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Enantioselective Organocatalytic Addition of Nitromethane to Trifluoromethyl Aryl Ketimines Promoted by Electron-Rich Bifunctional Iminophosphoranes

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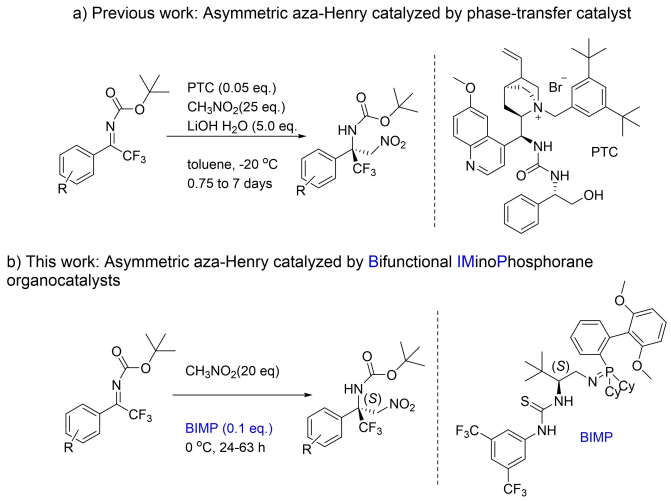
Abstract: Thiourea-based iminophosphorane (BIMP) organocatalysts featuring SPhos- or BI-DIME phosphine units have been developed and successfully applied in the asymmetric addition of nitromethane to *N*-Boc-protected trifluoromethyl aryl ketimines. α-Trifluoromethyl β-nitroamines were obtained in 40–82% isolated yields and 80–95% enantioselectivities. A careful evaluation of the catalytic activity of BIMPs indicates that the catalysts derived from the combination via Staudinger reaction of a chiral 1,2-amino alcohol-derived thiourea-organoazide with electron-rich phosphines, promote the aza-Henry reaction on fluorinated ketimines with the highest enantioselectivity, leading to the amine featuring a tetrasubstituted stereocenter in up to 95% ee. The reaction was performed also on gram scale, without loss of enantioselectivity.

Keywords: aza-Henry reaction; asymmetric organocatalysis; chiral organosuperbases; iminophosphoranes; trifluoromethyl 1,2-nitroamines

Enantio-enriched β-nitroamines synthetized by aza-Henry (nitro-Mannich) reaction are important molecular scaffolds in asymmetric synthesis. The enantioselective addition of nitromethane to aldimines or ketimines has been described by different groups.[1a–n] Various organocatalysts such as chiral thioureas,[1n] Cinchona-derived bifunctional thioureas,[1c,h] guanidine and phosphazene bases,[1f] bifunctional thiourea-ammonium salts (phase transfer catalysts),[1a,j] bifunctional thiourea-tertiary amines derived from quinine,[1i] iminophosphorane catalysts[1o] were used to promote these reactions and produce trisubstituted or tetrasubstituted nitroamines, depending on the selected imines as starting material. The reaction products can be easily converted by reduction to 1,2-diamines, or by Nef reaction to *α*-amino acids.[1n] An easy access to different functional groups in a few steps makes these molecular units perfect as building blocks or chiral auxiliaries.[1m] In particular, we were interested in the catalytic asymmetric synthesis of tetrasubstituted amino derivatives containing CF_3 group.[2] The relevance of organofluorine molecules in pharmaceutical and agrochemical industry is well recognized.[1k] Trifluoromethyl group within the target molecule can intensify lipophilicity and bioavailability and may affect metabolic stability.[1k] To our knowledge, asymmetric addition of nitromethane to trifluoromethylated ketimines was described only in an asymmetric phase transfer catalytic reaction.[1a] Wang et al. performed this reaction by using excess of strong inorganic base, $LiOH{\cdot}H_2O$, with the reaction time up to 7 days (Scheme 1a). Our goal was to develop a mild, experimentally simple, stereoselective, catalytic synthetic method applicable for industrial production of enantiomerically pure, CF_3 functionalized amino derivatives featuring a tetrasubstituted stereocenter (Sche-



Scheme 1. Synthesis of tetrasubstituted α-trifluoromethyl *N*-Boc protected β-nitroamines.

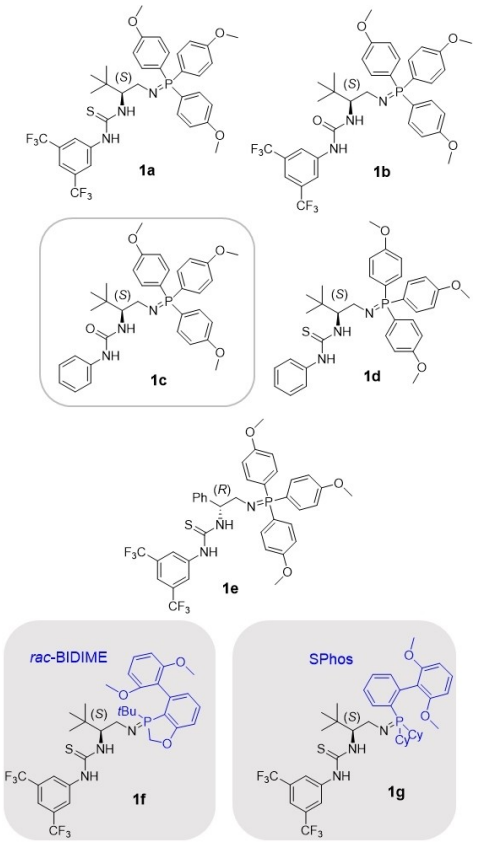


Figure 1. Selected Bifunctional IMinoPhosphorane organocatalysts.

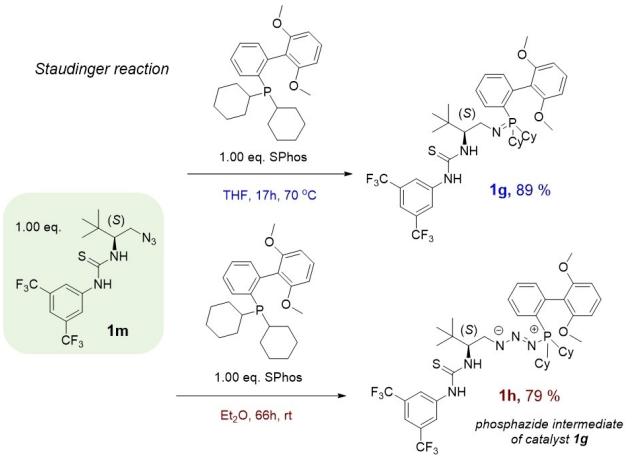
me 1b). In particular, bifunctional iminophosphorane organocatalysts have shown great potential in base-catalyzed transformations, due to their modular design. This relatively new class of superbases was introduced by Dixon and his group,[1o] and has several positive features, such as high tunability and stability, access to high pKa pronucleophiles, easy modifications, by using available chiral amino alcohols as starting materials.[3a–e] They act as a Brønsted base (basic nitrogen of -N=>P functional group), but also as a hydrogen bond donor, due to the presence of a thiourea or urea moiety. Therefore, it is possible to perform double activation of both pronucleophile (via deprotonation) and electrophile (via H-bonding interactions).[4]

Based on the seminal contribution by Dixon in 2013, for the nitro-Mannich reaction of nitromethane with *N*-diphenyl-phosphinoyl ketimines,[1o] we decided to explore such class of catalysts in the preparation of chiral amines bearing CF_3 group. *N*-Boc trifluoromethyl aryl ketimines[5] proved to be very suitable starting materials, enabling the introduction of the CF_3 group within the target molecules and the possibility of easy removal of the protective Boc group. Herein, we show that the asymmetric addition of nitromethane to *N*-Boc-protected trifluoromethyl aryl ketimines could be efficiently catalysed by new chiral iminophosphoranes. Catalysts **1 f** and **1 g** (Figure 1), derived from L-*tert*-leucine, bearing a thiourea moiety with electron-withdrawing groups (CF_3) on phenyl ring and an electron rich, sterically hindered phosphine (SPhos or *rac*-BIDIME), were found to be the privileged catalysts in asymmetric aza-Henry reaction with *N*-Boc trifluoromethyl aryl ketimines.[6]

A small library of BIMP catalysts, derived from L-*tert*-leucine (**1 a**, **1 b**, **1 c**, **1 d**, **1 f** and **1 g**) or (*R*)-(−)-2-phenylglycine (**1 e**) was synthesized according to the literature procedures (**1 a**, **1 b**, **1 d**, **1 e**),[1o] or designed and prepared as new catalysts (**1 c**, **1 f** and **1 g**). Changing the nature of the catalysts helped us to understand the interaction between the catalyst and the substrates in asymmetric nitro-Mannich reaction of *N*-Boc ketimines. We investigated the role of electron withdrawing groups on a phenyl ring of hydrogen-bond donor moiety (thiourea or urea), as well as the influence of very electron-rich phosphines.

Chiral organoazide **1 m** was prepared through a modified procedure of a known synthesis,[1o] (see supporting information). The preparation of the iminophosphorane organocatalyst (formation of N=>P bond) is usually performed via a Staudinger reaction, a coupling between a chiral organoazide and the corresponding phosphine, by stirring in diethyl ether at room temperature.

Surprisingly, in the case of catalyst **1 g**, different results were observed depending on the reaction solvent and temperature (Scheme 2). According to the published calculations by Rzepa et al.,[7a] we found out that the reaction performed at room temperature led to the formation of phosphazide intermediate **1 h**. Although these species usually are not stable, due to the very fast conversion to iminophosphoranes, some



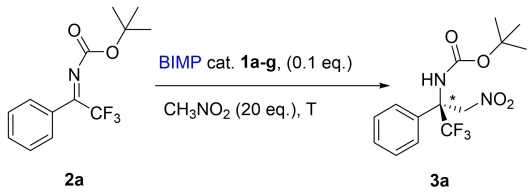
Scheme 2. Reaction conditions for the synthesis of BIMP catalysts **1 g** and **1 h**.

phosphazide have been isolated. Accordingly, the presence of electron donating and bulky substituents on phosphorus atom as well as possible hydrogen bonding within the molecule make them more stable.[7a,b] For the formation of N = > P bond via nitrogen loss, based on the reported X-ray data, s-*cis* configuration of phosphazide central N- > N bond is required.[7a] These structural data explain easier ring closure to 4-membered transition state necessary for nitrogen elimination, which is difficult to perform in s-*trans* configuration.[7b] Phosphazide intermediate **1 h** has been isolated and characterized by high temperature NMR analysis and HR-MS. However, preparing the catalyst **1 g** at 70 °C in THF (Scheme 2) the expected iminophosphorane was formed, as confirmed by NMR and high-resolution mass spectra analysis.

The bifunctional iminophosphorane organocatalysts **1 a–h** were screened in the model nitro-Mannich reaction between nitromethane and *N*-Boc imine **2 a** (Table 1). All reactions were performed using 10.0 mol% of the selected BIMP catalyst and 20.0 mol eq. of nitromethane, at indicated temperature.

The presence of CF_3 electron-withdrawing groups on a phenyl group of thiourea or urea moiety (catalyst **1 a** compared to **1 d** and catalyst **1 b** compared to **1 c**), showed to have a remarkable effect on the enantioselectivity of the final product **3 a** (entries 2–5, Table 1). To our surprise, even a small variation of hydrogen-bond donor group from thiourea to urea (catalyst **1 a** and catalyst **1 b**, entries 1 vs 3) resulted in a significant change in the stereoselectivity. The outcome of the reaction gave a clear evidence that the thiourea is a better hydrogen-bond donor due to the stronger acidity of -NH protons, thus leading to stronger hydrogen bonding coordination of the urea or thiourea with the substrate. Catalyst **1 e** showed a bit lower enantioselectivity compared to the catalyst **1 a** (Table 1, entries 1 and 6), possibly due also to the less stable benzylic stereogenic center.

Table 1. Screening of the BIMP catalysts in the model Aza-Henry reaction of imine **2 a** to afford the product **3 a**.



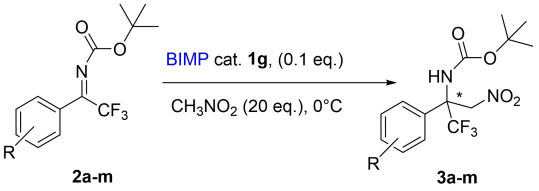
Entry	Catalyst	T (°C)	Reaction time (h)	Yield (%)[a]	ee%[b]
1	**1 a**	25	5	80	64
2	**1 a**	0	12	86	72
3	**1 b**	25	12	72	54
4	**1 c**	0	48	52	< 5
5	**1 d**	0	24	30	20
6	**1 e**	0	92	77	56
7	**1 f**[c]	0	24	85	92
8	**1 g**[d]	0	24	82	95
9	**1 h**[c]	0	24	60	73

[a] Isolated yields of the product **3 a**.
[b] Enantiomeric excess of the product **3 a** was determined by HPLC on chiral stationary phase.
[c] Staudinger reaction for the synthesis of catalysts **1 f** and **1 h** were performed at room temperature in dry Et_2O.
[d] Staudinger reaction for the synthesis of catalyst **1 g** was performed at 70 °C in dry THF.

The best result in terms of enantioselectivity was obtained using catalyst **1 g**: the product **3 a** was isolated in 82% yield and 95% ee, after 24 hours at 0 °C (Table 1, entry 8). The new, most effective catalysts were prepared by reacting the chiral azide **1** with different monophosphorus ligands such as oxaphosphole-based phosphine (*rac*-BIDIME) or acyclic biphenyl phosphine (SPhos). The use of sterically hindered and more electron-rich phosphines to generate the target iminophosphoranes (**1 f** and **1 g**), was the key element to enhance the enantioselectivity of the reaction leading to tetrasubstituted α-trifluoromethyl *N*-Boc protected β-nitroamines (catalyst **1 a** compared to **1 g**). The absolute stereochemistry of the product **3 a** was established by measurement of the optical rotatory value and comparison with the data reported in literature. By using catalyst **1 g**, synthesized starting from (S)-*tert*-leucinol, the product (S)-**3 a** was obtained as major enantiomer (for details see the Supporting Information).

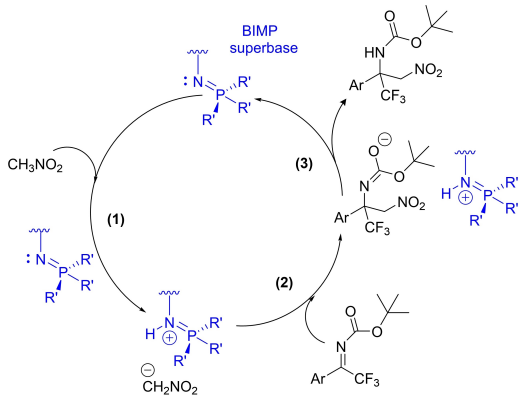
The catalyst **1 g** was selected as catalyst of choice to evaluate the scope of the asymmetric aza-Henry reaction (Table 2). Different *N*-Boc trifluoromethyl aryl ketimines were synthesized,[2a] having electron-withdrawing or electron-donating substituents (**2 a–m**). Most imines reacted with excellent enantioselectivities under mild reaction conditions (0 °C, 10.0 mol% of the

Table 2. Substrate scope of asymmetric nitro-Mannich reaction promoted by BIMP catalyst **1 g**.



Entry[a]	R–	Product	Time (h)	Yield (%)[b]	ee (%)[c]
1	C_6H_5–	**3 a**	24	82	95
2	*m*-MeC_6H_4–	**3 b**	48	40	93
3	*m*-BrC_6H_4–	**3 c**	48	50	91
4	*m*-*i*PrC_6H_4–	**3 d**	48	51	95
5	*p*-ClC_6H_4–	**3 e**	24	78	91
6	*p*-FC_6H_4–	**3 f**	48	85	84
7	*p*-$MeOC_6H_4$–	**3 g**	48	42	92
8	*p*-$CF_3C_6H_4$–	**3 h**	48	40	88
9	*p*-PrC_6H_4–	**3 i**	48	75	93
10	*p*-*t*BuC_6H_4–	**3 j**	63	75	93
11	3,5-$F_2C_6H_3$–	**3 k**	48	47	80
12	3,5-$FClC_6H_3$–	**3 l**	48	53	80
13	3,5-$Cl_2C_6H_3$–	**3 m**	48	45	82

[a] Unless otherwise noted, reactions were carried out with 10 mol% of the catalyst **1 g** and 20.0 eq. of CH_3NO_2 at 0 °C.
[b] Isolated yields of products **3 a–m**.
[c] Enantiomeric excess of the products **3 a–m** was determined by HPLC on chiral stationary phase.



Scheme 3. Proposed mechanism for aza-Henry reaction catalysed by BIMP catalysts.

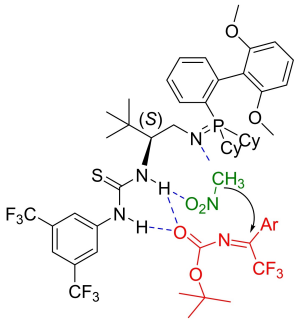


Figure 2. Proposed stereoselection model.

catalyst **1 g** and 20.0 mol eq. of nitromethane). It is known that electron donating groups on aromatic ring increase the electron density in ketimines, which makes them more prone to be coordinated by acidic protons of thiourea group, thus explaining higher values of e.e. % observed. With imines featuring electron-withdrawing groups on aromatic ring little lower enantioselectivities were observed (entries 11, 12, 13, Table 2). Under the present conditions, the reaction with nitroethane and 2-nitroethanol with imine **2 a** led to the formation of the product only in traces, and most of the ketimine was recovered as unreacted starting material.

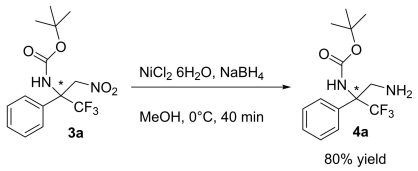
The proposed mechanism was inspired by Dixon's previous work.[3e] After deprotonation of nitromethane the nucleophilic attack of nitromethane anion to ketimine probably coordinated by hydrogen bonding to the thiourea group, occurs (Scheme 3). Then, a proton shift from the protonated iminophosphorane to the negatively charged *N*-Boc protected reaction product, affords the expected *N*-Boc protected 1,2 nitroamine and releases the catalyst.

Based on the described activation strategy of the substrates by the chiral catalyst, a tentative model of stereoselection can be proposed (Figure 2).

The iminophoshorane acts as bifunctional catalyst, interacting with both reactants through hydrogen bonding; the thiourea coordinated the Boc group of the imine and possibly also the nitro group of the nucleophile, activated by the basic site of the catalyst. Other coordination modes are possible, involving nitro group interaction with thiourea unit, and computational studies are currently underway in order to fully elucidate the mechanism.

Scaling up of nitro-Mannich reaction on gram scale under the same conditions of entry 1 of Table 2, with the catalyst **1 g** and ketoimine **2 a**, at 0 °C, afforded the product **3 a** in 65% yield and 92% ee. Increasing the scale of the reaction did not depress the enantioselectivity of the target β-nitroamine. An attempt to recover the catalyst **1 g** by column chromatography on silica gel, unfortunately, allowed only a partial recovery of the catalyst, that showed extensive signs of decomposition, thus confirming the instability of some iminophosphoranes even in the presence of very weakly acidic material like silica.

Chiral 1,2-diamines are important subunits of building blocks in organic chemistry.[9] This class of compounds shown broad utility in various fields of organic chemistry (pharmaceutical compounds, natural products, ligands in stereoselective organic synthesis). Therefore, we demonstrated conversion of trifluoromethyl β-nitroamine to trifluoromethyl β-dia-



Scheme 4. General synthesis of trifluoromethyl 1,2 diamine

mine following a known procedure.[1k] The chiral diamine **4a** (Scheme 4) was isolated in 80% yield without any loss of stereochemical integrity.

In conclusion, we have developed new iminophosphorane organocatalysts, bearing an electron rich phosphine unit. These catalysts were successfully employed in the nitromethane addition to fluorinated *N*-Boc protected ketimines. The aza-Henry reaction proceeds faster and under mild conditions, compared to the previously published report. Furthermore, the new iminophosphoranes featuring electron rich phosphine units catalyzed the reaction with higher enantioselectivities (up to 95% ee) than with the known BIMP catalysts. Computational studies are currently under evaluation in our group, in order to understand the exact coordination mode of the catalyst with substrates and to determine the transition states of the reaction.

Experimental Section

General Procedure for the Synthesis of Products 3 a–m

A 3 ml vial with septum connected to a nitrogen inlet, was charged with iminophosphorane catalyst (0.1 eq.) (**1 g**) and *N*-Boc trifluoro aryl ketimine (1.0 eq.) (**2 a–m**). The reaction mixture was cooled at 0 °C, nitromethane (20 eq.) were added, and the reaction mixture was stirred until the completion of the reaction. The reactions were monitored by TLC and ^{1}H NMR. Nitromethane was then removed under reduced pressure and the residue was purified by column chromatography on silica gel with *n*-hexane/ethyl acetate 9:1 to afford the desired products **3 a–m**. Determination of ee % was done by HPLC on chiral stationary phase (Chiralpak AD column, *n*-hexane/isopropanol 98:2 or 95:5 according to the sample, or Chiralcel OD–H, *n*-hexane/isopropanol 95:5).

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