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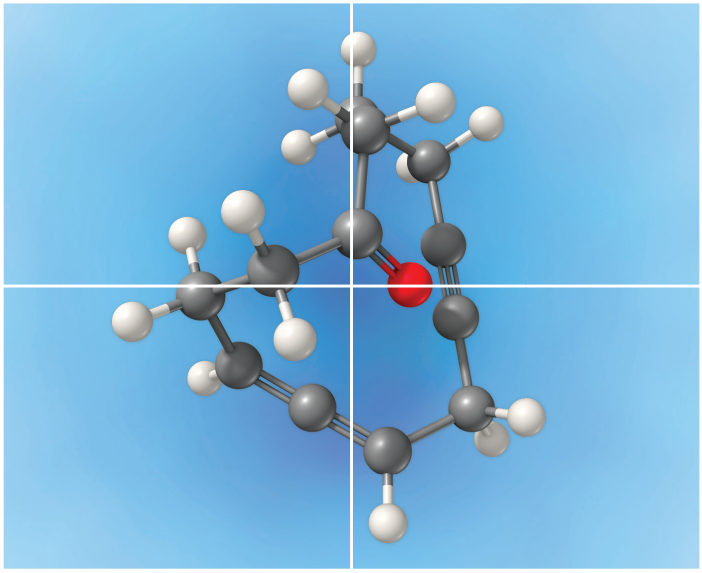

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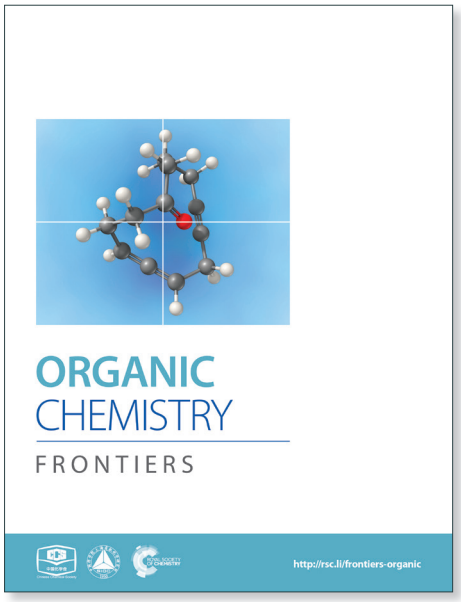

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Enantioselective Heterogeneous Brønsted Acid Catalysis

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This highlight describes the synthesis and catalytic activities of hetereogeneous chiral Brønsted acid catalysts. The hetereogeneous catalysts are stable, easily separable from the reaction mixture and can be used multiple times without loss of activities. As a remarkable particularity, the use of heterogeneous catalyst system has been exemplified for designing continuous flow reactor.

Introduction

Chiral BINOL-derived phosphonic acid catalysis is a very active area of research.[1] Various enantioselective reactions are published every week, amazing reactivities and selectivities are often observed, the number of applications in total synthesis is increasing. Clearly, success in enantioselective Brønsted acid catalysis is undisputed. However, the main drawback associated with this chemistry is that the catalysts are difficult to synthesize, highly expensive and of high molecular weights and therefore even at low catalyst loadings a lot of milligrams of catalyst needed to be used to perform small scale reactions. In addition, their recovery is difficult since those catalysts are soluble in organic solvents. Hence, it is a great challenge for synthetic organic chemists to develop heterogeneous Brønsted acid catalysts, by immobilizing catalysts on polymeric support, to perform the reactions. Such heterogeneous catalysis will be extremely useful since the starting materials can be easily converted into products and the catalyst can simply be filtered off for further use.[2] Though, the problem of the high molecular weight would still exist/intensify in this type of polymer immobilized chiral Brønsted acid organocatalysts, the fact that they can be easily recovered might compensate the drawbacks associated with their notoriously tedious synthesis. Surprisingly, until recently, there were no reports on the heterogenization of the Brønsted acid catalysts presumably due to the misconception that polymer-bound catalysts suffer from lower catalytic activity and enantioselection compared to their homogeneous counterparts.

In 2010, a research group of Rueping in collaboration with Sugiono reported the first example of immobilization of chiral Brønsted acid into polymer network.[3] The polymer-bound Brønsted acid catalyst can not only be easily recovered from the reaction mixture but it can also be easily reused in several catalytic cycles without loss of reactivity and selectivity. The heterogeneous catalysts **2** and **4** were prepared by cross-linking radical polymerization with styrene and divinylbenzene from catalyst **1** and **3**, respectively (Scheme 1). The catalytic ability of the polymer-supported catalysts **2** and **4** was subsequently evaluated in transfer hydrogenations of quinolines (**5a→6a**) and benzoxazines (**8→9**) as depicted in Scheme 2 and 3,

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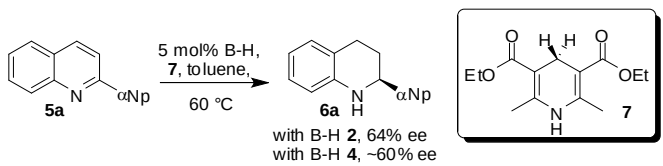
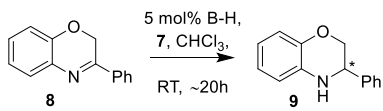
respectively. It was found that the catalytic activities and the asymmetric induction are comparable to those of the homogeneous reactions demonstrating the efficiency of this new catalyst system. Noteworthily, the catalysts **2** and **4** are in the form of polymer-stick and therefore after completion of the reaction the separation of the catalyst can be simply achieved by pulling the stick from the reaction mixture. The polymer stick was successfully recycled and reused for 12 cycles without loss of activity (Scheme 3).

In general, the bulky nature of the substituents at the 3,3' position of BINOL derived phosphoric acid is crucial for obtaining the high enantioselectivity.[1] This reason could be attributed to increase in rigidity of the catalyst structure which in turn develops a rigid chiral pocket which is necessary for enantioselective induction. The heterogeneous catalysts **2** and **4** developed by Rueping/Sugiono also bears bulky substituent at 3,3' position. In the case of catalyst **2**, the polymer is providing the steric hindrance; whereas, in the case of catalyst **4** the steric hindrance is already embedded in the monomer and the polymer chain is located far away from the active sites.

Scheme 2. Transfer hydrogenation of quinolines



Scheme 3. Multiple use of catalyst **4**



Entry	B-H	Yield [%]	*ee* [%]
1	**3**	96	96
2	**4**	97	96

Run[a]	Time [h]	Yield [%] **9**	*ee* [%]
1	16	97	96
2	21	96	94
3	20	94	94
4	20	96	94
5	19	91	94
6	19	89	94
7	29	93	94
8	24	86	94
9	24	88	94
10	20	87	94
11	24	87	94
12	24	91	94

[a] Reaction conditions: **7** (1.25 eq) and **4** (5 mol%) in $CHCl_3$ at r.t.

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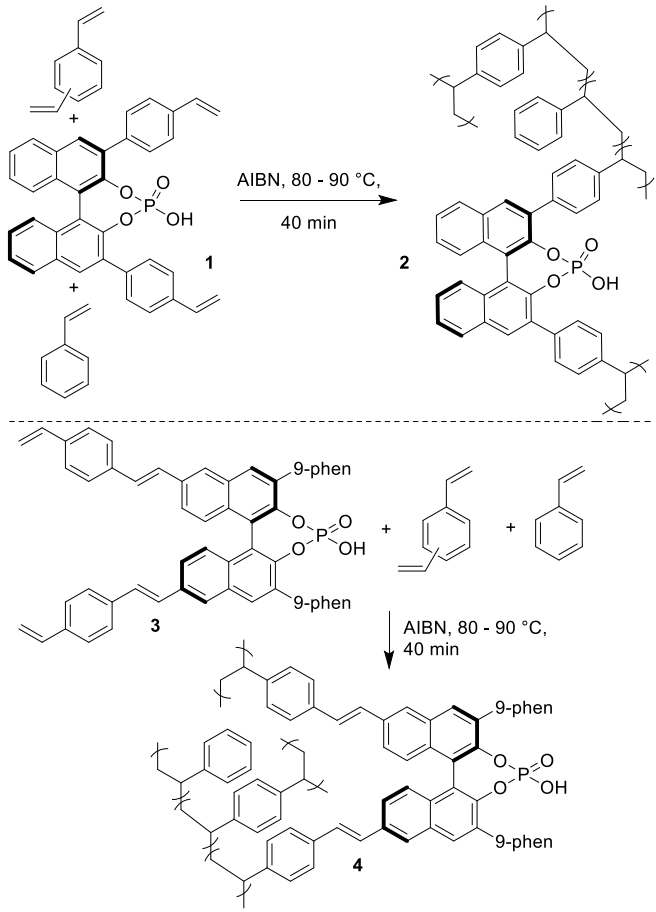
Scheme 1. Immobilization of chiral Brønsted acids



Very recently, collaborative efforts of the research group of Thomas and Blechert revealed a new chiral microporous recyclable heterogeneous catalyst made from a BINOL-derived phosphoric acid (BNPPA).[4] The first step in preparation of catalyst was the Suzuki coupling reaction between diboronic acid **10** with 3-(10-bromoanthracen-9-yl)- thiophene **11** to give **12** in good yield. Subsequent demethylation with BBr_3 followed by treatment with $POCl_3$ gave the BNPPA chloride **13** which on hydrolysis with aq. HCl afforded desired **14**. However, this monomer **14** turned out not to be suitable for oxidative coupling owing to solubility issues. Incidentally, the $FeCl_3$-mediated oxidative polymerization reaction was successful with the highly soluble **13** affording polymeric acid chloride **15**. Hydrolysis of **15** with aq. HCl and multiple washing with ethanol, THF, and $CHCl_3$ gave the desired product **16** as a powder, which was found to be insoluble in solvents such as EtOH, THF, $CHCl_3$ and CH_2Cl_2.

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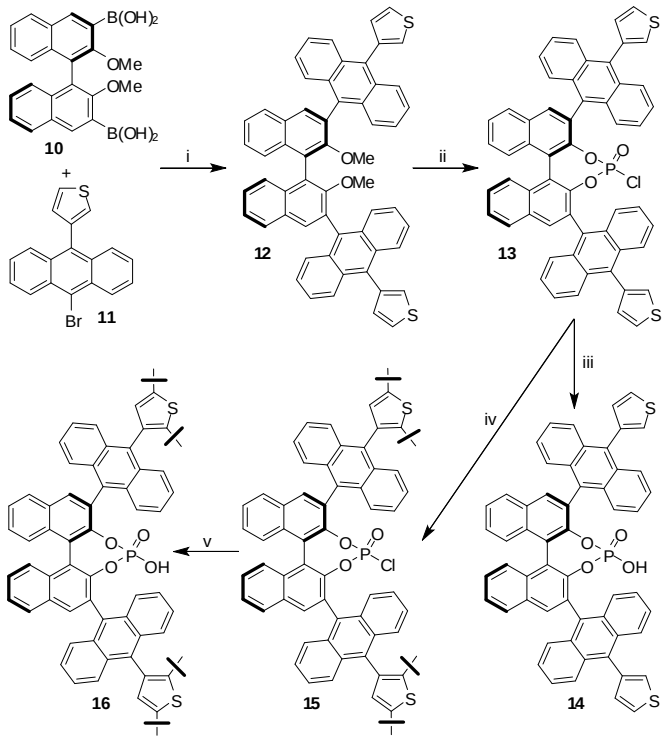
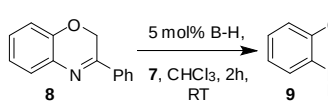
Scheme 4. Synthesis of polymeric network **16**



Reaction conditions: i) $[Pd(PPh_3)_4]$, K_2CO_3, THF/H_2O, 80 °C; ii) a) BBr_3, CH_2Cl_2, b) poly(4-vinyl pyridine), $POCl_3$, CH_2Cl_2; iii) THF, 1M HCl, RT; iv) $FeCl_3$, toluene, acetonitrile; v) aq. HCl.

The BNPPA derived heterogeneous catalyst with high permanent surface area was found to be highly active and selective in enantioselective organocatalysis. For instance, transfer hydrogenation of 3-phenyl-2H-1,4-benzoxazine has been performed with catalysts **14** and **16** (Scheme 5). The enantioselectivity was found to be 99% when **14** was used; and the use of polymeric network **16** afforded a product with an ee of 98%. The result clearly shows that nearly no loss in ee occurred when switched over to heterogeneous catalysis. The heterogeneous catalyst **16** was easily separated by centrifugation and reused for further repeating runs. For each run, 99% conversion and 98% ee were observed and even after 10 runs, the catalyst works without any loss in activity or enantioselectivity (Scheme 5).

Scheme 5. Multiple use of catalyst **16**



Entry	B-H	Yield [%]	*ee* [%]
1	**14**	99	99
2	**16**	99	98

10 runs, 99% conversion, 98% ee

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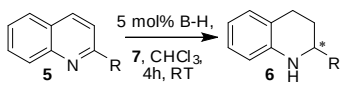
Not only benzoxazines but also quinolines were found to be hydrogenated under the established heterogeneous conditions. For instance, the asymmetric transfer hydrogenation reaction of 2-arylquinolines was carried out with polymer network **16** (**5→6**) and the results showed that the performance of the polymer network is comparable to the homogeneous reaction and gives high ee's for different aryl substituents (Scheme 6).

Scheme 6. Transfer hydrogenation of quinolines

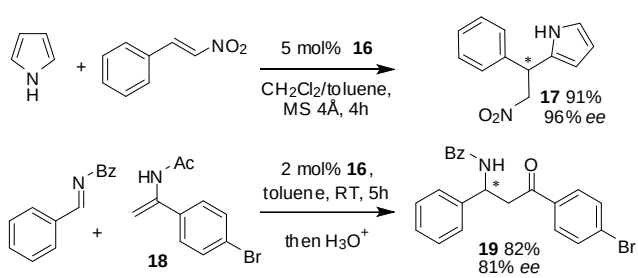


Entry	B-H	R	Yield [%]	*ee* [%]
1	**14**	Ph	99	95
2	**16**	Ph	99	99
3	**16**	α-Np	99	98
4	**16**	3-OMe-Ph	99	98

It must be noted that Rueping/Sugiono catalyst **4** which requires 20–24h time to achieve full conversion with 94% ee for asymmetric hydrogenation of **8** (Scheme 3) and the Thomas/Blechert catalyst **16** catalyzes the same reaction just in 2h with enhanced enantioselectivity (Scheme 5). The reaction rate with heterogeneous catalyst **16** was also monitored by kinetic experiments and found to be as fast as with homogeneous catalyst **14** owing to the microporous nature and high surface area (Scheme 5 and 6). The heterogeneous catalyst **16** can be easily separated by centrifugation and reused for several runs without any loss in activity or selectivity. The authors performed hot extraction experiments to check if the catalysis is truly heterogeneous in nature or not. After 50% conversion of substrate **8**, they filtered out catalyst **16**, and even after 24 h they observed no further conversion of substrate **8** to product confirming that the catalysis is truly heterogeneous.

As shown in Scheme 7, BNPPA-derived catalyst **16** can also be used for asymmetric Friedel–Crafts alkylation of unprotected pyrroles with nitroalkene. The reaction in a mixture of DCM and toluene at room temperature afforded a yield of 91% with a selectivity of 96% ee. The heterogeneous catalyst **16** is also very useful in catalyzing an aza-ene-type reaction between (N-(1-(4-bromophenyl)vinyl)acetamide) **18** and (*E*)-*N*- benzylidenebenzamide to give the corresponding adduct which on subsequent hydrolysis afforded the β-amino ketone **19** in 82% yield and 81% ee.

Scheme 7. Friedel-Craft alkylation and aza-ene-type reaction catalyzed by polymeric network **16**



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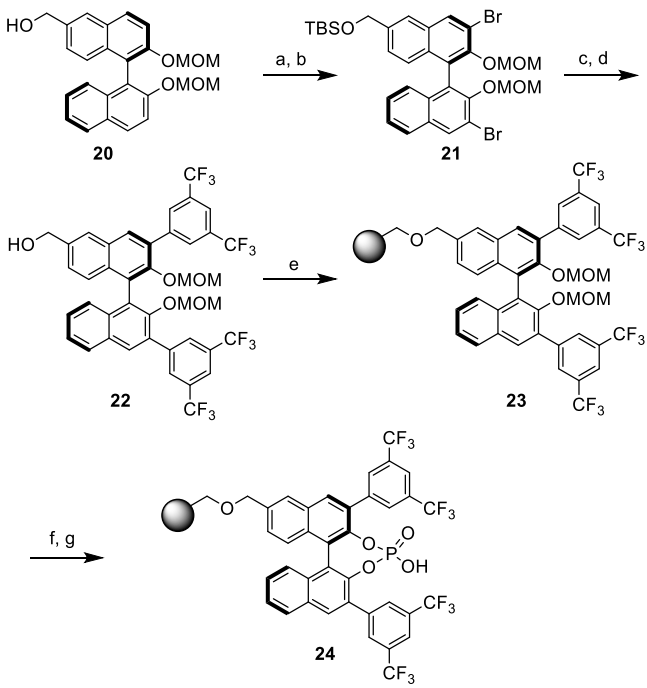
Very recently, Pericàs and coworkers designed polystyrene-supported chiral BINOL derived phosphoric acid.[5] As outlined in Scheme 8, it is evident that the immobilization was done at the remote position to avoid perturbation of the active site of the catalyst. The synthesis begun with the readily available 6-hydroxymethyl (*R*)-BINOL derivative **20**. Compound **20** was converted to the 6-hydroxymethyl derivative **22** in four steps (c.f. **21**) and, subsequently, this monomer was anchored onto a Merrifield resin by nucleophilic substitution of the chlorine atoms steps (c.f. **23**). The desired heterogeneous catalyst **24** was obtained after cleavage of the -MOM group and subsequent phosphoric acid formation followed by HCl wash.[6]

Scheme 8. Synthesis of polystyrene-supported chiral Brønsted acid



Reactions and Conditions: 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), NaH, Bu_4NI; f) HCl/EtOAc (2M); g) $POCl_3$ and pyridine, then HCl (1N, 70%).

Scheme 9. Enantioselective Friedel–Crafts reaction of indoles and sulfonylimine catalysed by PS-supported chiral Brønsted acid **24**.

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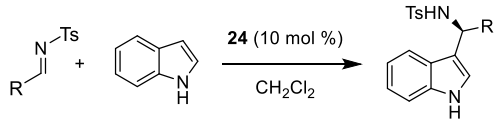

entry	R	time (h)	yield [%]	ee [%]
1	*p*-Cl C_6H_4	2.5	94	89
2	*p*-Br C_6H_4	2.5	86	87
3	*p*-Me C_6H_4	1.5	81	94
4	*m*-Me C_6H_4	2	94	91
5	*o*-Me C_6H_4	7	63	85
6	*p*-OMe C_6H_4	50	65	98

The immobilized catalyst **24** was found to be highly active for the enantioselective Friedel–Crafts reaction of indoles and sulfonylimine to afford 3-indolylmethanamines in high yields and excellent ee's (Scheme 9). It is interesting to note that the results obtained with this catalyst were comparable to those reported by You and co-workers with a homogeneous Brønsted acid catalyst.[7] The report by Pericàs and coworkers clearly demonstrates two striking observations over the superiority of heterogeneous catalysts compared to homogeneous: 1) with the PS-supported catalysts **24**, good ee's were obtained at room temperature and there is no need of cooling the reaction mixture at –68 ºC 2) the reaction works well only with 1.5 equivalents of indole and a large amount of indole is not necessary.

The catalyst proved to be recyclable up to six cycles without drop of yield and ee. However, a small drop in ee was observed in the seventh cycle. Very interestingly, the authors found that the activity of the catalyst could be regained with a simple acidic wash (HCl in EtOAc) of the catalyst. Notably, the reactivated catalyst was even more active than the initial one, which allowed for seven more cycles without any significant loss in activity or ee. This observation could be attributed to the presence of phosphate salt that remained during HCl work up in the final stage of phosphoric acid preparation.6 Thus, the authors decided to use HCl/EtOAc washings as the last stage of the preparation of **24**.

A research group of Pericàs further endeavoured to use PS-supported catalyst **24** for designing single-pass, continuous flow reactor.[8] Be noted that the use of chiral Brønsted acid in designing continuous flow micro-reactor has been shown for the first time by Rueping et al.[9] However, in this case the monomeric catalyst was pumped in solution and thus the advantages of a supported catalyst could not be fully exploited. With Pericàs's continuous flow reactor, indole reacted with imine, derived from tosylimine and *p*-tolualdehyde, was obtained in 80% yield and 94% ee.

Conclusions

This highlight describes the design, synthesis and potential applications of heterogeneous Brønsted acid catalysts. The fact that the heterogeneous catalysts are recoverable and can be easily reused several times would surely provide an impetus to area of enantioselective chiral Brønsted acid catalysis in industries or in large scale synthesis. While the immediate future research is most likely to expand the concept to a broader range of substrates with the design of new polymeric

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heterogeneous catalysts, it is author's belief that these reports would give birth to many research areas. A few ideas, though they are highly speculative, can easily be envisioned in the area of merging heterogeneous enantioselective Brønsted acid catalysis with homogeneous/heterogeneous:[10] 1) organocatalysis 2) metal catalysis, 3) enzyme catalysis. In addition, it will be interesting to see whether synergism,[11] which is fairly common in homogeneous catalysis, would take place when two catalysts (either homogeneous or heterogeneous) employed are chiral. Similarly, one may ask whether the asymmetric chiral counter anion catalysis (ACDC) strategy[12] which is very powerful in case of chiral phosphoric acid catalysis can be extended to polymeric Brønsted acids. The future efforts would more likely be centred on these areas and we believe the present highlight has set up an appropriate background.

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