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General and versatile synthesis of highly recyclable chiral phosphoric acid organocatalysts†

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The development of recyclable catalysts has gained more attention in recent years in order to minimize the environmental effect and the overall cost of catalytic processes. Some of the most broadly used chiral organocatalysts are BINOL-derived chiral phosphoric acids, making it necessary to develop efficient recycling strategies. While literature reports require up to 13 synthetic steps to access recyclable chiral phosphoric acids, here we report a general and concise 9-step approach to anthracene decorated heterogeneous chiral phosphoric acids (**PS-Anth**), which have shown high performance either in batch or continuous flow without observing catalyst degradation.

Introduction

BINOL (1,1′-Bi-2-naphthol), is one of the most commonly used chiral scaffolds in asymmetric catalysis. It is the key starting material in the synthesis of broadly used chiral ligands such as BINAP or phosphoramidites.[1] As the need for more sustainable methodologies steadily increases, the interest for developing easily recoverable and recyclable catalysts and ligands has grown in the last years.[2–5] The immobilization of simple BINOL on solid supports is rather straightfoward as the selective bromination or nitration of the 6 and 6′ positions can be achieved by treating it with bromine or nitric acid respectively,[6,7] leading to an ideal set point for further functionalization. However, immobilization of more complex 3,3′-substituted BINOL derivatives still represents a challenge, often requiring a large number of sequential steps.[8–12] These structures have high importance in the field of asymmetric catalysis (Fig. 1), as they have applications as chiral ligands in metal-catalyzed reactions[13–17] and chiral Brønsted acid organocatalysts.[18–22]

Despite the effectiveness of their methodologies, 11–13 synthetic steps are needed, making them highly challenging. One of the most exploited heterogeneous CPAs is the polymer-supported TRIP (3,3′ substituent of BINOL derived CPA: 2,4,6-$^{i}Pr_3$-C_6H_2) catalyst (**PS-TRIP**), developed by Pericàs (2016) (Fig. 2B).[23] In particular, For this reason, several authors have made efforts to immobilize chiral phosphoric acids (CPA) on solid supports (Fig. 2A).[24–29] For instance, Rueping[30] (2010), Pericàs[31] (2014), and, more recently Schneider (2024),[11] reported different approaches to access polymer or silica-supported chiral phosphoric acids.

PS-TRIP has demonstrated high robustness and applications either in batch or continuous flow processes, allowing high productivity and no visible deactivation in most cases.[32–35] Moreover, when deactivation was observed, PS-TRIP was easily reactivated by treating it with an acidic solution. However, the reported synthesis only allows immobilizing TRIP and closely related analogs, as the functionalization of 3,3′-aryl BINOLs has shown low selectivity to the 6,6′ positions for other BINOL derivatives.[36–40] On the other hand, Blechert[41] (2012) and You[12] (2022) reported different approaches to hyper cross-linked CPAs (Fig. 2B). However, their strategy only proved

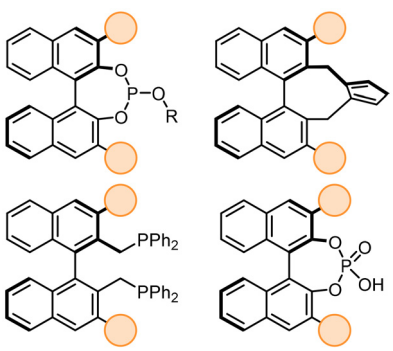

Fig. 1 3,3′-Disubstituted BINOL chiral ligands and organocatalysts.

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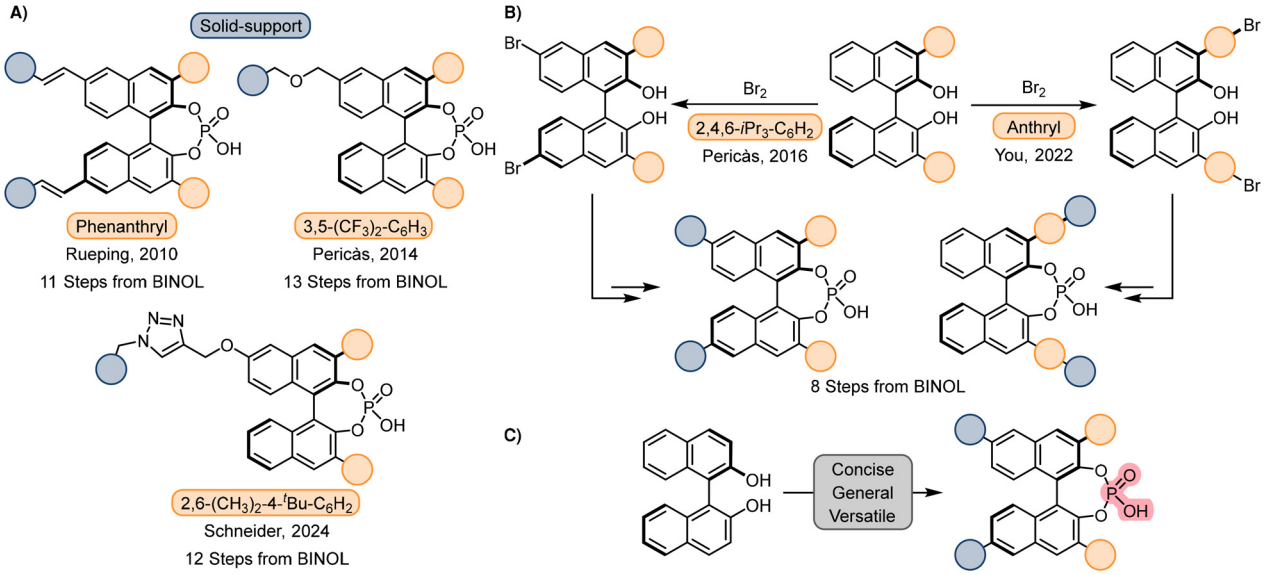


Fig. 2 (A) Highly challenging routes to heterogeneous CPAs. (B) Shorter synthetic approaches, strongly dependent on the aryl group (orange). (C) Aims of this manuscript.

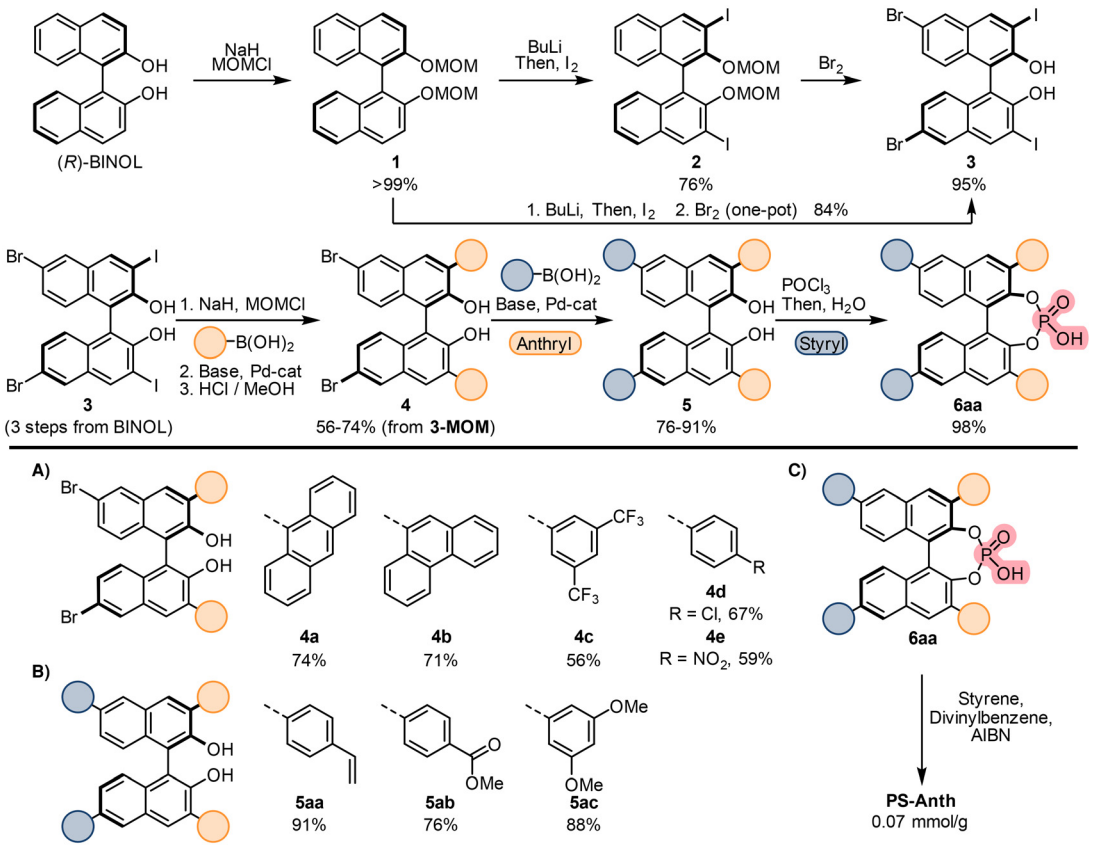
to be effective in accessing anthryl-substituted immobilized BINOL derivatives. Therefore, to further explore the applications of heterogeneous CPA derivatives as recyclable variants of their homogeneous counterparts, general and more efficient strategies to immobilize a broad range of 3,3′-aryl BINOLs are needed. Based on the previous reports from Pericàs and You (Fig. 2B), the most challenging step is the bromination, since it results in different substitution patterns depending on the 3,3′-diaryl BINOL used in the reaction. In this manuscript, we present a general and concise route to overcome this limitation. To avoid potential interferences of the support in the catalytic activity, immobilization through the 6,6′ positions of BINOL is proposed. This way, the accessibility of the catalyst site is expected to be similar to the homogeneous one, allowing straightforward transfer of known homogeneous methodologies to the use of recyclable CPAs.

Results and discussion

Our initial hypothesis consisted of using BINOL **3** as a new key intermediate to heterogeneous chiral phosphoric acids, thus avoiding unexpected functionalization during the bromination step. BINOL **3** was reported by Kobayashi in 2002 through a 6-step synthesis.[42] As one of our goals was minimizing the overall required steps to access immobilized CPAs, we explored more straightforward approaches to synthesize it. BINOL **2**, a well-known intermediate for the synthesis of 3,3′-functionalized BINOL derivatives, was used as the starting material (Scheme 1). In the presence of molecular bromine, **2** undergoes a selective 6,6′-bromination, affording **3** in almost quantitative yield. Further optimization resulted in a one-pot iodination/bromination protocol that afforded BINOL **3** in 84% overall yield from **1**, in contrast to the 72% yield obtained for the stepwise synthesis.

After protection of **3**, the initial Suzuki–Miyaura cross-coupling (SMCC) was carried out using 5 mol% of $Pd(PPh_3)_4$ as the catalyst (Scheme 1, A). To ensure high selectivity towards the iodine, only 2.5 equivalents of the boronic acid and temperatures not higher than 85 °C were used. Next, the crude reaction mixtures were stirred in MeOH in the presence of aqueous HCl to deprotect the BINOL moiety. The reaction was performed with some of the most commonly used aryl substituents in phosphoric acid-mediated enantioselective reactions such as anthryl or phenanthryl groups, as well as 3,5-bis$(CF_3)_2$ or *para*-substituted aryl groups. All of them were successful, overcoming the site-selectivity drawback of the previously reported brominations of 3,3′-substituted BINOL derivatives. Under these conditions, the desired BINOLs **4** were obtained in moderate to high yields (56–74%) over two-steps. Moreover, no 6,6′-cross-coupling product was observed in any of the performed reactions, and the main observed byproducts were identified as the protodeboronation of the boronic acid and 3-mono-coupled BINOL intermediates. Although preliminary experiments on the Kumada cross-coupling to access **PS-TRIP** intermediate[23] showed promising results, the additional step required with our synthetic route discouraged us to further explore that direction for this particular case.

To demonstrate the versatility of our methodology to synthesize highly functionalized BINOL derivatives, **4a** was used in sequential cross couplings. In contrast to the first cross-coupling, in this case, temperatures up to 110 °C and higher excess of the boronic acid was used to ensure high yields. For the 6,6′-position, boronic acids that have been previously used as binding points for immobilized chiral phosphoric acids were selected, introducing groups such as styryl (**5aa**),[23,30]



Scheme 1 Versatile synthesis to access highly substituted BINOL and CPA derivatives. (A) Scope of 3,3′-diaryl-6,6′-dibromo BINOL derivatives **4**. (B) Scope of BINOL derivatives **5**. (C) Immobilization of **6aa**.

methyl benzoate (**5ab**),[27,43,44] or 3,5-dimethoxyphenyl (**5ac**)[12] in yields ranging from 76 to 91% (Scheme 1B). Finally, phosphorylation of **5aa** afforded the chiral phosphoric acid **6aa** in almost quantitative yield, which was immobilized through radical polymerization with styrene and divinylbenzene (Scheme 1C).

The as-prepared **PS-Anth** was fully characterized using the usual techniques for polymers and solid materials. The physical properties of the resulting catalyst beads were analyzed by optical and scanning electronic microscopy (SEM) to analyze the surface (Fig. 3). We observed the formation of spherical structures of around 300 μm diameter and the surface was covered with multiple small pores and cavities. The chemical characterization of the material was performed using FTIR, providing the characteristic bands of polystyrene. The catalyst loading of the material (0.07 mmol g^{-1}) was determined based on the elemental analysis of P, which is only present on the phosphoric acid moiety.

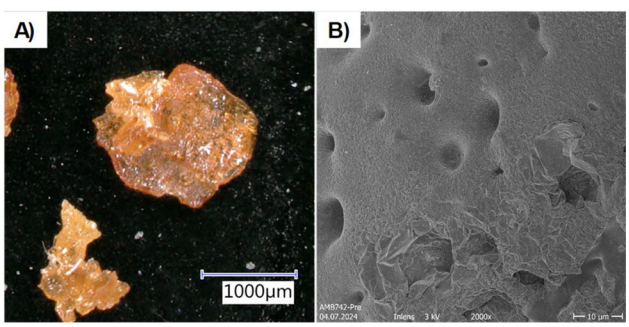
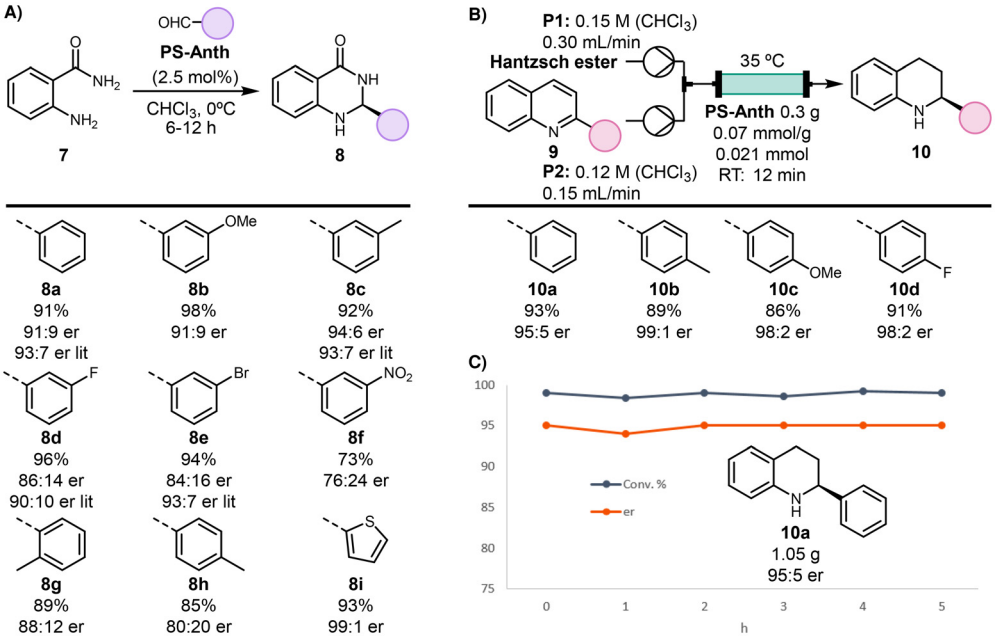


Fig. 3 (A) Optical microscopy of **PS-Anth**. (B) SEM image of **PS-Anth**.

Next, we evaluated our **PS-Anth** catalyst towards the synthesis of dihydroquinazolinones **8**, previously reported by several authors in the presence of homogeneous chiral phosphoric acids (Scheme 2A).[45–48] We compared the obtained data with Rueping's report,[46] where a 3,3′-anthryl-BINOL derived phosphoric acid was used. Notably, the only difference between their optimal catalyst and our **PS-Anth** is the immobilization through the 6,6′-positions. To our delight, when benzaldehyde was used in the reaction, a 91 : 9 er was obtained, close to the 93 : 7 reported in the literature. The scope of aromatic aldehydes bearing electron donating and electron-withdrawing groups afforded products **8** in high yield and enantiomeric ratios comparable to the homogeneous catalyst. The main limitations in terms of the enantiocontrol were found when using 3-nitrobenzaldehyde, where the selectivity dropped to around 3 : 1, and for 4-methylbenzaldehyde (4 : 1 er). Unfortunately, literature data is not available for comparison in those cases. On the other hand, sulfur-containing



Scheme 2 Application of **PS-Anth** catalyst. Isolated yields are shown; er determined by chiral HPLC. (A) Enantioselective synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones **8**. When available, literature data for the homogeneous catalyst has been included as a reference. (B) Enantioselective asymmetric transfer hydrogenation of 2-arylquinolines **9**. 1 h flow run was carried out for each compound. (C) 5 h preparative run of **10a** in continuous flow. Conversion (blue) was determined by GC-FID area %; er (orange) was determined by chiral HPLC (major enantiomer shown).

heteroaromatic aldehyde afforded almost exclusively the major enantiomer. All these experiments were carried out with the same sample of the catalyst, which was filtered and washed with $CHCl_3$ between runs. Moreover, when the scope was finalized, the reaction of 7 with benzaldehyde was repeated to ensure the catalytic activity remained unaltered, obtaining identical results to the initial experiment.

To further evaluate the recyclability of **PS-Anth**, an adjustable column was filled with 0.3 g of the catalyst, and the resulting packed bed column was used in a flow setup. The asymmetric transfer hydrogenation of Hantzsch esters and 2-arylquinolines has already been reported in flow and represents an excellent model reaction to benchmark the catalytic activity of our **PS-Anth** due to the absence of reaction byproducts (Scheme 2B).[11,34,49] After optimizing the process (ESI-Table S1†), we synthesized four 2-aryl tetrahydroquinolines in excellent yield and enantiocontrol under flow conditions. All the reaction mixtures were collected for 1 h in steady state. Then, a preparative run of **10a** was performed, analyzing the reaction outcome every hour for 5 h after steady state, showing identical results over the analyzed period (Scheme 2C). The combined collected fractions yielded 1.05 g of tetrahydroquinoline **10a** after purification, which represents a productivity of 3.35 mmol h^{-1} $g_{\textbf{PS-Anth}}^{-1}$. The turnover number (TON = 239.1) and space–time yield (STY = 71.99 kg m^{-3} h^{-3}) were calculated based on the data obtained from the 5 h preparative run, and the overall catalyst loading for the same period was 0.4 mol%. It should be noted that during all the flow experiments, the catalyst was only washed with pure $CHCl_3$ between runs, and no catalyst deactivation was observed in any case, demonstrating the high robustness of the new **PS-Anth** catalyst. To confirm the stability of **PS-Anth** beads, the used catalyst was fully characterized once again using FTIR, optical microscopy and SEM, observing no difference with respect to the as-prepared polymer-supported catalyst (ESI-Fig. S1–S4†).

Conclusions

In summary, we have developed a new synthetic approach to access highly functionalized BINOL derivatives through a sequence of two consecutive Suzuki–Miyaura cross-couplings and demonstrated their applicability for immobilizing catalysts such as chiral phosphoric acids. While most of the known methodologies to synthesize recyclable chiral phosphoric acids require 11–13 synthetic steps, our strategy allows obtaining them with a broad range of 3,3′-substituents in only 9 steps from commercially available BINOL, close to the 8-step syntheses developed by Pericàs and You, which represent the shortest routes known to date. Moreover, our methodology addresses the selectivity issues of the bromination step using a sequence of two consecutive Suzuki–Miyaura cross-couplings. This strategy represents a versatile approach to access a broad range of recyclable chiral phosphoric acids, being able to modulate not only the chirality directing group in 3,3′-positions but also the binding point that allows simple recycling of the catalyst.

In order to demonstrate the applicability of our methodology to access recyclable catalysts, we have synthesized **PS-Anth** phosphoric acid, which represents the first back-side immobilization of this particular CPA. Moreover, we have explored the potential of PS-Anth in two enantioselective reactions, demonstrating high robustness either in batch or continuous flow processes. The flow recyclability tests resulted in an overall catalyst loading of 0.4 mol% (TON = 239.1), and the comparison of the used catalyst with the as-prepared one, showed no relevant differences either in the catalytic activity or its physicochemical properties that could affect the performance of **PS-Anth** in future applications.

Procedure and characterization

All relevant experimental procedures, data and characterization details are provided in the ESI.†

Data availability

• Data for this article, including the detailed experimental procedures and characterization of organic molecules are available on the ESI.†

• The data supporting this article have been included as part of the ESI.†

• A preprint of this article has been deposited on ChemRxiv (**https://doi.org/10.26434/chemrxiv-2024-nqkmn-v2**).

Conflicts of interest

There are no conflicts to declare.

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