Organosuperbase-Catalyzed Carbon-Carbon Bond Forming Reactions

（有機超強塩基触媒を用いる炭素−炭素結合生成反応）

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Introduction

A base-catalyzed reaction that forms a carbon–carbon bond *via* proton transfer is an ideal reaction for constructing basic molecular skeletons from an atom economical point of view. Over the past decade, several base-catalyzed reactions have been intensively studied; however, available substrates for nucleophilic carbanion formation by deprotonation have been limited to those bearing relatively acidic hydrogens. Organobases, such as TEA (triethylamine) and others, offer relatively mild basicity. On the other hand, organosuperbases, such as phosphazenes and proazaphosphatranes, show stronger basicity and these superbases have recently been utilized in organic synthesis as reagents or catalysts. However, they have often been stoichiometrically employed in synthetic reactions and organosuperbase-catalyzed carbon–carbon bond forming reactions are limited. We focused on their characters, such as strong basicity, and decided to utilize organosuperbases as catalysts for reactions using less reactive substrates as nucleophiles.

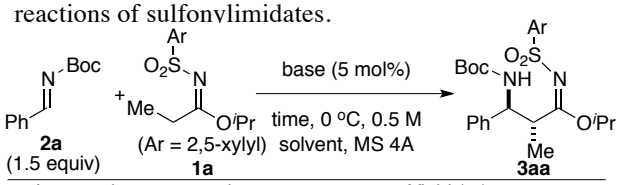
During the course of my Ph.D., I have investigated the following organosuperbase-catalyzed carbon-carbon bond forming reactions: (1) Highly efficient organosuperbase-catalyzed Mannich-type reactions of sulfonylimidates, and (2) Development of organosuperbase-catalyzed addition reactions of isonitriles and nitriles as nucleophiles.

1. Highly Efficient Organosuperbase-Catalyzed Mannich-type Reactions of Sulfonylimidates

Over the past two decades, Mannich-type reactions have been widely used for the synthesis of nitrogen-containing compounds. While most of these reactions utilize preformed enolates and their derivatives as nucleophiles for stereoselective reactions, the development of direct-type reactions, i.e., the *in situ* generation and use of carbonyl nucleophiles, has only recently become a focused area of research. Given the synthetic versatility of esters, the use of these substrates as nucleophiles is especially important. However, there are only a few examples of the use of ester equivalents bearing no activating α-substituents, such as COR or CN. This is due to the high pKa value of the esters α-hydrogen. 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) or an alkali earth metal alkoxide or

amide, and obtained the desired adducts in good yields with high stereoselectivities. 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 order to address these matters, I decided to utilize organosuperbases as catalysts for this reaction. I initially investigated the catalytic activity of organosuperbases in Mannich-type reactions of sulfonylimidates (Table 1). The reactions of 2,5-xylyl sulfonylimidate (**1a**) and benzaldehyde-derived *N*-Boc imine (**2a**) in the presence of organosuperbases, tert-butyliminotri(pyrrolidino)phosphorane (BTPP) and ^{i}Bu-proazaphosphatrane (^{i}Bu-PAP), (5 mol%) in DMF at 0 ºC afforded the desired product in high yields with high selectivities, whilst the reaction time was reduced. Further optimization of the reaction conditions revealed that the catalytic activities of BTPP and ^{i}Bu-PAP were much higher than that of DBU, and that ^{i}Bu-PAP showed the highest activity with high diastereoselectivity. The reaction conditions were further optimized, resulting in both high yield and selectivity (93% yield, *anti*/*syn* = 98/2; Table 1, entry 7). The optimized conditions were found to be applicable to a wide range of substrates (Table 2). *N*-Boc imines derived from various aromatic aldehydes bearing both electron-donating and -withdrawing substituents, *meta*- and *ortho*-substituted benzaldehydes, and heteroaromatic aldehydes, all provided the corresponding desired adducts in high yields with high *anti*-selectivity. I also examined reactions with aliphatic aldehyde-derived *N*-Boc imines (Table 2). It is remarkable that sterically hindered pivalaldehyde-derived *N*-Boc imine (**2h**) reacted smoothly to

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



entry	base	solvent	time (h)	Yield (%)[a]	*anti*/*syn*[a]
1	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[b])	98/2
8	^{i}Bu-PAP	THF	2	86	964
9	^{i}Bu-PAP	toluene	2	85	96/4

[a] Determined by ^{1}H NMR analysis of the crude products.
[b] Isolated yield.

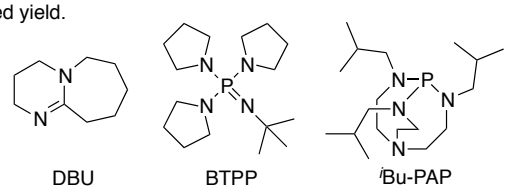
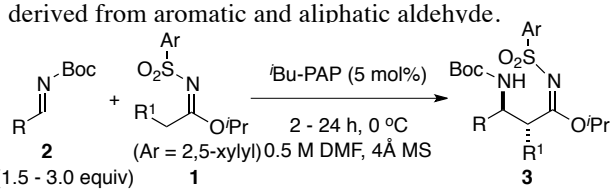


Table 2. Substrate scope: reaction with *N*-Boc imines derived from aromatic and aliphatic aldehyde.



entry	R	R^1	Yield (%)	*anti*/*syn*[a]
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
9[b]	^{t}Bu (**2h**)	Me (**1a**)	87	97/3
10[cd]	^{t}Bu (**2h**)	Me (**1a**)	0	-
11	^{c}Hex (**2i**)	Me (**1a**)	90	92/8
12	^{c}Hex (**2i**)	Et (**1b**)	99	92/8
13	^{i}Pr (**2j**)	Me (**1a**)	64	99/1
14	^{i}Bu (**2k**)	Me (**1a**)	90	89/11
15	^{n}Pr (**2l**)	Me (**1a**)	99	92/8
16	^{n}Bu (**2m**)	Me (**1a**)	95	91/9
17[c]	^{n}Bu (**2m**)	Me (**1a**)	21[a]	91/9

[a] Determined by ^{1}H NMR analysis of the crude product.
[b] 1.5 equiv of imine were used. [c] DBU instead of ^{t}Bu-PAP was used. [d] 20 ºC.

afford the desired adduct in high yield with high selectivity (Table 2, entry 9). However no desired product was obtained when using DBU as the catalyst (Table 2, entry 10). Enolizable aliphatic aldehyde-derived *N*-Boc imines, including linear aliphatic aldehydes, afforded the desired adducts in high yields with high *anti*-selectivity. In contrast to the DBU-catalyzed Mannich-type reactions of sulfonylimidates, ^{i}Bu-PAP showed high catalytic activity for both aromatic and aliphatic aldehyde-derived *N*-Boc imines. I then conducted a mechanistic investigation of ^{i}Bu-PAP-catalyzed reactions of sulfonylimidates. To clarify the reaction profile of the ^{i}Bu-PAP-catalyzed Mannich-type reaction, especially in the early stage, I monitored the reaction using a MIcro-Channeled Cell for Synthesis monitoring (MICCS) (Figure 1). The profiles of the initial stages of the ^{i}Bu-PAP-catalyzed reaction are summarized in Figure 2. While DBU was used as a base promoter, a linear relationship between time and conversion was observed (Figure 2, dashed line (□))**,** Figure 2, continuous line (◆) provides confirmation that the ^{i}Bu-PAP-catalyzed reaction had a clear induction period. A possible explanation for the induction period may be slow deprotonation of the α-hydrogen of the sulfonylimidate due to steric hindrance associated with ^{i}Bu-PAP. Based on this consideration, we changed the addition order of the substrates in the MICCS-NMR analysis. When *N*-Boc imine was the last reagent added (Figure 2, dotted line (△)), the reaction proceeded notably faster than for the reaction in which ^{i}Bu-PAP was added last. In the case of experiment (c) (△) no induction period was observed. This result also suggests that slow deprotonation of the α-hydrogen of the sulfonylimidate is the main reason for the induction period. This acceleration was also observed in the reactions with several *N*-Boc imines derived from aromatic and aliphatic aldehydes. The mechanistic study indicated that the ^{i}Bu-PAP worked as an initiator of these reactions; this could suppress undesired side reactions, for example, in cases where *N*-Boc imines derived from aliphatic aldehydes were employed.

Figure 1. MICCS

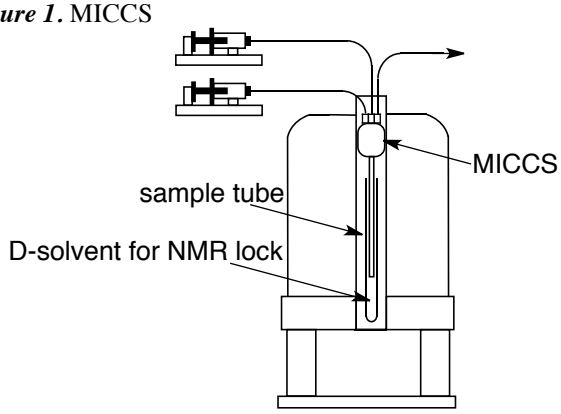
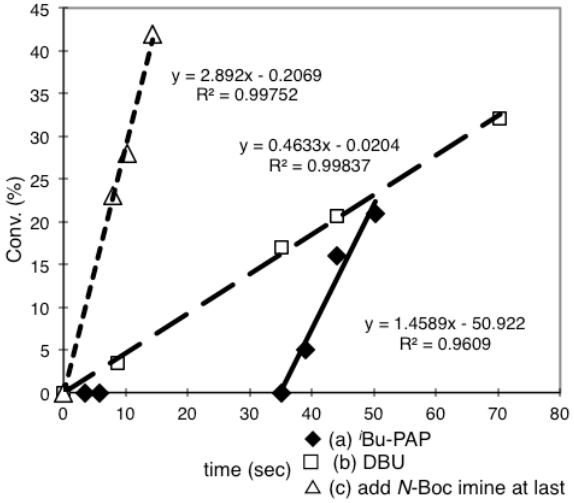


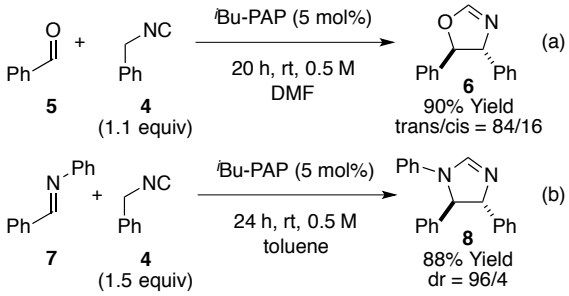
Figure 2. Reaction profile with varying bases monitored by ^{1}H MICCS-NMR spectroscopy.



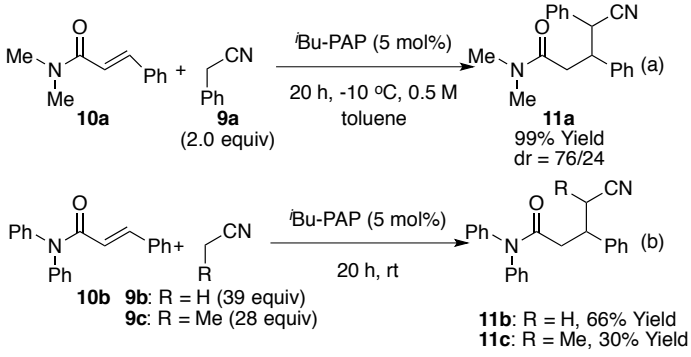
2. Development of Organosuperbase-Catalyzed Addition Reactions of Isonitriles and Nitriles as Nucleophiles.

Having investigation ^{i}Bu-PAP-catalyzed Mannich-type reactions of sulfonylimidates as nucleophiles, I next applied organosuperbase chemistry to addition reactions of less reactive substrates. While isonitrile (isocyanide) and nitrile are stable and offer synthetic versatility, there are few examples of the use of isonitriles or nitriles bearing no electron-withdrawing groups such as COR and CN at α-position due to the high pKa value of isonitrile or nitrile α-hydrogen. I conducted the reactions using isonitriles or nitriles as nucleophiles *via* activation of the generally inactive α-hydrogens by employing organosuperbases as catayst. The reaction of benzylisonitrile (pKa = 27.4) (**4**) with benzaldehyde (**5**) in the presence of ^{i}Bu-PAP (5 mol%) afforded the heterocyclic product, 2-oxazoline, in high yield with good selectivity (Scheme 1, (a)). Benzylisonitile (**4**) also reacted with the benzaldehyde-derived *N*-Ph imine (**7**) to afford the heterocyclic product, 2-imidazoline, in high yield with high selectivity (Scheme 1, (b)). These are rare examples of organosuperbase-catalyzed cycloaddition reactions of benzylisonitrile as a nucleophile for the synthesis of 2-oxazoline and 2-imidazoline. Furthermore, nitriles bearing no electron-withdrawing groups at its α-position, which are less reactive substrates, were successfully employed in the organosuperbase-catalyzed Michael reactions. Compared to simple non-activated nitriles, the relatively reactive benzylnitrile (pKa = 21.9) (**9a**) reacted with *N*,*N*-dimethylcinnamamide (**10a**), an α,β-unsaturated amide, to afford the desired adduct in high yield with good selectivity (Scheme 2, (a)). On the other hand, in the case of using less reactive acetonitrile (pKa = 31.3) (**9b**) or propionitrile (pKa = 32.5) (**9c**), as nucleophiles, the reactions proceeded to afford the desired adducts in moderate yields respectively (Scheme 2, (b)).

Scheme 1. Organosuperbase-catalyzed cycloaddition reactions of benzylisonitriles.



Scheme 2. Organosuperbase-catalyzed Michael reactions of nitriles.



Conclusion

In conclusion, by using oraganosuperbases as catalysts, less reactive substrates such as ester equivalents, isonitriles and nitriles were catalytically activated *via* deprotonation of an α-hydrogen and directly employed as nucleophiles for carbon-carbon bond forming Mannich-type reactions, cycloaddition and Michael reactions.