GDCh Research Article Angewandte International Edition Chemie www.angewandte.org

How to cite: *Angew. Chem. Int. Ed.* **2026**, *65*, e21508
doi.org/10.1002/anie.202521508

Asymmetric Hydrogenation | Hot Paper

Unlocking the Continuous Flow Asymmetric Hydrogenation of Olefins Through the Development of a Non-Deactivating Immobilized Iridium Catalyst

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Abstract: Asymmetric hydrogenation (AH) is a leading method for producing enantiopure compounds and several industrial processes rely on its chemical efficiency. However, these processes involve noble metals and even sophisticated ligands that are costlier than the metal itself. The recovery of these expensive catalysts remains an unsolved issue. Despite efforts to develop supported catalysts for continuous-flow AH, none have been used industrially, as most suffer depletion of selectivity and/or activity (from catalyst deactivation or metal leaching), and its heterogenization often lengthens the catalyst's synthetic route. Here, we report a simple synthetic approach to air stable, Ir-P,S catalysts covalently immobilized onto polystyrene resins, without increasing the number of synthetic steps. The Ir-loaded functional resin fully retains the catalytic performance of the homogeneous Ir-complex. Remarkably, they were successfully applied to the continuous-flow AH of olefins, far beyond the typical benchmark substrates. The products are continuously produced over long periods of time with high yields and selectivities, with low residence time, even at pressures far below to the corresponding batch reaction. No deactivation or leaching of Ir is observed, and a practical simple procedure for storage and reuse of the immobilized catalysts after flow hydrogenation secures their immediate availability for extended periods of time.

Introduction

Enantiopure compounds have a wide range of applications, particularly in the pharmaceutical and agrochemical fields.[1] Metal-catalyzed asymmetric hydrogenation (AH) provides cost-effective and environmentally friendly procedures for the large-scale preparation of these compounds as required by industry.[2–12] Some advantages of AH are excellent performance with low catalyst loadings and perfect atom economy. Over the last 50 years, the work from numerous academic and industrial groups has resulted in the development of many efficient catalysts with a variety of chiral ligands for substrates ranging from olefins with coordinating functional groups to non-functionalized olefins, passing through olefins with intermediate coordinating properties. However, AH achievements are critically influenced by the type of substrate.[13–23] The AH of functionalized olefins has been thoroughly studied for decades and can now be considered a mature field. With a few exceptions, Rh- and Ru-catalysts, mostly based on diphosphine ligands, have performed the best.[18,20,22,24–28] When coordinative groups are absent, the introduction of chirality represents a much challenging endeavor and, in this field, Ir-catalysts with heterodonor P,X-ligands (X = N, S, and O) have performed the best.[15,17,19,29–33] Compared to functionalized olefins, the AH of non-functionalized olefins and their congeners with poorly coordinative groups is less mature, although several successful industrial examples underscore the high potential of these specific transformations.[3–12] An aspect of the AH of non-chelating olefins with Ir-catalysts relevant to our work is that, unlike Rh/Ru-catalysts, the Ir-species are prone to deactivation via irreversible formation of di- and trimeric species[34–36] and this hampers the possibility of reaching the levels of TONs required for industrial viability. Thus, in contrast to Rh/Ru-catalysts, the high activities with turnover numbers in the thousands have scarcely been reported with Ir-P,X-type catalysts, except for a very few non-challenging substrates.[4]

Although nowadays the synthesis of several large-scale pharmaceutical, agrochemical, and high-value chemicals

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already use AH, a common characteristic is that they involve noble metals.[2–12] Noble metals are costly, their price may fluctuate considerably if the supply is limited and, given their toxicity, the tolerated threshold in fine chemicals and APIs is very low, which increases purification costs (solvents, energy, generation of waste). Despite the remarkable progress in the AH with earth-abundant metal-based catalysts, their catalytic performance is far below (except for a very few cases) that of late transition metals with, in general, harsher operation conditions and an increase of catalyst loading respect to the noble metals, and none have achieved industrial-scale implementation.[37–39] It should also be considered that the chiral ligands used in AH are usually highly sophisticated and quite often more expensive than the noble metals responsible for the catalytic event. Thus, to be industrially interesting, the ligands should be accessible in few steps from readily available enantiopure materials and be easy to handle. Following this principle, our laboratory has developed efficient Ir-catalysts for AH involving modular, bespoke ligands prepared through short sequences from cheap enantiopure precursors.[40–46]

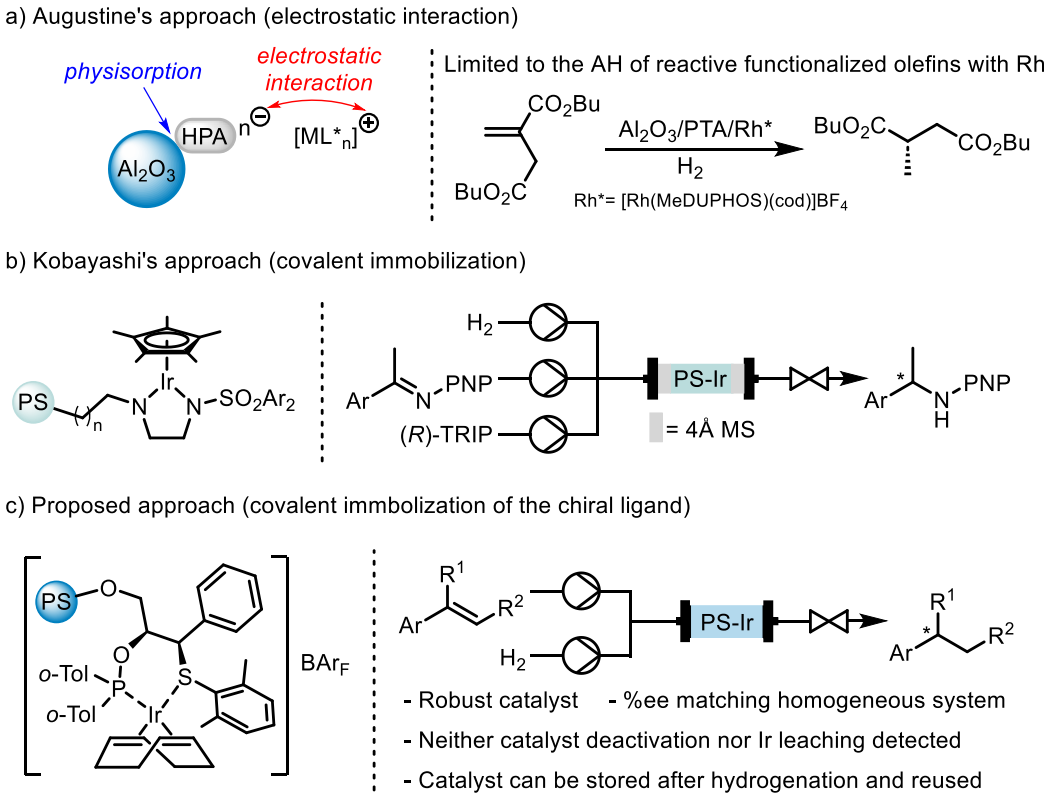
Separating, recovering, and recycling expensive catalysts remains a challenge in the industrialization of metal-catalyzed AH. A practical solution to this problem may come from the immobilization of the catalyst onto a solid support, which allows recycling and reuse of the catalytic material by simple filtration.[47–51] Despite the suitability of immobilized transition metal complexes as industrial catalysts was put into question in an assay a decade ago,[52] progress in the understanding of the advantages of immobilized catalysts[52] has consistently boosted their industrial development and application for bulk production. Beside the well-recognized advantages associated to the use of immobilized transition metal complexes in batch processing (easy catalyst recovery and reuse, avoidance of product contamination by metals), their suitability for use in continuous flow adds the inherent advantages of this technique (safety, low energy consumption, and straightforward scalability) and, not less important, the advantages derived from the solid nature of the catalyst (process intensification resulting from simultaneous reaction plus filtration).[53–60] When such catalysts are applied to flow hydrogenation reactions, other benefits can be anticipated such as nor requiring special high-pressure equipment. Additionally at the molecular level, catalytic species resulting from covalent ligand immobilization onto low-functionalization, microporous polystyrene resins (such as Merrifield or Wang types) operate under site-isolation conditions.[61–63] This fact is of particular importance in the case of Ir-based catalysts, whose deactivation in solution takes place through the formation of inactive multimeric species. Under site isolation conditions this deactivation route is closed, and this should result in a catalyst with an extended life cycle.

Asymmetric hydrogenation with immobilized metal catalysts has received considerable attention for its potential as a completely atom-economic, fully sustainable process.[47–50] However, despite remarkable progress, none of the studied immobilization strategies has fulfilled the requirement of stability under the operating conditions to allow its transfer to flow operation in industry.[48–50,53–60] Most of these immobilized catalysts developed for AH suffer from depletion of activity (from either catalyst deactivation or leaching of the metal) and/or selectivity, and/or involve complex preparations of the catalytic material that make the overall synthesis less cost-effective. Among the catalyst immobilization methods for AH, the non-covalent binding has been the most studied, being the Agustine's method[62–65] the most used (Scheme 1a).[64–72] The Agustine's approach uses a heteropolyacid (HPA) anchored on Al_2O_3 as a support which also binds to the metal catalyst through ionic interactions. The main advantage of this approach is that the ligand is not involved in the anchoring of the catalyst, maintaining its structure; therefore, the chirality is not altered, and the catalyst can be as selective and active as its homogeneous counterpart. This non-covalent interaction strategy has been applied with success in AH.[64–67] However, such immobilized catalysts have only been applied to the reduction of a narrow type of benchmark olefins, the more reactive functionalized olefins (dehydroamino acid and itaconate derivatives), with Rh-based catalysts.[64–67] In most cases metal leaching has been observed, leading to catalyst deactivation, which suggests a too weak interaction between the support and the catalyst.[64–66,73] In addition, with this strategy, it is difficult to control the distribution of the metal catalyst on the anionic surface. The control of this factor is crucial when using catalysts whose deactivation pathways involve the formation of inactive multimeric species as commented above.

Both drawbacks can be suppressed by designing a continuous flow process with a suitable covalent immobilization strategy. Although covalent immobilization was early recognized as the ideal method for obtaining robust metal-catalysts, its practical implementation in asymmetric metal catalysis has been rather slow. The reason for that lies in the fact that it often requires ligand functionalization, which implies more synthetic steps, and in most cases, the covalently immobilized catalyst exhibits decreased activity and enantioselectivity in comparison with the original homogeneous catalyst. In many cases, this is due to non-optimal strategy for the anchoring of the ligand leading to unfavorable perturbation of the transition states responsible for catalytic activity and enantioselectivity.[47–60] Consequently, the development of a simple synthetic method for a stable covalent anchoring of transition-metal catalysts suitable for continuous-flow AH, far beyond typical benchmark substrates, and without chemical modification of the chiral ligand is still highly appealing.

Kobayashi's group recently reported an elegant solution to this problem by covalently binding an achiral version of a Noyori's type Ir-catalyst onto polystyrene and introducing the chirality via de addition of an external chiral phosphoric acid (TRIP, see Scheme 1b).[74] The polymer-immobilized achiral diamine-Ir complex combined with the TRIP was successfully used in the hydrogenation of imines (with TON up to 200). The most important drawback of this approach is that a continuous feed of expensive TRIP ligand into the reactor is required to sustain enantioselectivity, which requires some extra steps in the continuous flow system for recovering of the TRIP ligand.

We envisaged that the drawbacks of Augustine's and Kobayashi's approaches could be overcome by a proper



Scheme 1. Precedent approaches and present work in the development of robust immobilized metal chiral catalysts for continuous flow asymmetric hydrogenation (PS = polystyrene; cod = 1,5-cyclooctadiene).

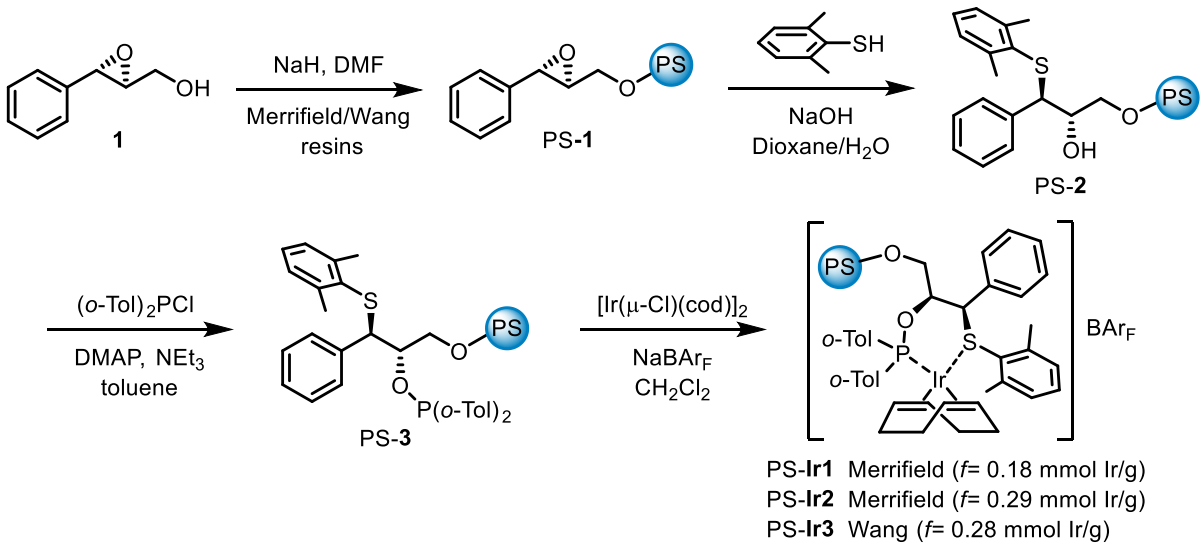
covalent immobilization strategy of the chiral ligand. This requires the following conditions to be met: a) the ligand must be designed so that the immobilization occurs far away from the catalytic center to guarantee that the polymer backbone does not perturbate the enantiodetermining TS and thus the catalyst can be as selective as its homogeneous counterpart; b) a flexible linker between the support and the ligand is needed to ensure that the catalyst behaves as in solution without interference of the support; and c) the support must have a low functionalization level to ensure isolation of the active sites, therefore preventing the formation of inactive multimeric species.

Having these requirements in mind, we present here the covalent immobilization of a family of chiral Ir-heterodonor catalysts containing arylglycidol-derived phosphinite-thioether ligands[45] (Scheme 1c). This family was selected for three main reasons. First, their homogeneous analogs outperform most Ir-catalysts reported so far as they have a broader substrate scope, covering different substitution patterns (even the challenging disubstituted ones), with different functional groups, ranging from unfunctionalized olefins, through olefins with poorly coordinative groups, to olefins with coordinative functional groups, including examples of industrial relevance. Second, their Ir-complexes are solid and air-stable, can be prepared in only four steps from readily available enantiopure arylglycidols and both enantiomeric series of the target P,S-ligands are equally available. Third, the design incorporates an innate functionalization (an ether) located far away from the metal coordination sphere, which in the homogeneous analogs showed no detrimental effect on the catalytic performance and appears as the ideal point for covalent linking to the polymeric support.[45] Quite interestingly, the synthesis of these immobilized ligands does not introduce any additional step with respect to the homogeneous analogs.

Result and Discussions

Catalysts immobilization and initial evaluation

For the immobilization, we selected as supports polystyrene (PS) resins with low cross-linking (1% divinylbenzene) and low functionalization degrees (0.6 and 1.2 mmol g^{-1}). Concretely, we used two Merrifield resins, with a different degree of functionalization, and a Wang resin with a similar functionalization (1.2 mmol g^{-1}), but with a longer spacer to study the effect of these parameters on the catalytic performance. These resins allowed us an easy covalent immobilization of the target ditopic ligand through the free hydroxyl group of the starting enantiopure arylglycidol. As already mentioned, the use for immobilization of this innate hydroxy group makes available the final catalytic resin in the same number of steps as the analogous homogeneous catalyst. Furthermore, they incorporated long enough linker/spacers assemblies to secure that the supported catalyst behaved as "in solution," thus overcoming mass transfer limitations. In addition, the low functionalization of the resulting catalytic resins allowed



Scheme 2. Preparation of the PS-**Ir1**–**3** catalyst precursors (BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate anion).

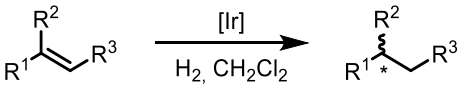
effective site isolation, with increased mechanism homogeneity with respect to the use of the original molecular Ir-catalysts in solution and blocks deactivation through the formation of oligomeric, inactive Ir species. Another advantage of these polystyrene supports is that the resulting resin swelled well in common organic solvents and could therefore be easily characterized by standard NMR techniques, while providing an homogeneous-like environment for the catalytic process.

The synthetic route used for immobilization onto the three supports is shown in Scheme 2. The synthesis starts by grafting the enantiopure phenylglycidol **1** onto the selected PS resin as an ether substituent. From this point, the synthesis of the immobilized Ir-catalyst precursors, PS-**Ir1**–**3**, follows the same synthetic route as for the unsupported Ir-catalyst precursor (regio- and stereospecific ring opening to yield PS-**2**, followed by incorporation of the phosphinite group to give PS-**3**, and finally complexation with Ir). It is worth noting that the synthetic protocol with the immobilized intermediates is more user friendly than the homogeneous one. Thus, for example, the purification of the immobilized hydroxyl-thioether compounds, PS-**2**, is performed by simple filtration and subsequent washing of the resins avoiding the use of column chromatography as required for the homogeneous counterpart. Another synthetic advantage is that the three resins with the immobilized P,S-ligand, PS-**3**, are more air and moisture stable than the homogeneous P,S-ligand. Accordingly, while the purification of the homogeneous ligand must be carried out by column chromatography under strict inert atmosphere, PS-**3** can be purified by simple filtration in air without using dry and/or degassed solvents.[75] All intermediates and catalyst precursors PS-**Ir1**–**3** were characterized by $^{13}C\{^1H\}$, $^{31}P\{^1H\}$, and $^{19}F\{^1H\}$ NMR spectroscopy as well as elemental analysis. The functionalization of immobilized intermediates and catalyst precursors PS-**Ir1**–**3** was calculated from the elemental and/or ICP analysis (see Supporting Information for details).

We initially evaluated under batch conditions the performance of immobilized catalysts precursors PS-**Ir1**–**3** in the reduction of two non-chelating olefins, the benchmark trisubstituted **S1** and the more challenging **S2**, as representative substrates (Table 1). The disubstituted **S2** is less hindered than **S1** and face-selectivity is more difficult to control, and effective enantioselective reduction has only been achieved recently with a limited number of catalysts.[76,77] For comparison, we used the same optimized reaction conditions as for the non-supported Ir-catalysts.[45] The hydrogenations were carried out at room temperature in dichloromethane under 100 bars of H_2 for **S1** and 1 bar of H_2 for the disubstituted olefins **S2**.

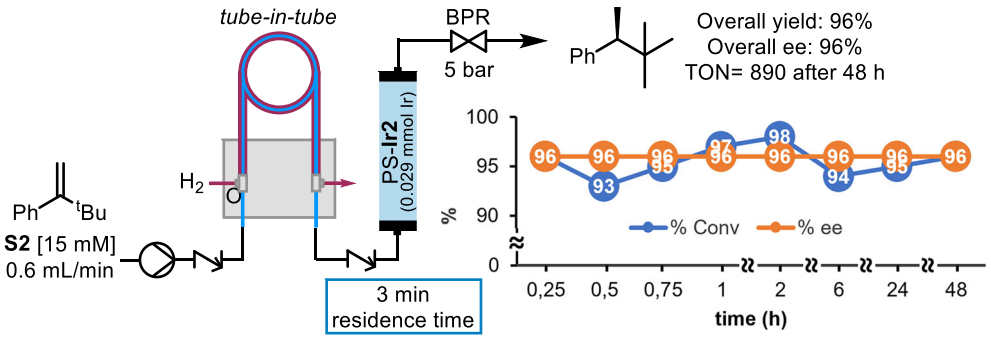
The hydrogenation of both substrates led to full conversion and was hardly affected by the degree of functionalization of the resin or the length of the spacer (Merrifield vs. Wang; entries 1–3). Positively, all the immobilized Ir-catalyst precursors had comparable enantioselectivities to the

Table 1: Asymmetric hydrogenation of two types of non-functionalized substrates, **S1** and **S2**, under batch conditions.[a]



		S1		S2	
Entry	Catalyst precursor	% Conv.	% ee	% Conv.	% ee
1	PS-**Ir1**	100	95	100	92
2	PS-**Ir2**	100	96	100	94
3	PS-**Ir3**	100	96	100	95
4	[Ir**3**(cod)]BAr_F[b]	100	96	100	96
5	PS-**Ir2** (2nd run)	100	96	99	94
6	PS-**Ir2** (3rd run)	64	96	73	93
7	PS-**Ir2** (4th run)	48	95	52	93

[a] Reaction conditions: 1 mol% Ir-catalyst precursor, olefin (0.5 mmol), CH_2Cl_2, rt for 16 h. P_{H2} = 100 bar for **S1**. P_{H2} = 1 bar for **S2**. [b] Data from Ref.[45] TON = 50.



Scheme 3. Optimized continuous flow hydrogenation of **S2** using PS-**Ir2** catalyst precursor. BPR = back-pressure regulator.

homogeneous [Ir**3**(cod)]BAr_F catalytic system (entries 1–3 vs. 4).[78] This, together with the complete conversion, reveals that the different supports facilitate active site isolation, so PS-**Ir1**–**3** behave as in solution.

We next examined the catalysts recycling, and the results indicated that the catalyst could be in fact recycled (Table 1, entries 2 and 5–7). However, the activity decayed in the third run, from either catalyst deactivation or Ir-leaching. The latter was ruled out, since no traces of iridium were observed by ICP analysis in any of the filtered solutions after each of the four-recycling cycles. This indicates a strong interaction between the catalysts and the support. Therefore, the observation of decreased activity with no affection of enantioselectivity during recycling is a clear indication of partial catalyst deactivation during intercycle manipulation. In those cases, the problem is satisfactorily solved by shifting the operation from batch mode to continuous flow, where the system remains isolated during the whole operation. As discussed below, the complete absence of catalyst deactivation was confirmed when the hydrogenation was translated to flow regime.

Continuous flow reactions

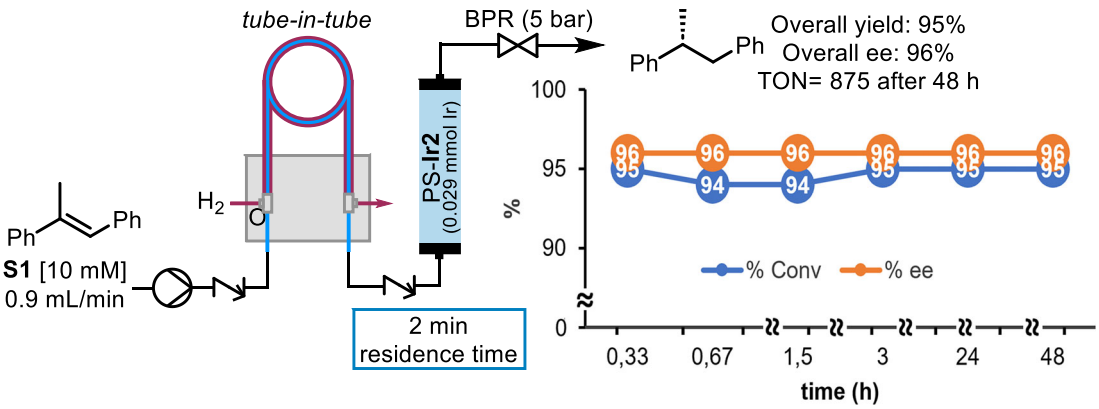
We then focused on improving the sustainability of the process by developing its continuous flow version, suitable for the preparation of large amounts of the enantiopure hydrogenated compounds.

We first developed a continuous flow system for **S2** reduction that requires much lower hydrogen pressure than **S1**. We used a tube-in-tube mixer to saturate the substrate solution with H_2 gas thus avoiding the use of a large excess of H_2 typically required in batch conditions.[79] A packed bed reactor was assembled by placing PS-**Ir2** (100 mg, 0.029 mmol) in a size-adjustable glass column. After swelling the resin with dichloromethane, a **S2** solution (0.1 M) was pumped for 15 min at 0.6 mL min^{-1}. Hydrogen (at 1 bar) was subsequently introduced into the system via the tube-in-tube mixer. However, under these conditions, a very low conversion (ca. 3%) was observed once the steady state was reached. The low conversion was attributed to the lack of sufficient solubilized hydrogen since the presence of H_2 was not detected after the back-pressure regulator (BPR).[80] So, we decided to increase the H_2 pressure to 5 bars and reduce the **S2** concentration to 15 mM (Scheme 3).[81] After optimizing the residence time, the hydrogenated product was obtained with high yields and enantioselectivity, comparable to the homogeneous system, in just 3 min residence time. Furthermore, catalytic performance remained constant over a long period of 48 h. Accordingly, no deactivation or leaching of Ir-species was observed by ICP. Under these conditions, the hydrogenated product was obtained with a high enantioselectivity of 96% ee and a good overall productivity, with TON of 890 that corresponds to ca 70 g product $mmol^{-1}$ Ir per day, which is 18 times higher than that of the reported homogeneous batch system.

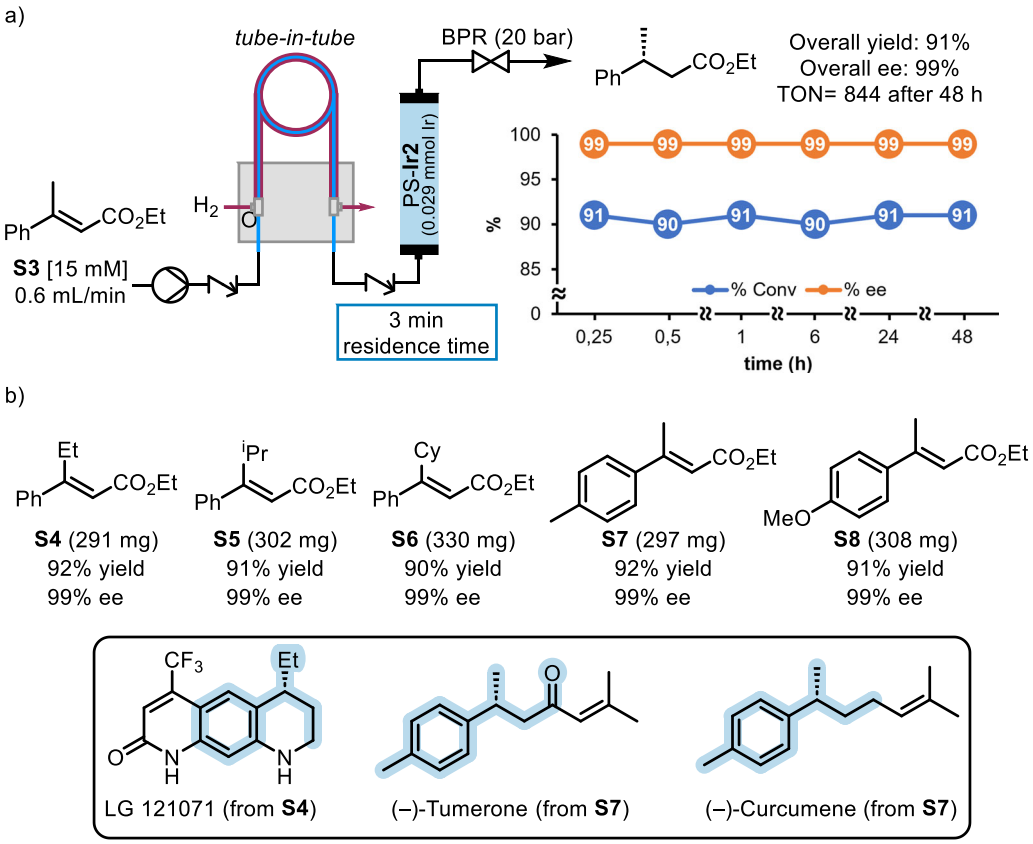
We then applied PS-**Ir2** in the reduction of trisubstituted substrate **S1** in continuous flow with the same set-up as for **S2**. After optimization, the hydrogenated product was obtained in high overall yield (95%) and enantiocontrol (96% ee) with no observable loss of activity and enantioselectivity over a 48 h run (TON = 875 that corresponds to ca 70 g product/mmol Ir * per day) using a 10 mM solution of **S1** and a residence time of 2 min (Scheme 4). Again, neither deactivation nor metal leaching was observed. Moreover, the continuous flow reaction afforded the hydrogenated product for 2 days even at pressures much lower (5 bars) than those in the corresponding batch reaction (100 bars), with the same level of enantioselectivity.

Next, taking advantage of the large substrate scope of our Ir-arylglycidol-derived P-S containing ligands and with the aim to further demonstrate the utility of our developed efficient flow catalytic AH protocol, we prepared a small library of enantioenriched esters-bearing chiral tertiary benzylic stereogenic centers. Carboxylic acid derivatives containing this particular chiral motif are present in natural products and high value compounds, such as fragrances, agrochemicals, and pharmaceuticals.[82–88] However, most methods used for their preparation produce large amounts of chemical waste.[89–94] The AH of α,β-unsaturated esters opens up an atom-efficient route to synthetize them.[95–97] The use of esters instead of the free acids is a better alternative, since they are easier to handle and can be later converted to the desired target molecule.

Initial experiments were carried out with ethyl (*E*)-3-phenylbut-2-enoate **S3** as a model. After optimization, we again observed a highly stable flow process, yielding (*R*)-ethyl 3-phenylbutanoate in excellent enantiomeric excess, 99% ee, good overall yield (91%) and with an accumulated TON of



Scheme 4. Optimized continuous flow hydrogenation of substrate **S1** using PS-**Ir2** catalyst precursor.



Scheme 5. a) Optimized continuous flow hydrogenation of substrate **S3** using PS-**Ir2** catalyst. b) Results obtained in the asymmetric hydrogenation of a set of α,β-unsaturated esters **S4**–**S8**. In parenthesis, the productivity of product formed after a 3 h run. Indicated yields and ees refer to the overall measurements after the 3 h run.

844 after 48 h (Scheme 5a). Again, neither deactivation nor metal leaching was observed, and the hydrogenated product could be produced at much lower H_2 pressures (20 bars) than those in the batch reaction (100 bars) with the same level of enantioselectivity. We then proceeded to sequentially replace **S3** by other β,β-disubstituted α,β-unsaturated esters (**S4**–**S8**) and run the hydrogenation reaction for 3 h for each of the substrates (Scheme 5b). This allowed access to ca. 300 mg of each of the esters bearing chiral tertiary benzylic stereogenic centers in excellent enantioselectivities of 99% ee (Scheme 5b). Note that some of the compounds prepared are key intermediates for the synthesis of bioactive compounds and natural products,[95] such as the orally active nonsteroidal androgen receptor modulator LG121071 (from **S4**)[98] and several bisabolene sesquiterpenes such as (–)-tumerone and (–)-curcumene among others (from **S7**).[99]

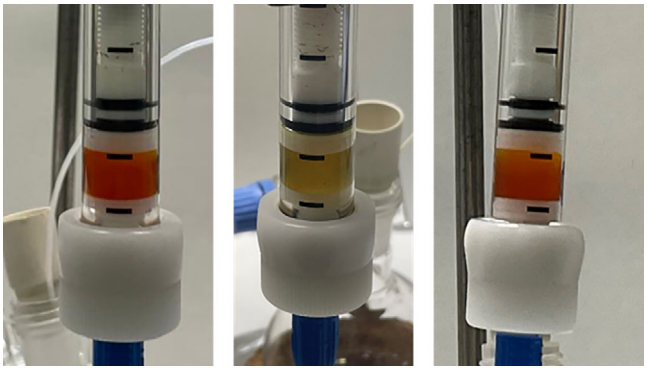


Figure 1. Color of the immobilized catalyst before(left) and during (center) hydrogenation and after stabilization with cod (right) of the PS-**Ir2**.

Evaluation of storage and reuse of the catalysts after flow hydrogenation

At this point, we found interesting to first evaluate the stability of our immobilized Ir-catalyst precursors, PS-**Ir1**–**3**. We took a sample of PS-**Ir2** that had been stored in the fridge under air during ca. 3 years and performed the hydrogenation of **S2** affording the same overall yield and enantioselectivity as with a freshly prepared one (overall yield 97% and 96% ee after 24 h run). This demonstrated the robustness of our immobilized catalyst precursors.

Finally, we studied how to stabilize the catalyst after flow hydrogenation for its storage and reuse. We were able to stabilize the catalyst by flushing trough the column packed with PS-**Ir2** a solution of 1,5-cyclooctadiene (cod) in dichloromethane (15 mM) for 15 min first under hydrogen pressure, and then without hydrogen until the color of the active immobilized catalytic species changed from light yellow to red/orange (ca. 20 min), which is the color of the starting PS-**Ir2** catalytic precursor (Figure 1). In accordance, the $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra of the recovered resin showed the signals of the starting PS-**Ir2** species. We then stored the wet column of the recovered PS-**Ir2** and reused it after 1 day and 1 week. After 1 day catalytic activity did not change and after 1 week ca. 85% of the catalytic activity remained (**S2** was therefore hydrogenated in 84% overall yield and 96% ee in a 2 h run). We later found that we could improve the stability of the catalyst by storing it in solid form. For this, after flushing the column packed with the cod solution, following the previous procedure, the immobilized red/orange catalyst precursor was cleaned with dichloromethane in air and dried under vacuum. The resulting solid was stored for 1 week. Positively, the hydrogenation of **S2** using the recovered solid PS-**Ir2** afforded catalytic performance comparable to that using a fresh batch of catalyst (93% yield and 96% ee after a 2 h run). In summary, at the end of the flow hydrogenation, and through a simple procedure, we were able to recover the catalyst precursor in the same packed-bed reactor, which can be stored and used at the user's convenience, very similar to an HPLC column.

Conclusion

We have developed a simple synthetic method for stable covalent anchoring of a successful homogeneous AH Ir-P,S catalyst family on polystyrene resins (PS), without increasing the number of synthetic steps. Noteworthy, the process does not require any ad hoc chemical modification of the chiral P,S ligand, and the Ir-loaded functional resin fully retains the performance (activity and enantioselectivity) of the referable homogeneous Ir-complex. From a practical perspective, the preparation of these immobilized catalyst precursors (PS-**Ir1**–**3**) involves only four high-yielding steps from commercially available enantiopure arylglycidols, and both enantiomeric series of the target P,S-ligands are equally available, providing access to both enantiomers of the hydrogenated products. Furthermore, these new immobilized Ir-complexes are air stable, allowing their manipulation and storage in air for years. Their application in the catalyzed AH of non-chelating olefins provided full conversions and enantioselectivities as high as the homogenous counterpart, confirming that the selected supports allow active site isolation, so the PS-**Ir1**-**3** behave as in solution. Positively, we have subsequently extended their efficient use in the continuous-flow AH of a variety of olefins, including key intermediates for the synthesis of bioactive compounds and natural products. The hydrogenated products were produced continuously over a long period of time (48 h) with overall yields and enantioselectivities (up to 99% ee) comparable to the homogeneous system, with low residence time (between 2 or 3 min), and even at pressures far below those used in the corresponding batch reaction. No deactivation or leaching of Ir was observed in the flow process confirming strong interaction between the catalyst and the support and the high robustness of the catalysts. In this respect, the hydrogenated products were obtained with a good overall productivity with TON up to 890 that corresponds to ca 70 g product $mmol^{-1}$ per day, which is about an 18-fold increase over that reported for the homogeneous batch system. Key to this success was selecting a covalent immobilization to the support to avoid leaching of the catalyst and far away from the catalytic center which, together with a support with low cross-linking, low functionalization and long enough linker/spacers, allowed to maintain a homogeneous environment, with minimal interference of the support on the activity/selectivity and at the same time preserve the formation of inactive multimeric species. In addition, a simple and practical procedure for storage and reuse of the immobilized Ir-catalysts after flow hydrogenation was also achieved. In this respect, we were able to recover the catalyst precursors in the same packed bed reactor where the reaction took place, which can then be stored in air and used at the user's convenience, very similar to an HPLC column. All these findings improve previously reported immobilized chiral metal-catalysts, opening a new perspective in the growth of stable, robust, and reusable heterogeneous chiral metal catalysts for an efficient continuous flow AH, where covalent anchoring of successful homogenous catalyst families on resins with low cross-linking and low functionalization degree could be a good choice for further developments. Moreover, the use of alternative reaction setups allowing more efficient

mass transfer, like packed bed reactors operating under segmented gas-liquid flow regime,[100] offer good opportunities for improved productivity.

Supporting Information

Experimental procedures for batch and flow asymmetric hydrogenations, synthesis of immobilized Ir catalyst precursors, characterization details and enantiomeric excess determination of products, copies of NMR spectra and GC or HPLC traces.

Acknowledgements

This work was supported by grants from the FEDER/Ministerio de Ciencia e Innovación (MICINN)/AEI (PID2022-139996NB-I00). Grant 2021SGR00163 funded by the Catalan Government is also gratefully acknowledged. J.F. also thanks the Ministerio de Ciencia, Innovación y Universidades for FPU18/06352 fellowship.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Asymmetric hydrogenation · Catalyst immobilization · Continuous flow · Iridium · P,S-ligands

[1] The global chiral chemicals market was estimated at USD 66 billion in 2024 and is projected to reach USD 171 billion by 2033. Its rapid expansion is mainly driven by the rising demand from pharmaceutical applications (approx. 72%), followed by agrochemicals (approx. 19%), where enantiomer-specific activity is critical, ending by flavors/fragrances, at 6%. In 2024, over 61,500 metric tons of chiral intermediates were consumed globally in pharmaceutical industry alone. See: Chiral Chemicals Market report, https://www.marketgrowthreports.com/market-reports/chiral-chemicals-market-105813.

[2] Metal-catalyzed AH has matured into one of the leading methods for installing stereocenters in molecules, and several industrial processes rely on its chemical efficiency. Its high commercial value justifies the continued interest of major pharmaceutical companies. Thus, very recent examples include the first large-scale application of a Crabtree/Pfaltz-type Ir catalyst, developed by Bayer (see Ref. [4]) or the launch in March 2024 of a new catalyst by BASF, which has already been implemented in 30 pilot operations worldwide (see Ref. [1]).

[3] For a recent review on the industrial applicability of AH see: M. Biosca, M. Diéguez, A. Zanotti-Gerosa, *Adv. Catal.* **2021**, *68*, 341–383. For recent specific examples not included in this review see Refs. 4–12 below.

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Manuscript received: October 01, 2025
Revised manuscript received: December 17, 2025
Manuscript accepted: December 17, 2025
Version of record online: December 23, 2025