Organocatalysis

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Highly Efficient Organosuperbase-Catalyzed Mannich-type Reactions of Sulfonylimidates with Imines: Successful Use of Aliphatic Imines as Substrates and a Unique Reaction Mechanism**

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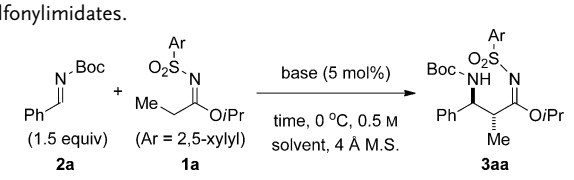
A base-catalyzed reaction that forms a carbon–carbon bond by proton transfer is an ideal reaction for constructing basic molecular skeletons from the point of view of atom economy.[1] Over the past decade, several base-catalyzed reactions, including asymmetric transformations, have been intensively studied.[2] However, available substrates for nucleophilic carbanion formation by deprotonation have been limited to those bearing relatively acidic hydrogens; catalytic activation of substrates with less acidic hydrogens remains difficult.[3] One typical example of a less reactive substrate is an ester without any activating group in the α-position.[1a,3] We have recently developed a reactive ester equivalent, a sulfonylimidate, and successfully applied it to Mannich-type reactions with imines in the presence of a catalytic amount of 1,8-diazabicyclo[5.4.0.]undec-7-ene (DBU)[4a,c] or an alkali earth metal alkoxide or amide,[4b] and obtained the desired adducts in good yields and with high stereoselectivities.[5] However, catalyst activity was not sufficient for achieving high catalyst turnover number (TON) or turnover frequency (TOF), and substrates were limited to aromatic imines. In many cases, the reactions of aliphatic imines are sluggish owing to rapid isomerization to enamine forms under both basic and acidic conditions.

Organobases, such as TEA (triethylamine), TMG (tetramethylguanidine), DBU, and others, offer relatively mild basicity and possess highly tuneable structures; they have been widely applied in organic synthesis as reagents or catalysts.[6] Among this class of compounds, organosuperbases, for example, phosphazene and proazaphosphatrane, show stronger basicity (the pKa values of *t*ert-butyliminotri(pyrrolidino)phosphorane (BTPP) and *i*Bu-proazaphosphatrane (*i*Bu-PAP) are 28.35[7] and 33.53,[8] respectively, in acetonitrile) and these superbases have recently been utilized in organic synthesis.[9] They have often been stoichiometrically employed in synthetic reactions, such as in the synthesis of oxazoles and pyrroles,[10] monoalkylation reactions,[11] and in the synthesis of Wittig products.[12] Organosuperbase-catalyzed carbon–carbon bond-forming reactions such as nitroaldol (Henry) reactions,[13] the synthesis of β-hydroxy nitriles,[14] 1,2-addition reactions,[15] and Michael-type reactions have all been reported by Verkade et al.[16] However, to the best of our knowledge, there are no reports of organosuperbase-catalyzed Mannich-type reactions.

Herein, we report on an organosuperbase-catalyzed highly efficient Mannich-type reaction of sulfonylimidates. The reaction has a broad substrate generality, which includes linear aliphatic *N*-Boc imines, and only requires low catalyst loading (ca. 0.5 mol%) to afford the desired products in high yields. A unique reaction mechanism based on NMR experiments is also proposed.

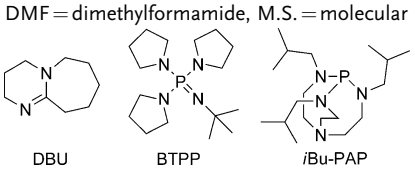
We first investigated the catalytic activity of organosuperbases in Mannich-type reactions of sulfonylimidates (Table 1). The reaction between 2,5-xylyl sulfonylimidate (**1a**) and benzaldehyde derived *N*-Boc imine (**2a**) in the presence of DBU (5 mol%) in DMF at 0°C afforded the desired product in 95% yield and high selectivity.[4a] The organosuperbases BTPP and *i*Bu-PAP also worked well as catalysts, and the desired products were obtained in high

Table 1: Organosuperbase-catalyzed direct Mannich-type reactions of sulfonylimidates.



Entry	Base	Solvent	*t* [h]	Yield [%][a]	*anti*/*syn*[b]
1[c]	DBU	DMF	24	95	96:4
2	BTPP	DMF	4	99	97:3
3	*i*Bu-PAP	DMF	4	96	98:2
4	DBU	DMF	1	49	95:5
5	BTPP	DMF	1	61	98:2
6	*i*Bu-PAP	DMF	1	90	98:2
7	*i*Bu-PAP	DMF	2	96 (93)[d]	98:2
8	*i*Bu-PAP	THF	2	86	96:4
9	*i*Bu-PAP	toluene	2	85	96:4

[a] Yield based on NMR specroscopy. [b] Determined by ^{1}H NMR analysis of the crude product. [c] Ref. [4a]. [d] Yield of isolated product. DMF = dimethylformamide, M.S. = molecular sieves.



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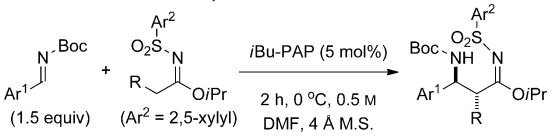
yields with high diastereoselectivites in a shorter reaction time (Table 1, entries 2 and 3 vs. entry 1). Further optimization of the reaction conditions revealed that the catalytic activities of BTPP and *i*Bu-PAP were much higher than that of DBU (Table 1, entries 5 and 6 vs. entry 4), and that *i*Bu-PAP showed the highest activity with high diastereoselectivity (Table 1, entry 6 vs. entry 5). The reaction conditions were optimized, resulting in both high yield and selectivity (93% yield, *anti*/*syn* = 98/2; Table 1, entry 7). The reaction also proceeded smoothly in less polar solvents such as THF and toluene (Table 1, entries 8 and 9).

With the optimum conditions determined (Table 1, entry 7), the substrate scope of this reaction was surveyed (Table 2). The ethyl substituted product was obtained in similarly high yield and selectivity (Table 2, entry 2). *N*-Boc imines derived from various aromatic aldehydes bearing both electron-donating and -withdrawing substituents, *ortho*- and *meta*-substituted benzaldehydes, and heteroaromatic aldehydes, all provided the corresponding desired adducts in high yields and with high *anti*-selectivities (Table 2, entries 3–8).

Table 2: *i*Bu-PAP catalyzed direct Mannich-type reactions of sulfonylimidates with aromatic aldehyde derived *N*-Boc imines.

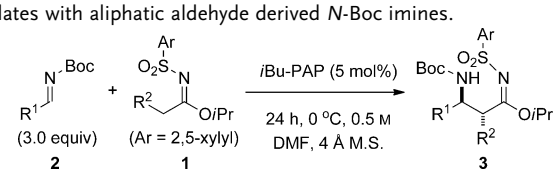


Entry	Ar^1	R	Yield [%][a]	*anti*/*syn*[b]
1	Ph (**2a**)	Me (**1a**)	93	98:2
2	Ph (**2a**)	Et (**1b**)	97	98:2
3	*p*-$MeOC_6H_4$ (**2b**)	Me (**1a**)	91	97:3
4	*p*-FC_6H_4 (**2c**)	Me (**1a**)	82	>99:1
5	*m*-MeC_6H_4 (**2d**)	Me (**1a**)	94	97:3
6	*o*-MeC_6H_4 (**2e**)	Me (**1a**)	88	94:6
7	2-furyl (**2f**)	Me (**1a**)	87	>99:1
8	2-thienyl (**2g**)	Me (**1a**)	92	98:2

[a] Yield of isolated product. [b] Determined by ^{1}H NMR analysis of the crude product. M.S. = molecular sieves.

We also examined reactions with aliphatic aldehyde derived *N*-Boc imines (Table 3). It is remarkable that sterically hindered pivaldehyde derived *N*-Boc imine (**2h**) reacted smoothly to afford the desired adduct in high yield with high selectivity (Table 3, entry 1). No desired product was obtained when using DBU as the catalyst (Table 3, entry 2). Cyclohexanecarboxaldehyde derived *N*-Boc imine (**2i**) was also found to be a good substrate, and the Et-substituted sulfonylimidate (**1b**) was also successfully employed (Table 3, entries 3 and 4). Isobutyraldehyde derived *N*-Boc imine (**2j**) also afforded the desired adduct in good yield and with high selectivity (Table 3, entry 5). Enolizable aliphatic aldehyde derived *N*-Boc imines, including linear aliphatic aldehydes such as isovaleraldehyde, *n*-butyraldehyde and valeraldehyde, afforded the desired adducts in high yields and with high selectivities (Table 3, entries 6–8). For these substrates, DBU was an ineffective catalyst; for example, in the reaction with a linear aliphatic aldehyde (entry 9), the yield was low and

Table 3: *i*Bu-PAP catalyzed direct Mannich-type reactions of sulfonylimidates with aliphatic aldehyde derived *N*-Boc imines.



Entry	R^1	R^2	Yield [%][a]	*anti*/*syn*[b]
1[c]	*t*Bu (**2h**)	Me (**1a**)	87	97:3
2[d,e]	*t*Bu (**2h**)	Me (**1a**)	0	–
3	*c*Hex (**2i**)	Me (**1a**)	90	92:8
4	*c*Hex (**2i**)	Et (**1b**)	99	92:8
5	*i*Pr (**2j**)	Me (**1a**)	64	99:1
6	*i*Bu (**2k**)	Me (**1a**)	90	89:11
7	*n*Pr (**2l**)	Me (**1a**)	99	92:8
8	*n*Bu (**2m**)	Me (**1a**)	95	91:9
9[d]	*n*Bu (**2m**)	Me (**1a**)	21[b]	91:9

[a] Yield of isolated product. [b] Determined by ^{1}H NMR analysis of the crude product. [c] 1.5 equiv of imine used. [d] DBU used instead of *i*Bu-PAP. [e] 20°C. M.S. = molecular sieves.

^{1}H NMR analysis of the crude mixture indicated that undesired side reactions took place.[17]

In contrast to the DBU catalyzed Mannich-type reaction of sulfonylimidates, *i*Bu-PAP showed high catalytic activity for both aromatic aldehyde derived *N*-Boc imines and aliphatic aldehyde derived *N*-Boc imines. To study this, we conducted a mechanistic investigation of *i*Bu-PAP catalyzed reactions. First, NMR experiments were carried out using **1a** and **2a** as model substrates. The product yields were determined at specified intervals by ^{1}H NMR analysis with *p*-dimethoxybenzene as an internal standard. The profiles of the initial stages of the *i*Bu-PAP catalyzed reaction are summarized in Figure 1. Unexpectedly, the *i*Bu-PAP cata-

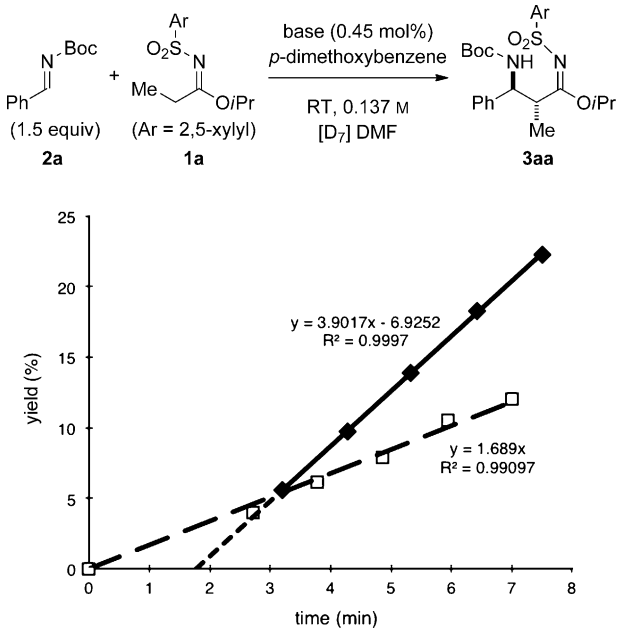


Figure 1. Initial reaction profiles obtained for DBU and *i*Bu-PAP catalysts. *i*Bu-PAP (◆), DBU (□).

lyzed reaction showed an induction period (Figure 1, ◆). We conducted the DBU catalyzed reaction of the same substrates for comparison (Figure 1, □), and found that the DBU catalyzed reaction showed no induction period.

To clarify the reaction profile of the *i*Bu-PAP catalyzed Mannich-type reaction, especially in the early stage (before 2 min in Figure 1, ◆), we monitored the reaction using a micro-channeled cell for synthesis monitoring (MICCS).[18] The ^{1}H MICCS-NMR analysis was carried out using **1a** and **2a** as model substrates again. The results are summarized in Figure 2 (see also Table S1 in the Supporting Information).[19]

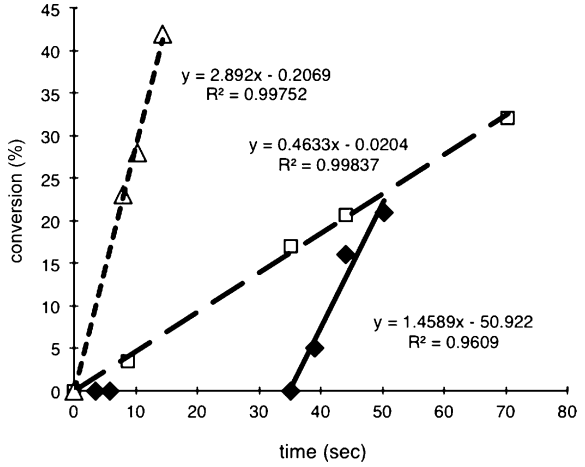
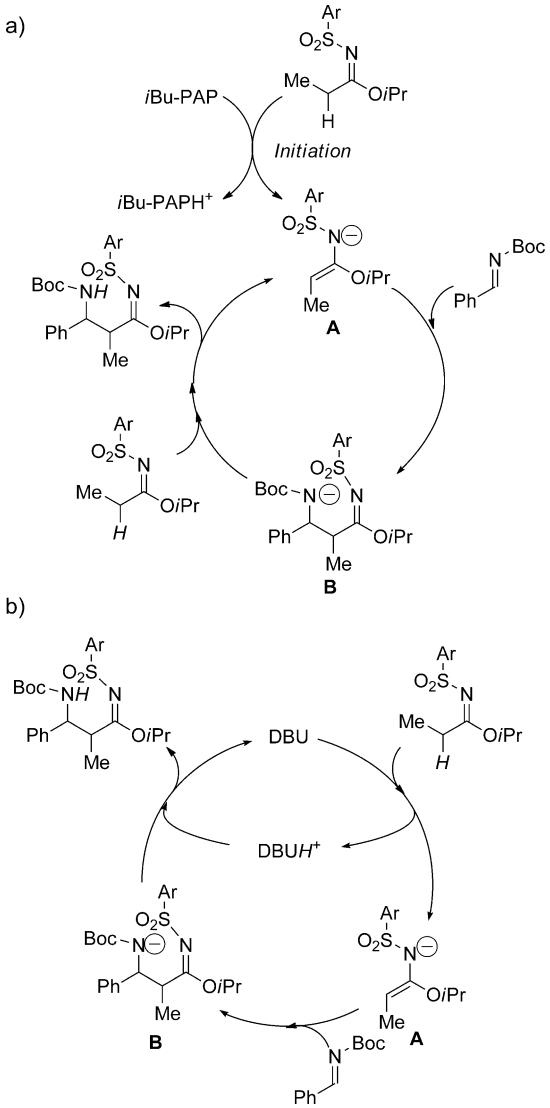


Figure 2. Early reaction profile with varying bases monitored by ^{1}H MICCS-NMR spectroscopy. *i*Bu-PAP (◆), DBU (□), with *N*-Boc imine added last (△).

The conversions were determined at each of the specified periods by ^{1}H MICCS-NMR analysis, under different flow rates of the DMF solutions of **1a**, **2a**, and *i*Bu-PAP. Figure 2, ◆ provides confirmation that the *i*Bu-PAP catalyzed reaction had a clear induction period. Based on the conversions at flow rates of 9 μL/min (Table S1, entry 3) and 10 μL min^{-1} (Table S1, entry 4), the experimentally determined induction period was 35–39 seconds. On the other hand, when DBU was used as a base promoter no induction period was observed (Figure 2, □), which corresponds to a typical NMR experiment with DBU.[4c] A possible explanation for the induction period may be slow deprotonation of the α-hydrogen of the sulfonylimidate because of the steric bulk of *i*Bu-PAP. Based on this consideration, we changed the addition order of the substrates in the MICCS-NMR analysis. In a typical procedure, a solution of sulfonylimidate (**1**) in DMF was added to a solution of *N*-Boc imine (**2**), and then a solution of *i*Bu-PAP in DMF was added. In contrast, when *N*-Boc imine (**2a**) was the last reagent added (Figure 2, △), the reaction proceeded notably faster than the reaction in which *i*Bu-PAP was added last and no induction period was observed (Figure 2, ◆ vs. △). This result strongly suggests that slow deprotonation of the α-hydrogen of the sulfonylimidate is the main reason for the induction period.

Based on these experimental results, we proposed a mechanism for the *i*Bu-PAP catalyzed reaction (Scheme 1 a). The



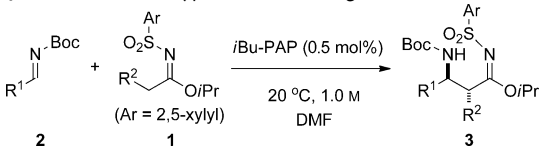
Scheme 1. Proposed mechanisms for the *i*Bu-PAP and DBU catalyzed Mannich-type reactions of sulfonylimidates.

reaction is initiated by the deprotonation of the α-hydrogen of the sulfonylimidate by *i*Bu-PAP to generate reactive enamide anion **A** and *i*Bu-PAPH$^+$, which is thermodynamically stable. The Mannich-type reaction of **A** with the *N*-Boc imine affords key anionic intermediate **B**, which subsequently deprotonates the α-hydrogen of the next sulfonylimidate, leading to formation of the desired product along with regeneration of **A** for the next catalytic cycle. In this mechanism, *i*Bu-PAP functions as an initiator for the Mannich-type reaction, instead of as a catalyst, unlike DBU in Scheme 1 b.[20] The successful Mannich-type reactions with primary aliphatic *N*-Boc imines using *i*Bu-PAP could be rationalized by the steric bulk of anionic intermediate **B**, which could not effectively deprotonate the hydrogen atom of the aliphatic imine because of steric hindrance, but could deprotonate the sulfonylimidate for smooth catalytic turnover. This effect was different from the reaction using DBU, in which primary aliphatic *N*-Boc imines did not work well.

To examine the rate-determining step of this *i*Bu-PAP catalyzed Mannich-type reaction, several kinetic investigations were undertaken using **1a** and **2a** as model substrates.[21] The product yields were determined at intervals by ^{1}H NMR analysis with *p*-dimethoxybenzene as an internal standard. The results of studies in which the concentration of each component was varied revealed the rate dependency on *i*Bu-PAP to be 4.09. Given this high rate dependency on *i*Bu-PAP, the deprotonation of the α-hydrogen of the sulfonylimidate might be contained in the rate-determining step, although further investigations are required to understand this unusual value.[22]

Finally, the Mannich-type reactions were conducted using a lower loading of *i*Bu-PAP, as it was shown in Figure 2 that the reaction proceeded much faster when the addition order was changed; that is, when the imine was added last. We conducted the reactions using 0.5 mol% of *i*Bu-PAP, and found that the desired Mannich-type adducts were obtained in high yields and with high stereoselectivities (Table 4). It has

Table 4: Direct Mannich-type reactions using 0.5 mol% of *i*Bu-PAP.



2 **1** **3**

Entry	R^1	R^2	Yield [%][a]	*anti*/*syn*[b]
1[c,e]	Ph (**2a**)	Me (**1a**)	99	96:4
2[c,f]	Ph (**2a**)	Et (**1b**)	92	96:4
3[c,g]	*p*-MeOC$_6$H$_4$ (**2b**)	Me (**1a**)	88	96:4
4[c,g]	*p*-FC$_6$H$_4$ (**2c**)	Me (**1a**)	88	98:2
5[c,h]	2-thienyl (**2g**)	Me (**1a**)	98	95:5
6[d,i,j]	*c*Hex (**2i**)	Me (**1a**)	90	90:10

[a] Yield of isolated product. [b] Determined by ^{1}H NMR analysis of the crude product. [c] 1.5 equiv of imine used. [d] 3.0 equiv of imine used. [e] 10 min. [f] 6 h. [g] 1 h. [h] 3 h. [i] 24 h. [j] 0 °C.

been recognized that non-metal catalysts (organocatalysts) show lower catalyst efficiency than metal catalysts in many cases, although several efforts to address this issue have been made. It is noted that a TOF of $>1000\ h^{-1}$ has been attained in a base-catalyzed carbon–carbon bond forming reaction.

In summary, we have developed highly efficient organosuperbase-catalyzed Mannich-type reactions of sulfonylimidates with several Boc protected imines, and the desired products were obtained in high yields and with high selectivities. An organosuperbase, *i*Bu-PAP, was shown to be much more effective than DBU in these reactions. *N*-Boc imines were readily prepared from both aromatic aldehydes and enolizable aliphatic aldehydes. A mechanistic study indicated that the *i*Bu-PAP catalyzed reaction had an induction period, and that the organosuperbase worked as an initiator of these reactions; this could suppress undesired side reactions, for example, in cases where *N*-Boc imines are derived from aliphatic aldehydes. Based on our mechanistic study, we changed the addition order of the substrates and the catalyst, which resulted in high catalytic efficiency. Further detailed mechanistic studies and applications in asymmetric catalysis are ongoing.

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Keywords: carbanions · imines · Mannich reaction · organosuperbases · phosphorus

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[19] The MICCS-NMR experiments were conducted with higher catalyst concentrations (*i*Bu-PAP and DBU) than the experiments in Figure 1.

[20] A similar mechanism was proposed in the nitroaldol (Henry) reaction by Verkade et al. See Ref. [13].
[21] Details are shown in the Supporting Information.
[22] If *i*Bu-PAP functions only as an initiator for the Mannich-type reaction and the initial deprotonation step is the rate-determining step in the proposed mechanism (Scheme 1 a), the value of the rate dependency on *i*Bu-PAP should be 1. Based on the observed rate dependency value (4.09), *i*Bu-PAP may function as more than just an initiator in the reaction. This possibility was also suggested by one of referees.

