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Creation through Immobilization: A New Family of High Performance Heterogeneous Bifunctional Iminophosphorane (BIMP) Superbase Organocatalysts

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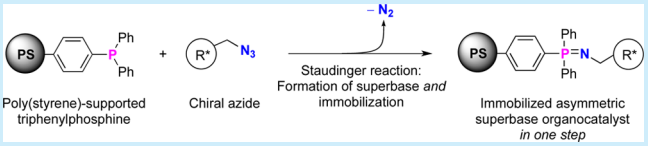
Supporting Information

ABSTRACT: An immobilized chiral bifunctional iminophosphorane superbase organocatalyst has been developed and applied in a range of challenging enantioselective reactions. A unique feature of this novel catalytic system is that the final step creation of the iminophosphorane occurs at the point of immobilization. The utility of the immobilized catalyst system was demonstrated in the nitro-Mannich reaction of ketimines as well as the conjugate addition of high pK_a 1,3-dicarbonyl pronucleophiles to nitrostyrene. Catalyst recycling was also demonstrated.



Heterogeneous catalytic processes employing catalytically competent species attached to insoluble supports can bring distinct advantages over homogeneous catalysis such as facilitating simple separation of the catalyst from the product and reaction mixture, catalyst recycling, and, in certain cases, applications in flow chemistry. In pursuit of these benefits, many organocatalysts such as proline-based nucleophilic catalysts,[1] MacMillan-type imidazolidinones,[2] chiral phosphoric acids,[3] cinchona alkaloids,[4−6] and bifunctional organocatalysts such as Takemoto's catalyst,[7] Jacobsen's thioureas,[8] or squaramides[9−11] have been immobilized on a diverse range of solid supports. However, catalyst immobilization often has severe detrimental effects on inherently modest catalyst reactivity and stereoselectivity and often necessitates the incorporation of a linker into the catalyst structure through additional synthetic steps.[12] Arguably, an ideal immobilized organocatalyst should retain high reactivity and stereoselectivity without the need for additional synthetic steps to attach it to the solid support.

The use of organic superbases, instead of tertiary amine bases, offers one potential solution to the problem of low catalyst reactivity in bifunctional Brønsted base/H-bond donor organocatalysis.[13,14] Accordingly, the immobilization of a chiral superbase-derived bifunctional organocatalyst would be anticipated to result in a solid-supported organocatalyst that possesses superior activity. However, to the best of our knowledge, in this class only one chiral guanidine organocatalyst has been immobilized to date,[15,16] and its performance in any type of challenging enantioselective transformations has yet to be proven.

Our research group has recently introduced a novel class of bifunctional iminophosphorane (BIMP) organocatalysts.[13,17] These catalysts are synthesized via a Staudinger reaction between a triarylphosphine and a chiral azide bearing the H-bond donor motif, forming the active iminophosphorane moiety in the final step. As solid-supported triphenylphosphine is a widely available commercial material, we saw the opportunity to utilize it as a replacement for the soluble triarylphosphine component. Thus, we envisaged the synthesis of a novel heterogeneous bifunctional organocatalytic system through a practically convenient formation of the iminophosphorane superbase *at the point of immobilization* (Figure 1). Although the tether-free formation of an organocatalyst immobilised via the H-bond donor in a 2-step process has been recently reported,[9] this would constitute an unprecedented one-step formation of a solid-supported organocatalyst immobilised via the formation of the Brønsted base. We believed this combined method of catalyst creation/immobilization would greatly assist catalyst synthesis, handling, library generation and heterogeneous enantioselective bifunctional organocatalysis applications in general.

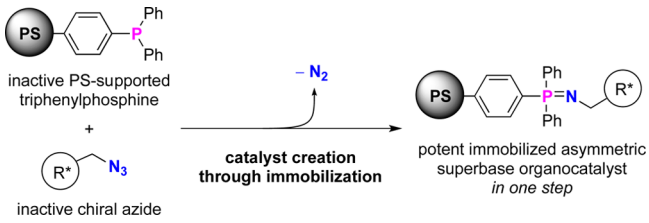


Figure 1. Simultaneous catalyst formation and immobilization concept (PS = polystyrene; R* = chiral scaffold).

The enantioselective nitro-Mannich reaction of diphenylphosphinoyl-protected ketimines, already known to be successful under bifunctional iminophosphorane catalysis,[13] was chosen to demonstrate proof of concept in the formation of the immobilized bifunctional catalyst from azides **2** and **3**, derived from phenylglycine and *tert*-leucine, respectively (Scheme 1).

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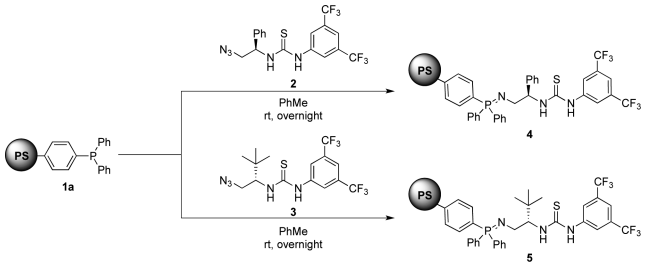
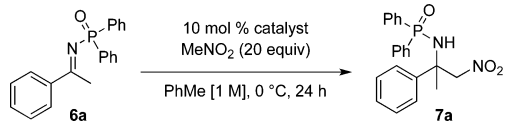
Scheme 1. Formation of Immobilized Bifunctional Iminophosphorane Organocatalysts from Azide Precursors



Conversion to product and high enantiomeric ratio were taken as evidence of catalyst formation. In initial experiments, we compared commercial polystyrene-supported triphenylphosphine (PS−PPh_3) with PS−PPh_3 prepared from poly(4-bromostyrene) using the method of Spring and co-workers.[18] This procedure was appealing as it opened the possibility of preparing a variety of differently substituted polystyrene-supported phosphines. In-house prepared PS−PPh_3 generated catalysts gave higher conversion in the nitro-Mannich reaction when compared to commercial material (Table 1) and accordingly was selected for the remainder of this study.

Table 1. Formation of Immobilized Bifunctional Iminophosphoranes and Use in the Nitro-Mannich Reaction of Ketimine 6a[a]



PS−PPh_3 source	catalyst	conversion[b] (%)	er[c]
commercial	**4**	54	6:94
in-house	**4**	65	5:95
in-house	**5**	88	98:2

[a]Catalyst was formed in situ by reaction of PS−PPh_3 and azide **2** or **3**. Compound **6a** and nitromethane were then added to the reaction mixture. [b]Determined by ^{1}H NMR analysis of crude reaction mixture. [c]Enantiomeric ratio (er, *R*:*S*) was determined by HPLC analysis on a chiral stationary phase.

Gram-scale catalyst preparation was readily carried out and spectroscopic evidence for the formation of the polystyrene-supported catalyst in the form of gel-phase ^{31}P NMR spectra of PS−PPh_3 **1a** and of *tert*-leucine-derived catalyst **5** was obtained (Figure 2). These spectra distinctly show the disappearance of the PPh_3 peak at −5.0 ppm and the formation of a new, broad peak at 23.8 ppm corresponding to the iminophosphorane (cf. 21.9 ppm for the corresponding homogeneous catalyst). A minor peak at 30.0−31.0 ppm, which corresponds to a trace of polymer-bound triphenylphosphine oxide, is visible in both spectra.

With sufficient quantities of immobilized catalysts in hand we undertook to demonstrate their performance in a range of challenging organocatalyzed reactions.

The immobilized bifunctional iminophosphorane organocatalysts had been demonstrated to be effective in the nitro-Mannich reaction (Table 1); therefore, we chose to further investigate the scope of this reaction (Table 2). Optimal reaction conditions employed 10 mol % of catalyst **5** and 20 equiv of nitromethane at 0 °C in toluene. Catalysts incorporating differently substituted polystyrene-supported phosphines were

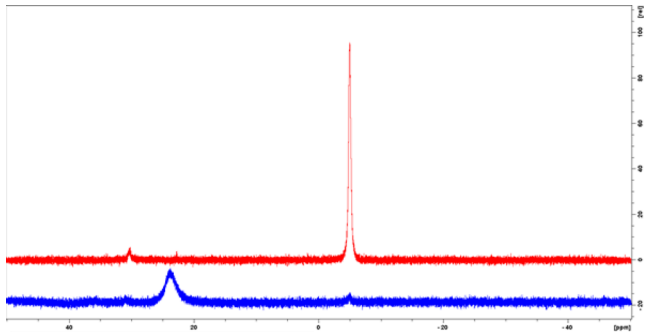
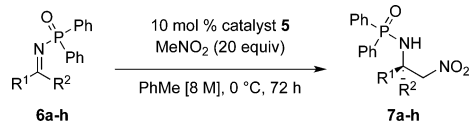


Figure 2. Gel-phase ^{31}P NMR ($CDCl_3$) of polystyrene-supported triphenylphosphine **1a** (red, top) and polystyrene-supported catalyst **5** (blue, bottom).

Table 2. Nitro-Mannich Reaction of Diphenylphosphinoyl-Protected Ketimines[a]



7	R^1	R^2	conv[b] (%)	yield (%)	er[c]
7a[d]	phenyl	Me	99	73	98:2
7b	4-methylphenyl	Me	94	82	97:3
7c	4-methoxyphenyl	Me	88	75	96:4
7d	2-methoxyphenyl	Me	98	96	97:3
7e	4-chlorophenyl	Me	99	88	97:3
7f	3,4-dichlorophenyl	Me	99	87	95:5
7g	phenyl	Et	95	71	97:3
7h	3-pyridyl	Me	99	95	93:7

[a]Absolute stereochemistry determined by comparison with literature compounds (see Supporting Information).[13] [b]Conversion determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase. [d]The reaction time for **7a** was 24 h.

also prepared;[18] however, PS−PPh_3 gave the best compromise between results and ease of preparation (see Supporting Information). The yields and enantiomeric ratios of the nitro-Mannich products were comparable to those obtained previously with the homogeneous bifunctional iminophosphorane under similar conditions.[13] A variety of diphenylphosphinoyl-protected ketimines were subjected to the nitro-Mannich reaction using the immobilized catalyst−electron withdrawing (**7e**−**f**) as well as electron donating (**7b**−**d**) substituents were all well-tolerated, as were heterocyclic substrates (**7h**) and extension of the methyl substituent of the ketimine to an ethyl group (**7g**). Performing the reaction under identical conditions with the corresponding homogeneous catalyst and ketimine **6a**, we obtained the product in 92% conversion and 97:3 er in 14 h (see Supporting Information).

Substituted malonates are an example of a synthetically useful class of high pK_a pro-nucleophile. Isolated examples of the organocatalyzed addition of substituted malonates to nitrostyrenes have been reported,[19−22] most notably using highly basic chiral guanidine catalysts.[23] However, the scope of this reaction has not been systematically explored, therefore justifying the need for further in-depth studies. After optimization studies we observed that by using 5 mol % of catalyst **5** at −20 °C in THF we were able to perform the conjugate addition of a variety of substituted malonates to nitrostyrene in very good to excellent

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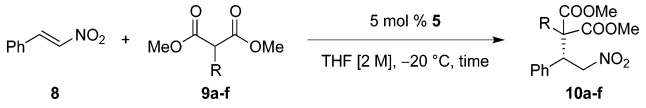
yields and enantiomeric ratios (Table 3). Malonates with an unbranched alkyl substituent gave the best reactivity and

Table 3. Conjugate Addition of Substituted Malonates to Nitrostyrene[a]



8 9a-f 10a-f

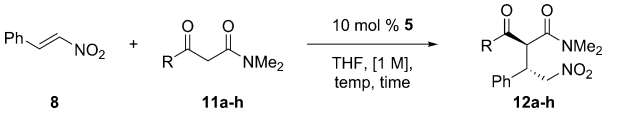
10	R	time	yield (%)	er[b]
10a	Me	16 h	93	98:2
10b	Et	16 h	92	97:3
10c	allyl	16 h	98	96:4
10d	propyl chloride	48 h	80	98:2
10e	isobutyl	4 d	63	94:6
10f	Bn	4 d	76	94:6

[a]Absolute stereochemistry determined by comparison with literature compounds[23] and by analogy (see Supporting Information). [b]Enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase.

enantioselectivity (**10a−c**). Branching at the γ position of the alkyl substituent is well-tolerated but led to a small reduction in yield and enantiomeric ratio (**10e,f**).[24] Performing the reaction under identical conditions with the corresponding homogeneous catalyst and malonate **9a**, we obtained the product in 93% yield in 4 h and 97:3 er (see Supporting Information).

In a similar fashion to substituted malonates, β-keto amides are a challenging class of high pK_a pro-nucleophile. To the best of our knowledge, only a single report exists on the use of acyclic β-keto amides in organocatalyzed conjugate additions.[25] By using 10 mol % of immobilized catalyst **5** in THF at −20 °C we were able to add a number of *N,N*-dimethyl β-keto amides, bearing a range of substituents at the ketone, to nitrostyrene in very good yields and diastereo- and enantiomeric ratios (Table 4). Substrates with primary or secondary alkyl substituents (**12a,b**) gave the highest diastereo- and enantiomeric ratios. The use of heteroatom-containing (**12f**) and aryl-substituted (**12g**) ketones resulted in reduced dr but very good er. The *tert*-butyl-substituted substrate (**12h**) required additional reaction time and also gave a reduced dr but very good er. Performing the reaction under identical conditions with the corresponding homogeneous catalyst and keto-amide **11a**, we obtained the product **12a** in 77% yield, 38:62 dr and 94:6 er (major diastereomer) in 2 h at −20 °C followed by 24 h at 0 °C (see Supporting Information).

Table 4. Conjugate Addition of β-Keto Amides to Nitrostyrene[a]



8 11a-h 12a-h

12	R	temp (°C)	time (h)	dr[b]	yield (%)	er[c]
12a	Me	−20 then 0	4 then 20	20:80	74	96:4
12b	Bu	−20	24	90:10	67	93:7
12c	Bn	−20	24	94:6	58	96:4
12d	*i*Pr	−20	24	96:4	71	96:4
12e	cyclohexyl	−20	24	95:5	82	93:7
12f	CH_2OMe	−20	24	74:26	64	94:6
12g	Ph	−20	24	65:35	54	96:4
12h	*t*Bu	−20	48	75:25	70	95:5

[a]Absolute stereochemistry determined by comparison with literature compounds[25] and by analogy (see Supporting Information). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Enantiomeric ratio (er) of major diastereomer was determined by HPLC analysis on a chiral stationary phase.

Having successfully applied our immobilized bifunctional iminophosphorane to a range of enantioselective reactions, we next demonstrated its recyclability. The nitro-Mannich reaction of ketimine **6a** with nitromethane was repeated using the same catalyst (recovered by washing off the reaction product) over 11 runs. The conversion (as measured by ^{1}H NMR analysis) remained greater than 95% until the 11th run (Figure 3). The er

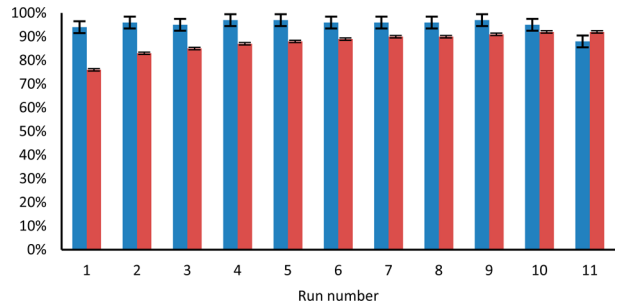


Figure 3. Recycling of catalyst **5** in the nitro-Mannich reaction of ketimine **6a**. Reaction performed with 10 mol % catalyst and 20 equiv of $MeNO_2$ [8 M] in PhMe at room temperature (cf. 0 °C in Table 2), 24 h reaction time. Blue columns represent conversion as measured by ^{1}H NMR; red columns represent ee. Error bars indicate typical error range for the above measurements.

was observed to rise slightly over the course of the recycling experiment, which we propose is due to decreased reversibility of the nitro-Mannich reaction as the catalyst activity decreased (see Supporting Information).

In conclusion, we have described the development and application of a high-performance immobilized bifunctional iminophosphorane superbase organocatalyst. Because of its strong basicity the catalyst remains highly active despite immobilization, and the efficient, one-step catalyst creation/immobilization via Staudinger reaction avoids the need for additional synthetic steps to affect immobilization. The catalyst was successfully applied to three challenging enantioselective reactions: the nitro-Mannich reaction of diphenylphosphinoyl-protected ketimines and to the conjugate addition of substituted malonates and *N,N*-dimethyl β-keto amides to nitrostyrene. Catalyst recycling without significant loss of activity or stereoselectivity was demonstrated over 10 cycles. Further work to broaden the range of reactions catalyzed by **5** and related catalysts, and to demonstrate its utility in flow chemistry, is underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, NMR spectra, and HPLC traces of novel compounds. Details of immobilized catalysts with variation at the phosphine, demonstration of reversibility of nitro-Mannich reaction, absolute stereochemistry determination, and comparisons with homogeneous system. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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