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Catalysis

Enantioselective Continuous-Flow Production of 3-Indolylmethanamines Mediated by an Immobilized Phosphoric Acid Catalyst

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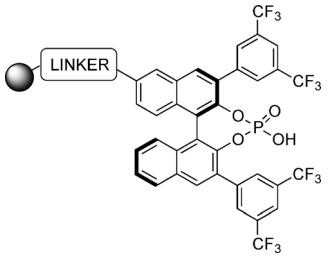
Abstract: A polystyrene-supported 1,1′-bi-2-naphthol derived phosphoric acid has been synthesized and applied in the enantioselective Friedel–Crafts reaction of indoles and sulfonylimines. The immobilized catalyst was highly active and selective, and gave rise to a broad range of 3-indolylmethanamines (19 examples) in high yields and excellent enantioselectivities (up to 98% enantiomeric excess) after short reaction times under very convenient reaction conditions (RT in dichloromethane). Moreover, repeated recycling (14 cycles) was possible with no substantial loss in catalytic performance and the system could be adapted to a continuous-flow operation (6 h). Finally, the applicability of the system was further confirmed by rapid access to a library of compounds with three points of diversity in a single continuous-flow experiment that involved sequential pumping of different substrate combinations.

Introduction

In recent years, 1,1′-bi-2-naphthol (BINOL)-derived phosphoric acids (PA) have emerged as powerful and versatile catalysts for many asymmetric transformations.[1] Such catalysts bear both a Brønsted acidic (P—OH) and a Lewis basic site (P=O) that can act cooperatively, which makes them unique candidates to promote a large variety of organic reactions. Moreover, they are air stable and can be easily stored. However, to achieve optimum enantiodifferentiation, bulky substituents are required at positions 3 and 3′,[1a,d] which infers multistep syntheses and, therefore, an increased cost of the catalysts. Consequently, we thought that it would be highly desirable to immobilize the catalyst onto a solid support (Scheme 1) to allow recovery and reuse.

Interest in the immobilization of homogeneous chiral catalysts onto different solid supports has spread in recent years due to an increase in environmental concerns in the practice of organic synthesis.[2] It is well known that these immobilized catalysts present the additional advantages of easy product isolation, recyclability, and the possibility of use under continuous-flow conditions.[3] Rueping et al. already envisioned these potential advantages by development of a PA polymeric stick that could be applied in catalytic asymmetric transfer hydrogenation.[4] Recently, the same group have reported the use of a chiral phosphoric acid in a flow system,[5] but in this case the catalyst was pumped in solution and, thus, the advantages of a supported catalyst could not be fully exploited.



Scheme 1. Schematic representation of the immobilized chiral phosphoric acid.

The enantioselective Friedel–Crafts alkylation of indoles and aldimines has proven to be one of the most important C—C bond-forming reactions in modern organic chemistry because the resultant 3-indolylmethanamine derivatives are structural motifs for many biologically active natural and natural-like products.[6] A variety of organocatalytic systems that involve chiral Brønsted acids have been successfully developed to carry out this transformation.[7–9] A highlight among them is the work developed by You et al., in which a BINOL-derived phosphoric acid efficiently catalyzed this reaction with very high enantioselectivities.[10]

Herein, we now report the easy and reproducible synthesis of a polystyrene (PS) supported BINOL-derived PA and its use as a highly enantioselective and recyclable catalyst for the Friedel–Crafts reaction of sulfonylimines and indoles.

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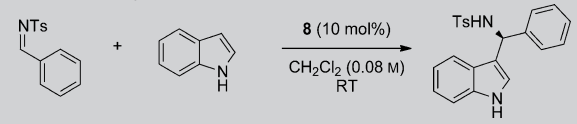
Results and Discussion

From previous experience in our laboratory, we planned to immobilize at a remote position to avoid perturbation of the active site of the catalyst.[11] (*R*)-6-Hydroxymethyl- 2,2′-bis(methoxymethyloxy)-1,1′-binaphthalene (**1**) was synthesized from commercially available (*R*)-BINOL by a reported procedure.[12] Compound **1** was converted to the 6-hydroxymethyl derivative **5** in four steps and, subsequently, this monomer was anchored onto a Merrifield resin by nucleophilic substitution of the chlorine atoms (Scheme 2). After fine-tuning the reaction conditions, a quantitative functionalization could be achieved by addition of an excess of BINOL-derivative **5**. Very conveniently, unreacted **5** could be further recovered from the solution after separation of the resin by filtration. The use of a triazole linker, introduced by click chemistry,[13] was also considered as an alternative approach for this immobilization.[14] However, this strategy was finally abandoned due to reproducibility issues, likely ascribable to triazole-catalyzed background reaction. The final heterogeneous catalyst **8** was obtained after cleavage of the methoxymethyl ether (MOM) groups and subsequent phosphoric acid formation. We reasoned that if the latter transformation was performed after the immobilization step the purification of the resulting Brønsted acid would be greatly simplified: excess reagents could simply be washed off. Indeed, one of the main problems in the preparation of phosphoric acids is product isolation, which can lead to the formation of undesired species.[15]

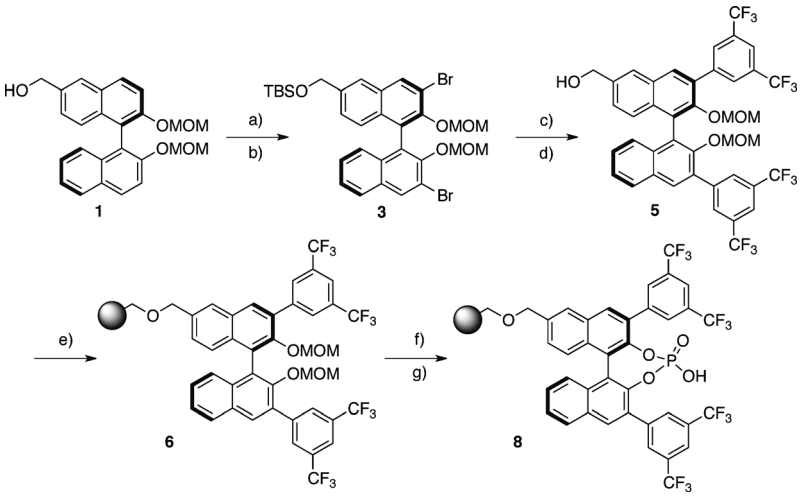
With the supported catalyst in hand, we proceeded to screen different parameters for the aza-Friedel–Crafts reaction with the tosylimine derived from benzaldehyde and indole as model substrates.

Table 1. Screening of the reaction conditions.



Entry	Cat. loading [mol%]	*t* [h]	Indole [equiv]	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1[a]	8	2.5	1.3	>99	96	85
2	8	21	1.3	91	63	97
3	16	21	1.3	97	63	97
4	10	5	2	>99	92	92
5	10	5	3	>99	95	91
6	10	6	1.5	98	77	94
7[e]	10	2.5	1.5	>99	81	93

[a] Toluene was used as the solvent. [b] Conversion was determined by ^{1}H NMR spectroscopy. [c] Yield of the isolated product. [d] Enantiomeric excess was determined by chiral HPLC analysis with a Chiralcel OD-H column. [e] $c = 0.16$ M.



Scheme 2. Synthesis of the immobilized catalyst: a) imidazole, TBSCl (quant.); b) BuLi, Br_2 (70%); c) 3,5-$(CF_3)_2C_6H_3B(OH)_2$, $[Pd_2(dba)_3]$, SPhos, K_3PO_4 (86%); d) TBAF (89%); e) Merrifield resin (0.5 mmol g^{-1}), NaH, Bu_4NI (quant. functionalization); f) HCl/EtOAc (2 M); g) $POCl_3$ and pyridine, then HCl (1 N, 70%); MOM = methoxymethyl, dba = dibenzylidene acetone, SPhos = 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl, TBAF = tetrabutylammonium fluoride.

The first parameter to be evaluated was the solvent. Although the reaction proved to be faster in toluene than in CH_2Cl_2, the enantiomeric excess (*ee*) turned out to be substantially lower (85 vs 97% *ee*; Table 1, entries 1 and 2). Therefore, CH_2Cl_2 was the preferred solvent for further screening. An increase in the equivalents of indole resulted in much shorter reaction times, as well as higher yields (Table 1, entries 4–6), whereas doubling the catalyst loading did not lead to any significant improvement (Table 1, entry 3). Finally, when the reaction was performed at higher concentration (imine: $c = 0.16$ M) only a slight excess of indole was required and good yield (81%) and excellent enantioselectivity (93% *ee*) were obtained after only 2.5 h (Table 1, entry 7). We were very pleased to see that the results obtained with the PS-supported catalyst **8** were comparable to those reported with a homogeneous phosphoric acid catalyst.[10] Remarkably, when catalyst **8** was used, good enantioselectivities were obtained at room temperature, instead of the rather inconvenient −60 °C previously described. Moreover, with our system a large amount of indole could be saved because only 1.5 equivalents were necessary, in sharp contrast with the 5 equivalents required in the homogeneous reaction.

Once the reaction conditions were optimized, one of the main aims of this work was addressed: the recyclability of the immobilized catalyst. To our delight, the catalyst not only proved to be highly recyclable (six cycles) but could also be reactivated by a simple acidic wash when a small drop in activity

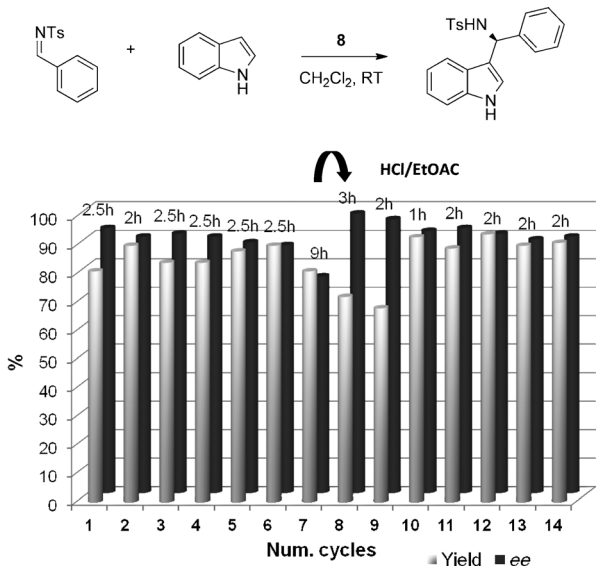
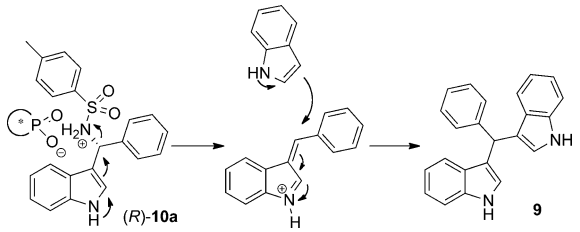


Figure 1. Recycling experiments.

was observed. Notably, the reactivated resin was even more active than the initial one, which allowed for seven more cycles without any significant loss in activity or enantioselectivity, in shorter reaction times (Figure 1). On the fourteenth cycle, the resin still showed excellent levels of activity (91% yield, 90% *ee* obtained after 2 h). We reasoned that the acidic treatment in EtOAc might have protonated traces of phosphate salt that remained after phosphoric acid formation. Thus, we decided to include HCl/EtOAc washings as the last stage of the resin preparation.

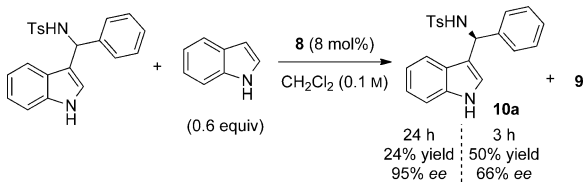
It is important to mention that the difference between conversion (100%) and yield in the experiments shown in Figure 1 is due to the formation of bis(indolyl)methane **9** as a by-product (Scheme 3), which is generally observed in acid-catalyzed



Scheme 3. Proposed mechanism for the formation of by-product **9**.

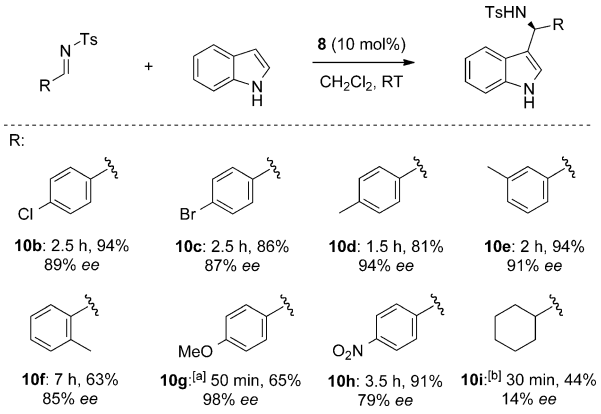
aza-Friedel–Crafts reactions.[10,16] Careful analysis of the results summarized in Figure 1 revealed an interesting trend: experiments that gave lower isolated yields provided the best enantioselectivities. This indicated that a kinetic resolution was taking place. According to our hypothesis, the destruction of the final product **10a** would be assisted by the chiral PA, with a higher decomposition rate for the minor enantiomer (*R*)-**10a** (Scheme 3).

To confirm this hypothesis, racemic 3-indolylmethanamine **10a** was treated with indole (0.6 equiv) and PS-supported phosphoric acid **8**. Interestingly, almost enantiopure **10a** was recovered after 24 h (95% *ee*, 24% yield); after 3 h, **10a** (66% *ee*, 50% yield) was obtained (Scheme 4). Indeed, similar kinetic resolutions have been previously reported with indole[9] or *N*-methylindole[16c] as the nucleophile.



Scheme 4. Kinetic resolution of **10a** with indole.

The next step was to explore the scope of the reaction. With regard to tosylimines (Scheme 5) good-to-excellent yields and enantioselectivities were observed with imines derived from both electron-poor (**10b**, **10c**, **10h**) and electron-rich (**10d**, **10e**, **10g**) benzaldehydes. *Ortho* substituents resulted in longer reaction times (**10f**). Analogously to what has been reported with related homogeneous catalysts,[8b–c,10,16j–k] PS-supported phosphoric acid **8** was limited to aromatic imines as substrates; very poor performance was observed with an aliphatic imine (**10i**).

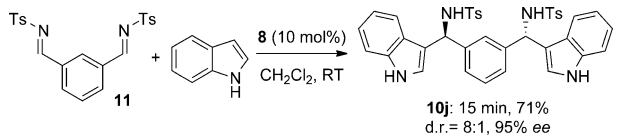


Scheme 5. Scope of the tosylimine. Reaction conditions: tosyl imine (0.07 mmol), indole (0.1 mmol), catalyst **8** (10 mol%), CH_2Cl_2 (0.45 mL), RT. [a] Indole (3 equiv) was used to minimize by-product formation. [b] Conversion = 82%.

Remarkably, when the reaction was performed with bisimine **11** the C_2 symmetric double-adduct **10j**, which offered ample opportunity for further functionalization, could be obtained with very high enantioselectivity (95% *ee*) after only 15 min (Scheme 6).

The absolute configuration of **10j** (Figure 2) was confirmed to be (*S*,*S*) by single-crystal X-ray diffraction.[17] The configuration of the rest of the molecules reported herein was assigned by analogy to this compound and in accordance with previous reports from the literature.[18]

The use of substituted indoles, as well as imines other than tosylimine was also examined. The results are summarized in



Scheme 6. Enantioselective aza-Friedel–Crafts reaction with bisimine **11**.

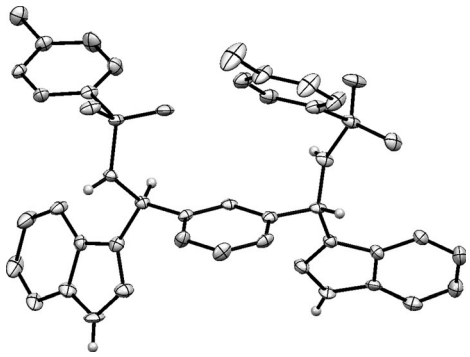


Figure 2. Single-crystal X-ray structure of (*S*,*S*)-**10j**.

Table 2. The reactions proceeded smoothly and afforded the products in high yields and enantioselectivities, regardless of the electronic properties and substitution pattern of the indole (Table 2, entries 1–4). Very good results were also achieved when benzene sulfonylimine was the substrate; remarkably, the reaction was complete after only 45 min (Table 2, entry 5). We were very pleased to observe that this system could be also applied to a range of 2-pyridyl sulfonylimines (Table 2, entries 6–9). Although longer reaction times were usually required in these cases, it is important that, to the best of our knowledge, the products obtained have not been previously reported.[19]

Once the recyclability and versatility of resin **8** were successfully evaluated and, in view of its high catalytic activity, translated into remarkable reaction times, we decided to study the implementation of a single-pass, continuous-flow Friedel–Crafts reaction of indole and the tosylimine derived from *p*-tolualdehyde. The experimental setup consisted of a Teflon tube ($^1/_4$-inch diameter) with two adjustable endpieces, loaded with PS-supported phosphoric acid **8** and connected to two syringe pumps that fed the column with the respective reagents. This system had to be equipped with a backpressure-regulator device to avoid the formation of bubbles that originated from the use of CH_2Cl_2 as solvent. Furthermore, in situ IR spectroscopy could be performed to get qualitative information on the extent of the reaction (Figure 3).[20] Thus, the absence of the band at $\tilde{\nu}=1600\ cm^{-1}$ (starting imine) was taken as an indication of full conversion.

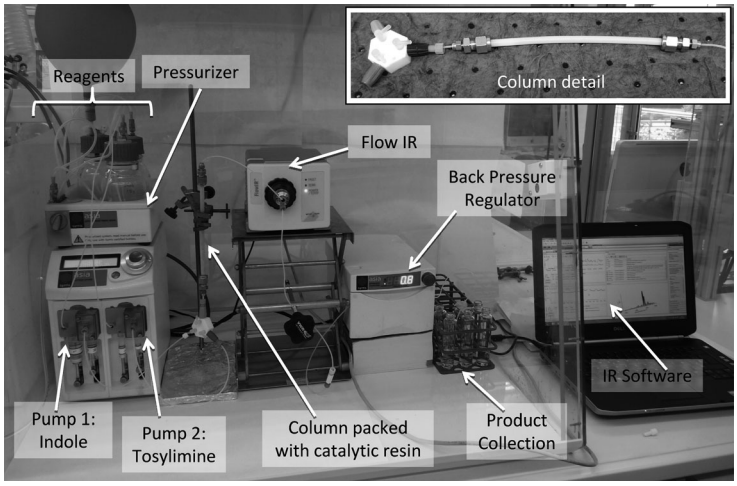
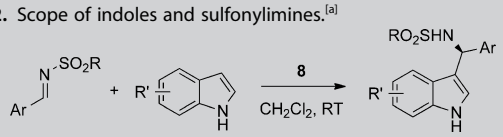


Figure 3. Continuous-flow setup. Inset: column.

Table 2. Scope of indoles and sulfonylimines.[a]



Entry	Ar	R	R′	*t* [h]	Yield [%][b]	*ee* [%][c]
1	Ph	4-tolyl	5-MeO	1.5	89	90
2	Ph	4-tolyl	5-Me	0.75	84	97
3	Ph	4-tolyl	5-Br	1.5	90	84
4	Ph	4-tolyl	6-Cl	2.5	92	90
5	Ph	Ph	H	0.75	83	94
6[d]	Ph	2-Py	H	24	90	90
7[d]	4-$NO_2C_6H_4$	2-Py	H	24	84	77
8[d]	4-$MeOC_6H_4$	2-Py	H	20	81	83
9	4-MeC_6H_4	2-Py	H	3	84	84

[a] Reaction conditions: sulfonylimine (0.07 mmol), indole (0.1 mmol), catalyst **8** (10 mol%), CH_2Cl_2 (0.45 mL), RT. [b] Yield of the isolated product. [c] Enantiomeric excess was determined by chiral HPLC analysis with a Chiralcel OD-H or Chiralpak IA column. [d] Reaction conditions: 2-pyridyl sulfonylimine (0.04 mmol), indole (0.05 mmol), catalyst **8** (8 mol%), CH_2Cl_2 (0.5 mL), RT. Py = pyridine.

To maintain the optimized conditions from the batch synthesis, solutions of imine ($c=0.32$ M) and indole ($c=0.48$ M) in CH_2Cl_2 were pumped through a column loaded with **8** (0.36 g, $f=0.25\ mmol\,g^{-1}$, 0.09 mmol) at a combined flow rate of $0.2\ mL\,min^{-1}$. The system was submitted to continuous-flow operation for 6 h and, to our delight, both conversion and enantioselectivity remained high throughout the entire process (conversion $\geq$ 97%, *ee* $\geq$ 91%; Figure 4).

In this single continuous-flow operation, highly enantioenriched compound **10d** (94% *ee*) was isolated in 80% (3.6 g) overall yield, which represents a turnover number (TON) of 102 and a productivity of $4.3\ mmol\,h^{-1}\,g_{resin}^{-1}$. In other words, the catalyst loading of the global process was as low as 0.8 mol% (with a residence time of 9.3 min), which is more than a twelvefold decrease with respect to the batch conditions.

Taking into account the inherent advantages of using continuous-flow systems (such as workup suppression and simplified scale-up) and in view of the biological importance of the resultant 3-indolylmethanamines,[5] we next explored the preparation of a small library of enantioenriched compounds. This

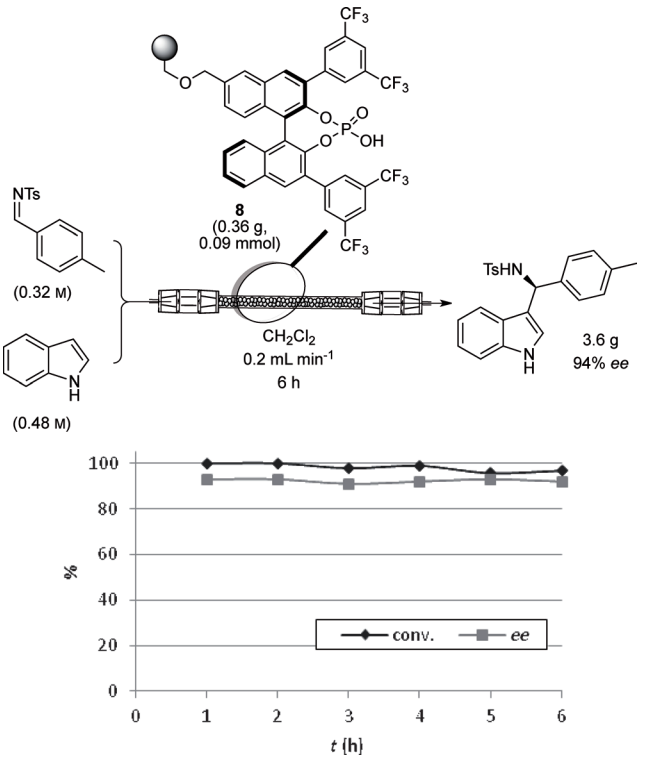


Figure 4. Continuous-flow enantioselective Friedel–Crafts reaction catalyzed by **8**.

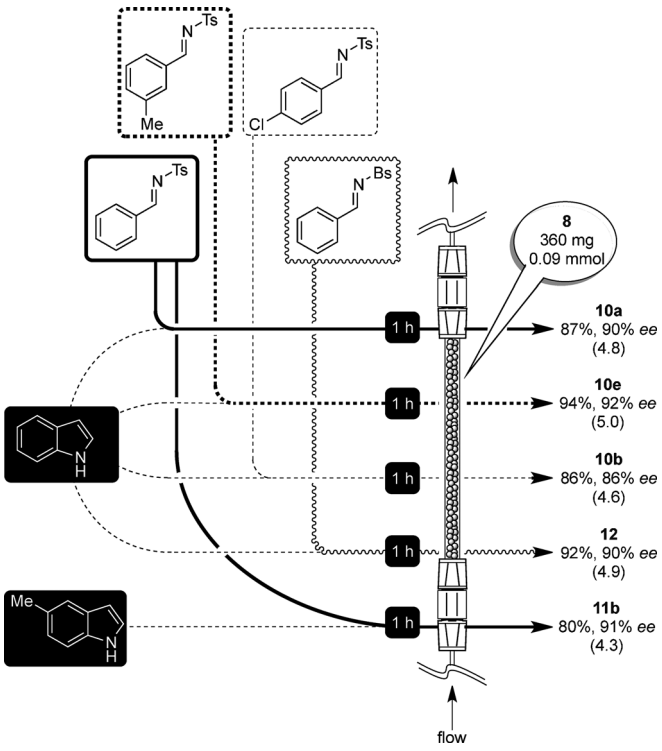


Figure 5. Enantioselective continuous-flow production of a library of 3-indolylmethanamines. Productivities [mmol h^{-1} g_{resin}^{-1}] are shown in parentheses.

is a common need in the early stages of drug discovery that could be readily satisfied by sequential synthesis in a flow device. Thus, by using the same continuous-flow setup, combinations of different sulfonylimines and indoles were passed through the packed-bed reactor in a consecutive fashion. Each of them was run for 1 h (combined flow rate = 0.2 mL min^{-1}) and the column was rinsed by circulation of CH_2Cl_2 for 30 min between each pair of reagents. The process was repeated for five different combinations of indole donor and imine acceptor, the results of which are summarized in Figure 5.

Very high productivities (4.3–5.0 mmol h^{-1} g_{resin}^{-1}) were obtained with all the substrates tested. Furthermore, an elevated degree of variability was achieved in the library of compounds because diversity could be introduced at three different levels: the indole, the aromatic ring of the imine, and the sulfonyl group. It is important to highlight the remarkable robustness shown by this specific resin: the same 360 mg batch of resin was used for all the continuous-flow processes performed, which include the 6 h operation experiment (Figure 4), the compound library synthesis (Figure 5), as well as all the preliminary experiments devoted to parameter optimization.

Conclusion

A very robust polystyrene-supported chiral phosphoric acid catalyst has been developed. Its high applicability was successfully demonstrated in the Friedel–Crafts reaction of indoles and sulfonylimines to afford the corresponding products with high yields and enantioselectivities. Furthermore, this catalyst has shown to promote kinetic resolution of a racemic 3-indolylmethanamine. A single-pass, continuous-flow process could be implemented to allow easy scale-up. In addition, the versatility of our approach has been demonstrated in the rapid and convenient production of a library of enantioselective compounds. To the best of our knowledge, this constitutes the first continuous-flow application of a supported chiral phosphoric acid. Taking into account the cost of their homogeneous counterparts, as well as the robustness of the catalytic resin introduced, we believe this method represents an interesting alternative for the scale-up of enantioselective processes mediated by BINOL-derived phosphoric acids. Efforts towards the preparation of analogous supported chiral phosphoric acids and their application to other reactions are currently underway in our laboratory.

Experimental Section

General procedure for the phosphoric acid catalyzed Friedel–Crafts reaction

N-Sulfonylimine (0.07 mmol), indole (0.1 mmol), and resin **8** (10 mol%) were placed in a vial and CH_2Cl_2 (0.44 mL, 0.16 M) was added. The reaction mixture was shaken until complete consumption of the starting imine was detected by TLC. Then, the resin was filtered and the filtrate was directly purified by column chromatography on silica gel.

Acknowledgements

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Keywords: asymmetric catalysis · chiral phosphoric acids · flow processes · Friedel–Crafts reactions · immobilization

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