CHIRALTIPOCAT

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1. INTRODUCTION: Bifunctional organocatalysts

Bifunctional organocatalysts[1] offer unlimited opportunities for the discovery of powerful new asymmetric carbon-carbon and carbon-heteroatom bond forming reactions due to their capacity of simultaneously organizing and activating electrophilic substrates (through H-bonding interactions) and pro-nucleophilic reagents (through deprotonation), thereby catalysing their stereocontrolled union. However, despite the surge of interest over the last decade, low reaction rates and high catalyst loadings remain the major limitations within the field. Furthermore low acidity pro-nucleophiles or low energy electrophiles often do not react at all in the presence of the existing best bifunctional organocatalysts, owing to negligible activation of the pro-nucleophile by the weak and untunable organic base.

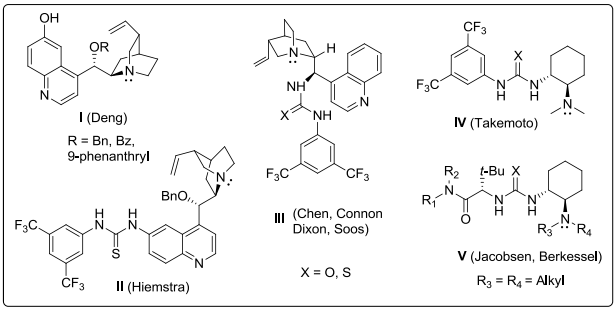


Figure 1 - Broadly useful bifunctional Brønsted base / H-bond donor organocatalysts

During this project, we have developed a new class of modular bifunctional iminophosphorane/thiourea catalysts which offer much broader scope and tunability whilst providing new and enhanced reactivity and maintaining high levels of enantiocontrol. We have used these new bifunctional systems in the first catalytic asymmetric metal-free scalable addition of nitromethane to ketimines (nitro-Mannich or aza-Henry reaction),[2] a transformation in which the best-in-class bifunctional organocatalysts or even metal catalysts need high temperatures and/or long reaction times to perform. The resulting enantioenriched α-nitroamines allow the construction of important building blocks for asymmetric synthesis such as 1,2-diamines or α-amino acids bearing at least one fully substituted carbon atom.

2. OBJECTIVES OF THE PROJECT

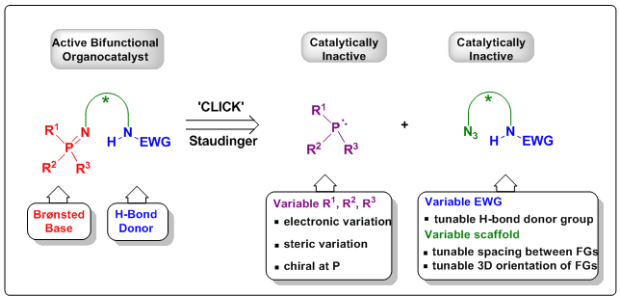


Figure 2 - Concept and design of a new class of bifunctional iminophosphorane/ thiourea organocatalysts

Triaminoiminophosphoranes ($(R^1N)_3P{=}NR^2$) have been used extensively as organic bases for synthetic transformations.[3] However, to the best of our knowledge, trialkyl- or triaryliminophosphoranes have not, despite also possessing a strongly basic nitrogen. Hence, we envisaged that key to the success of our novel bifunctional catalyst design would be the presence of a strongly Brønsted basic and variable/tunable iminophosphorane (whose basicity could be modified by the use of different phosphines) linked to a variable/tunable H-bond donor group via a variable/tunable chiral scaffold (Fig. 2).

*Therefore, the **overall objective** of this work is to develop (by design, synthesis and testing) a new family of potent asymmetric iminophosphorane organocatalysts which can efficiently catalyse a broad range new of synthetically useful asymmetric reactions between pro-nucleophiles (NuH) and weakly electrophilic reagents with exceptionally high enantioselectivity*. Furthermore the catalysts can be made in situ via a 'Click'-type Staudinger reaction of an organoazide and a phosphine to generate the strongly Brønsted basic iminophosphorane from catalytically inactive precursors thus providing a combinatorial method for best catalyst identification and facilitating rapid optimization in any reaction of interest (Fig. 2).

3. RESULTS

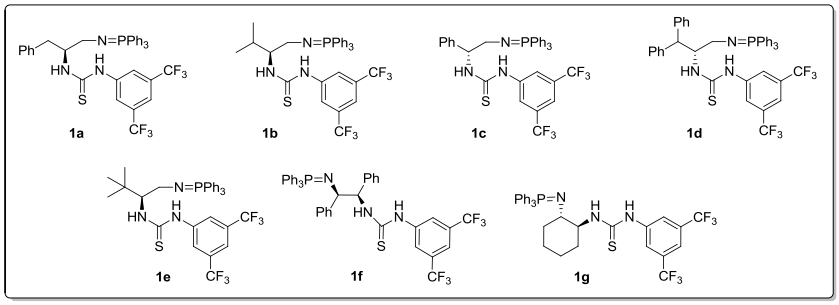
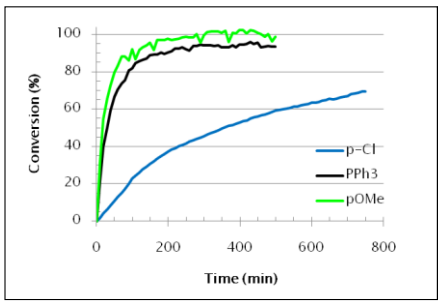


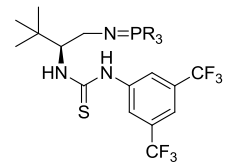
Figure 3. New family of bifunctional iminophosphorane/thiourea catalysts synthesized during this project

We have synthesized a range of iminophosphorane/thiourea bifunctional organocatalysts **1a** - **1g** derived from commercially available natural amino acids (**1a**, **1b** and **1d** from L-phenylalanine, L-valine and L-serine respectively), unnatural amino acids (**1c** and **1e** from D-phenylglycine and L-tert-leucine respectively), small chiral 1,2-diols (**1f**) or 1,2-diamines (**1g**) (Fig. 3).

In order to test this new family of organocatalysts, we selected the challenging asymmetric nitro-Mannich (or aza-Henry) reaction of ketimines. This catalytic enantioselective reaction has proved to be one of the most powerful and efficient methodologies for the synthesis of chiral vicinal diamines and α-amino acids through C-C bond formation.[2] However, due to the low reactivity of ketimines and difficulties in enantiofacial discrimination towards nucleophilic addition, the electrophilic substrates have been largely confined to imines derived from aldehydes. Only a few examples for the racemic[4] or diastereoselective[5] version have been reported and, to the best of our knowledge, to date, there have been reported only two catalyzed asymmetric nitro-Mannich reactions between ketimines and nitromethane.[6] Therefore, we realized that a simple, efficient protocol for an enantioselective nitro-Mannich reaction of ketimines to generate a chiral quaternary center using metal-free conditions still remained elusive and its development would be desirable.

N-Phosphinoyl ketimine **2a** (Table 1) was chosen as a model substrate and its reaction with nitromethane with catalysts **1a**-**g** was assessed for efficiency and enantiocontrol. Pleasingly, using optimized conditions (20 equiv. $MeNO_2$, rt) and 10 mol.% catalyst, all systems afforded the addition product **3a** with excellent reactivity. Enantioselectivities were good (77-85%) except with catalysts **1f** and **1g** (30 and 20% respectively), presumably due to the lack of proximity between the two catalytic active sites in these two scaffolds. *tert*-Leucine derived catalyst **1e** out-performed the others in terms of enantioselectivity (85% ee) and was therefore selected as the scaffold of choice for the remainder of the optimization studies.





R = *p*-MeOC$_6$H$_4$, ee = 81%
R = C$_6$H$_5$, ee = 85%
R = *p*-ClC$_6$H$_4$, ee = 81%

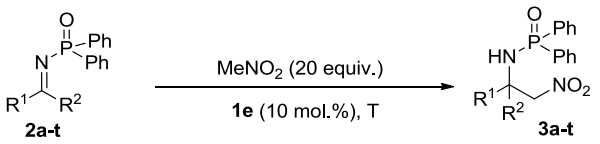
*Figure 4 - Comparison of reaction rate in the nitro-Mannich reaction of ketimine **5a** and nitromethane with different bifunctional iminophosphorane/thiourea catalysts and bifunctional cinchonine/thiourea catalyst **III**.*

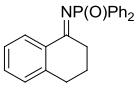
With the best scaffold and H-bond donor group in hand, we now turned our attention to the Brønsted base moiety and studied how the use of different aryl phosphines affected the basicity of the formed iminophosphorane and consequently, the reaction rate.

Catalyst **1e** and its analogues **1h** (R = *p*-MeOC$_6$H$_4$, Figure 3) and **1i** (R = *p*-ClC$_6$H$_4$, Figure 4) were used in the reaction of ketimine **2a** with nitromethane in deuterated tetrahydrofuran at RT. The conversion to addition product **3a** was measured by ^{1}H NMR spectroscopy at 10 min intervals over 12 h. As shown in Figure 4, reaction rate varies strongly with the aryl substituents in the iminophosphorane moiety: the reaction with **1h** is notably faster than the one with **1e** and the use of **1i** notably decreases the reaction rate. Interestingly, when the bifunctional cinchonine/thiourea derivative **III** (Fig. 1, X = O) was used as catalyst in the same NMR spectroscopy experiment, only traces (0.04 %) of product were observed after 24 h.

The above experiments clearly prove that the potent basicity of this new bifunctional system is necessary to catalyze the asymmetric metal-free nitro-Mannich reaction of ketimines. Moreover, this basicity can be properly tuned to the acidity of a given substrate, thereby providing a combinatorial method for optimal catalyst identification in each reaction of interest.

Table 1. Scope of asymmetric nitro-Mannich reaction of ketimines



Entry	R^1	R^2	T/°C	t/h	Conversion (%)	ee (%)
1	C_6H_5 (**2a**)	Me	-15	96	89	96
2	*p*-MeC_6H_4 (**2b**)	Me	0	48	96	90
3	*p*-$MeOC_6H_4$ (**2c**)	Me	0	48	94	89
4	*m*-$MeOC_6H_4$ (**2d**)	Me	0	48	98	91
5	*o*-MeO C_6H_4 (**2e**)	Me	0	48	99	90
6	*p*-PhC_6H_4 (**2f**)	Me	0	24	99	90
7	*p*-$NO_2C_6H_4$ (**2i**)	Me	-15	21	99	93
8	*o*-FC_6H_4 (**2j**)	Me	-15	96	99	93
9	*p*-FC_6H_4 (**2k**)	Me	0	48	98	85
10	*p*-ClC_6H_4 (**2l**)	Me	0	20	99	90
11	*p*-BrC_6H_4 (**2h**)	Me	-15	96	87	85
12	*m,p*-ClC_6H_3 (**2m**)	Me	0	20	99	84
13	*m,m*-$CF_3C_6H_3$ (**2n**)	Me	-15	96	99	89
14	C_6H_5 (**2o**)	Et	0	24	91	92
15	 (**2p**)		-15	96	50	92
16	2-thienyl (**2q**)	Me	-15	96	17	92
17	3-pyridyl (**2r**)	Me	-15	96	62	81
18	1-cyclohexyl (**2s**)	Me	-15	96	60	83

Reactions were carried out with **2** (0.2 mmol) and **1e** (0.02 mmol) in $MeNO_2$ (4.0 mmol) at the indicated temperature. Conversion was determined by ^{1}H NMR experiments of the crude reaction mixtures. Enantiomeric excess was determined on analytical pure samples (after purification by silica gel chromatography) by chiral HPLC analysis using commercially available columns.

As the above experiment shows, catalyst **1h** (R = *p*-$MeOC_6H_4$, Figure 4) is better in terms of reaction rate but gives slightly lower enantioselectivity than its analogue **1e** (R = C_6H_5, Figure 4). Therefore the latter was chosen as the catalyst to investigate substrate scope in the nitro-Mannich addition of nitromethane to ketimines. It proved effective and highly enantioselective with a series of aromatic ketimines bearing either electron-withdrawing or electron-donating substitutents (87 - 99 % conversion, 84 - 96 % ee; Table 1, entries 1 - 14). More sterically hindered substrates such as **2o** and **2p** also afforded the product with high enantioselectivities, although only with moderate conversion in the case of tetralone **2p** (Table 1, entries 15 - 16). Heteroaromatic ketimines **2q** and **2r** gave the desired product with good enantioselectivities and moderate conversion (Table 1, entries 16 - 17). Pleasingly, the reaction was also applicable to aliphatic ketimine **2s** (Table 1, entry 18).

Whereas recent developments in bifunctional Brønsted base / H-bond donor organocatalysts have enabled an array of transformations to be performed asymmetrically, long reaction times and a reduced range of substrates amenable to union remain the major restrictions in the field. In this project, we have shown here that our new bifunctional iminophosphorane / thiourea systems can overcome these limitations. Their use in the first metal-free catalytic asymmetric addition of nitromethane to unreactive ketimines offers a straightforward access to important chiral building blocks in asymmetric synthesis, and we expect them to be applicable in the synthesis of diverse natural products and biologically active molecules.

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