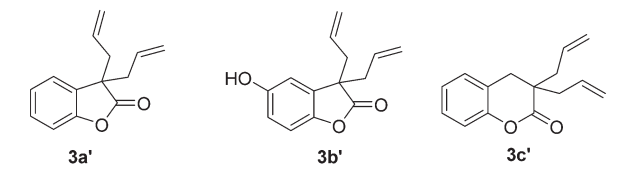
*C*- and/or *N*-substituted 2-oxindoles **1h–k** were also reacted (Table 3). *N*-Phenyl-2-oxindole **1h** was efficiently converted into the *C*,*C*-bisallylated derivative **4h** with 82% isolated yield (entry 1). However, with an electron donating group on the nitrogen, the *N*-methyl-2-oxindole **1i** was bisallylated with a moderate yield of 51% (entry 2). The 3-methyl-*N*-phenyl-2-oxindole **1j** was readily allylated and the corresponding product **4j** was isolated with a high yield of 98% (entry 3). Finally, a very good yield of 85% for derivative **4k** was obtained from 3-methyl-2-oxindole **1k** and only 10% of the *C*,*C*,*N*-trisallylated derivative **4k′** was observed (entry 4).

## Allylation reaction of 2-coumaranones

The reactivities obtained with 2-oxindoles (cyclic amides) raised the question of the reactivity of the lactone equivalent, 2-coumaranone **1a′** (Table 4). Allylation could be performed on the C3 atom leading to *C*-mono and *C*,*C*-bisallylated 2-coumaranones. It should be noted that in the presence of a nickel catalyst, the allylation reaction of a linear ester such as methyl phenylacetate with allyl alcohol always led to transesterification reaction and no allylation on the alpha carbon of the ester could be observed.[47] The stabilized cyclic structure of the lactone in 2-coumaranone avoids this transesterification reaction. Employing the same conditions as those used for 2-oxindole **1a** allylation, 2-coumaranone **1a′** was completely and selectively

**Table 4** Ni-catalyzed allylation of 2-coumaranones[a]




| | **3a′** | **3b′** | **3c′** |
|---|---|---|---|
| Yield[b] | 70 % | 80 % | 0 % |

[a] Reaction conditions: **1a′–c′** (1.8 mmol), **2a** (5.4 mmol), $Ni(cod)_2$ (0.054 mmol), dppf (0.108 mmol), DMSO (0.5 mL), 17 h, $T$ = 100 °C in a sealed Schlenk tube. [b] Isolated yield after silica gel chromatography.

transformed into the bisallylated product **3a′** which was isolated with a yield of 70%. Interestingly, no product of monoallylation was observed after 17 h. Similarly, an isolated yield of 80% for the bisallylated product **3b′** was also obtained from 5-hydroxy-2-coumaranone **1b′** with 100% conversion and a total selectivity towards **3b′**. Such as in the case of the reaction with 5-aminooxindole **1e** (entry 5, Table 2) that didn't show any allylation of the amino group, no allyl aryl ether is formed from 5-hydroxy-2-coumaranone **1b′**. One can expect that such a type of allylation of the phenol would be reversible while the *C*-allylation is more likely irreversible. Dihydrocoumarin **1c′** with a six-membered cycle was also evaluated. Various approaches have already been proposed, essentially with palladium-based catalysts.[48–52] We performed the nickel catalyzed allylation under the same operational conditions, but no product was observed. This lack of reactivity is attributed to the lower acidity of the proton on the carbon atom on the alpha position with respect to the carbonyl group. This shows the important stabilizing role of the aryl ring in the case of the 2-coumaranone.

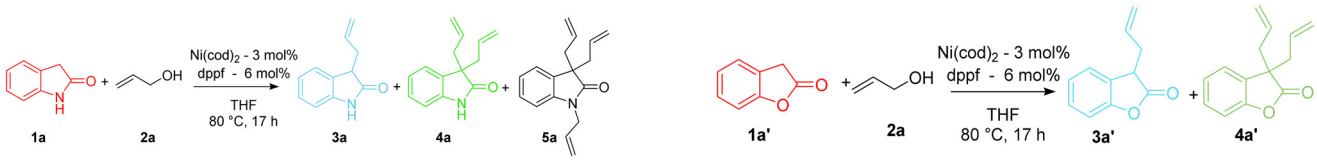
## Flow/batch synthesis: kinetic profile of the allylation reaction

**Allylation reaction of 2-oxindole and 2-coumaranone in a batch reactor.** In order to understand the evolution of the allylation reaction of 2-oxindole **1a** and 2-coumaranone **1a′**, kinetic studies were performed under batch conditions by taking samples at defined reaction times. Reactions were performed at 80 °C to achieve lower reaction rates that are more suitable for a sampling procedure. Nevertheless, at this temperature, the nickel catalyst was not fully soluble in DMSO. THF was then chosen for the kinetic studies as the nickel catalyst fully dissolved in this solvent at 80 °C and it was also suitable for the 2-oxindole **1a** allylation reaction as observed above (Table 1). Samples were analysed by gas chromatography which enables the determination of the evolution of the product distribution during the reaction course. Curves are reported in Scheme 2. In the case of 2-oxindole allylation in batch (Fig. 1), we observed the almost complete disappearance of the starting material after one hour with the formation of 85% of the *C*,*C*-bisallylated product **4a** and 10% of the *C*,*C*,*N*-trisallylated product **5a**. Afterwards, the *C*,*C*-bisallylated product **4a** was slowly converted to *C*,*C*,*N*-trisallylated **5a** up to a yield of 75% after 6 hours. **5a** was finally obtained as the sole reaction product after one night. With regard to the monoallylated product **3a**, only a few traces were observed at the beginning of the reaction, indicating that the monoallylated 2-oxindole is very reactive and more rapidly converted into a diallylated 2-oxindole. This is in accordance with the fact that the monoallylated product **3a** was hardly observed during the optimization work (Table 1). Similar trends could be observed during the 2-coumaranone **1a′** allylation (Fig. 2, Scheme 2). In this case, the substrate was completely converted into the diallylated product **4a′** after 30 minutes. Traces of the monoallylated product **3a′** appeared during the first few seconds of the reaction but were very rapidly converted to the diallylated product. Thus, under batch conditions, as the diallylcoumaranone could be produced selectively, in the case of 2-oxindoles, no selective formation of the diallyl product is possible.

**Allylation reaction of 2-oxindole and 2-coumaranone in a continuous flow reactor.** In order to optimize the selectivity of the allylation reaction, we envisaged performing experiments under continuous flow chemistry. In our case, we used a simple system based on a FEP tubing reactor connected to a back pressure regulator in order to increase the heat transfer and consequently to accelerate the allylation reaction rates. One key advantage of this approach is the ability to control the reaction time by applying a precise flow rate at the entrance of the reactor. As a consequence, after a kinetic study at various flow rates, it is possible to select the reaction time for which the selectivity toward one particular allylation product is the highest.

We first evaluated the 2-oxindole allylation under flow. After preparative experiments, we set up a reactor with FEP tubing (length = 1 meter; tubing i.d. = 800 μm; heated volume = 0.5 mL). The tube was immersed in a water bath at 80 °C. Substrates (2-oxindole and allyl alcohol) were introduced thanks to a unique syringe. A quenching module at the tube exit was not necessary since the reaction is immediately stopped in the presence of oxygen. A back pressure regulator (20 psi) should be installed because the reaction temperature was higher than the boiling point of the solvent (Scheme 3).

The experimental catalytic conditions were identical to those of the batch procedures ($Ni(cod)_2$/dppf/THF/80 °C). Thanks to the faster heat transfer, the catalytic transformation was greatly accelerated in the flow reactor with a very high chemoselectivity. Indeed, within 3 minutes, the bisallylated 2-oxindole product **4a** was obtained with




**Scheme 2** Evolution curve of allylation reaction of 2-oxindole **1a** and 2-coumaranone **1a′** with allyl alcohol **2a** in batch (solvent THF, 0.5 mL in a sealed Schlenk tube) (top) and in flow (100 μL $min^{-1}$) (bottom). Reaction conditions: **1a** or **1a′** (1.8 mmol), **2a** (5.4 mmol), $Ni(cod)_2$ (0.054 mmol), dppf (0.108 mmol), 80 °C.

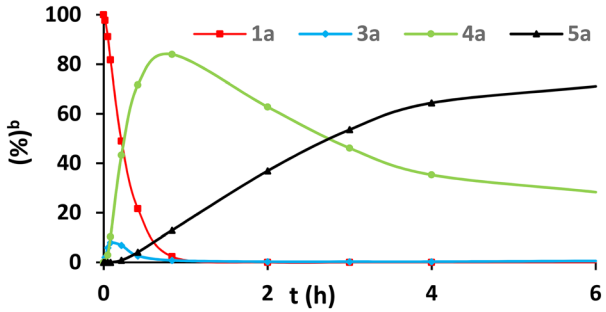



Fig. 1 Evolution curves of allylation reaction of 2-oxindole **1a** with allyl alcohol **2a** in batch mode.

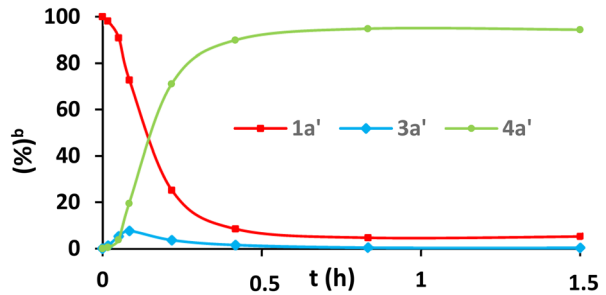



Fig. 2 Evolution curves of allylation reaction of 2-coumaranone **1a**′ with allyl alcohol **2a** in batch mode.

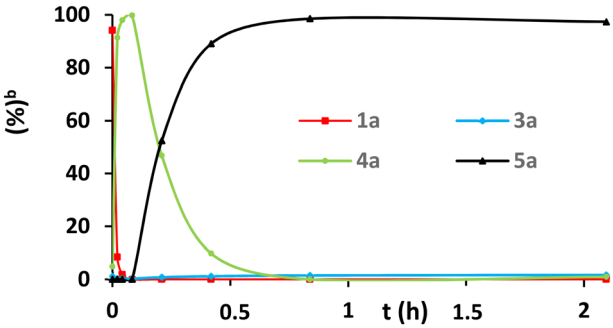



Fig. 3 Evolution curves of allylation reaction of 2-oxindole **1a** with allyl alcohol **2a** in flow.

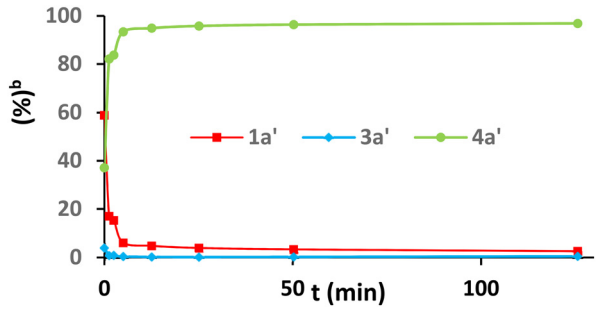
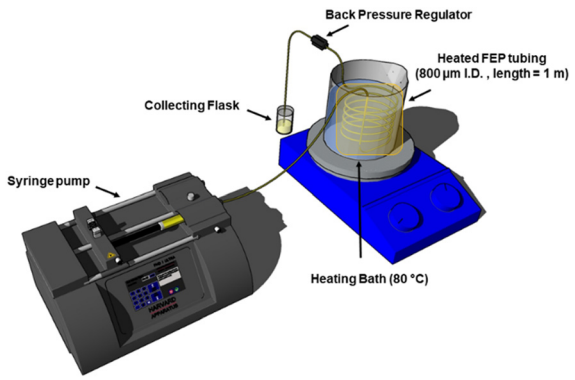



Fig. 4 Evolution curves of allylation reaction of 2-coumaranone **1a**′ with allyl alcohol **2a** in flow.

100% conversion (Fig. 3). Increasing the residence time to 25 minutes in the reactor tube by using a lower flow rate allowed converting **4a** to trisallylated product **5a** (Fig. 3). As in the batch (Fig. 1), the monoallylated product was not observed, which shows that the second allylation step is considerably much faster than the first one. This can be explained by an increased inductive effect between the two steps. In that way, by tuning the residence time of the substrates in the reactor, either *C*,*C*-bisallylated product **4a** or *C*,*C*,*N*-trisallylated 2-oxindole **5a** could be obtained selectively in a very short time.

Using the same conditions, a similar experiment was carried out with 2-coumaranone. The solution needed to be first passed into an ultrasound bath to dissolve reagents before introduction into the flow reactor and to avoid any clogging of the system. Surprisingly, at a flow rate of 100 μL $min^{-1}$, we observed that more than 80% of the *C*,*C*-bisallylated derivative **4a**′ was produced after 1 minute and 95% of 2-coumaranone had been transformed to the *C*,*C*-bisallylated 2-coumaranone **4a**′ after 5 minutes. In view of this noticeable result, we thought to perform the allylation reactions in batch at ambient temperature to compare. Indeed, only 2-coumaranone could be completely transformed into the diallylated product in 17 h while the other 2-oxindole substrates are unreactive under these conditions. This shows that these catalytic transformations are very sensitive to heat transfer conditions and the high level of control offered by flow chemistry enables greater selectivity to a chosen synthetic product just by varying the flow rate (Fig. 4).




Scheme 3 Fluidic reactor setup.

## Experimental

### General procedure for the allylation reaction under batch conditions

$Ni(cod)_2$ (15 mg, 0.054 mmol, 3 mol%) and dppf (60 mg, 0.108 mmol, 6 mol%) were weighed in a sealed Schlenk tube under nitrogen. 2-Oxindole or 2-coumaranone (1.8 mmol) and allyl alcohol (5.4 mmol, 0.313 g, 3 equiv.) in DMSO (0.5 mL) were added. The mixture was heated for 17 h at 100 °C. After reaction, the solvent was distilled under pressure

and the products were purified by silica gel column chromatography.

All experimental details and product characterization data can be found in the ESI.†

## Conclusion

In summary, we have developed an efficient and clean catalytic system for the allylation of 2-oxindoles and 2-coumaranones. The method is in great accordance with the principles of green chemistry allowing the synthesis of allylated 2-oxindoles and 2-coumaranones in the presence of nickel as a low cost catalyst and without any additive. The products are obtained with good to excellent yields in most cases under mild conditions. Chemoselectivities and reactions rates have been highly improved using flow chemistry conditions. Thus, this technology enables the continuous production of either *C*,*C*-bisallylated or *C*,*C*,*N*-trisallylated 2-oxindoles in only a few minutes. Beyond the selectivity control that can be reached thanks to the use of flow chemistry, the rising cost of energy should favor further the use of these flow processes and one can expect them to become widespread in the future. Catalytic salt free reactions with fast kinetics are particularly well adapted to this technology. In our further studies, this strategy will be developed with other substrates and catalytic reactions.

## Author contributions

Synthesis and catalysis, B. M. and A. S. P.; investigation, A. K., M. P., C. D. and M. S.; writing – original draft preparation, B. M. and I. S.; writing – review and editing, I. S. and M. S. All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

There are no conflicts to declare.

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