論文の内容の要旨

Development of Strong Brønsted Base–catalyzed Addition Reactions of Weakly Acidic Compounds via Product Bases
(生成物の塩基性に着目した強塩基触媒による低酸性化合物の付加反応の開発)

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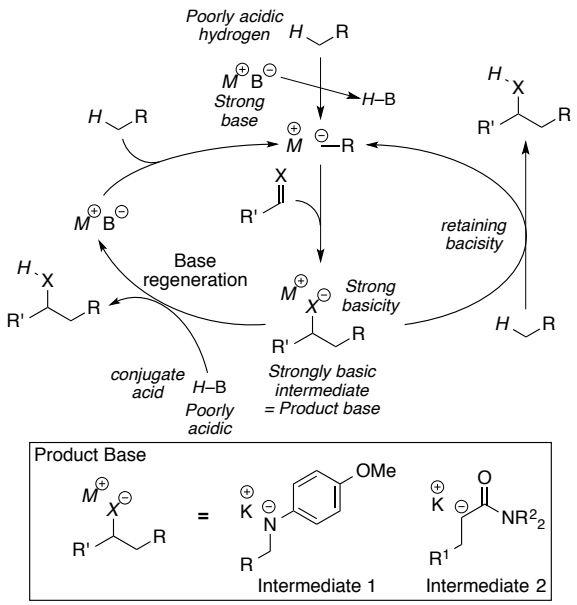
Introduction

Catalytic carbon-carbon (C–C) bond forming reactions are one of the most fundamental and promising methods for construction of complex organic molecules. Especially, Brønsted base catalyzed C–C bond forming reactions are very useful from the viewpoint of atom economy because the reactions proceed under simple proton transfer conditions. Up to now, many kinds of the catalytic reactions including asymmetric variants of it have been reported. Although there are many examples using relatively acidic nucleophiles such as nitromethane, only few reports to use poorly acidic nucleophiles have been investigated. A problem of the reactions using poorly acidic nucleophiles in Brønsted base catalyzed reactions is inactivity of a hydrogen of the pronucleophiles under mild basic conditions, and only strong Brønsted base species such as LDA can accomplish efficient deprotonation of the poorly acidic hydrogen. However, examples of strong Brønsted base catalyzed reactions have been rarely reported to date because the reactions have a problem in the catalytic cycle. The problem is that a base regeneration step hardly proceeds in the catalytic cycle due to poor acidity of a conjugated acid and weak basicity of a reaction intermediate, and the reaction gives the desired product theoretically in a stoichiometric manner. Thus, the most reliable methods for the formation of C–C bond from the poorly acidic compounds is to employ a stoichiometric amount of strong Brønsted base as a mediator



Scheme 1. Plausible Catalytic Cycle of Strong Brønsted Base Catalyzed Reaction

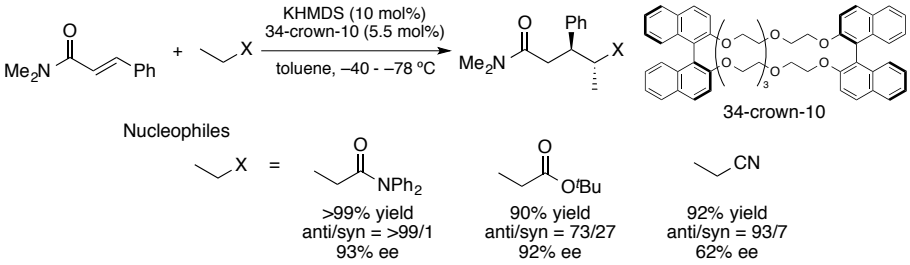
of deprotonating appropriate hydrogen. In order to improve the atom-economy of the reactions using the poorly acidic compounds, we focused on basicity of the reaction intermediate. If a strongly basic reaction intermediate (= product base) appeared after nucleophilic addition, the product base could deprotonate the hydrogen of the conjugated acid or poorly acidic hydrogen in the next nucleophile. Previously, we designed the product base to have strongly basic amide part, and have I investigated catalytic Mannich-type reactions of simple esters *via* the intermediate 1 in my master thesis. In my PhD. thesis, I focused on development of new electrophiles that give strongly basic product base and catalytic reactions using poorly acidic pronucleophiles.

1. Catalytic Asymmetric 1,4-Addition Reactions of Amides and Esters

Carbonyl moieties are contained in wide range of natural products and pharmaceuticals, and it is very important to introduce them stereoselectively. Aldehydes and Ketones are well known carbonyl nucleophiles under proton transfer conditions, and asymmetric variant of them have been developed broadly. On the other hand, the examples of amides and ester have rarely appeared to date because of poor acidities of a α-hydrogen of these carbonyl compounds. As far as we know, there is only one report of catalytic reaction using simple amide as a nucleophile reported by our group previously. However, the available nucleophiles are limited to ketone and amide, and the enantioselectivity of the reaction was moderate. Thus, I focused on a general method to accomplish catalytic asymmetric reactions using poorly acidic carbonyl and related compounds, amides, esters and alkylnitriles.

First of all, I designed the catalytic reactions using poorly acidic amides. A key to the catalytic reactions was strongly basic reaction intermediate. In this time, I focused on α,β-unsaturated carbonyl compounds as new candidates of electrophiles because the basicity of the reaction intermediate, metal enolate, could be determined the structure of the carbonyl moiety. As the results of the electrophile screening, only α,β-unsaturated amide gave the desired product in high yield in the catalytic 1,4-addtion reactions using poorly acidic amides.

Then, I tried to develop catalytic asymmetric 1,4-addition reactions using amides. As I mentioned above, I already reported racemic variant of it. The enantioselective reactions could be possible if a catalytic amount of a chiral ligand that is coordinated to metal center was introduced in the reactions. Consequently, I found a chiral macro crown ether, (*R, R*)-Binaphtho-34-crown-10, and KHMDS catalyst system gave the desired 1,4-adduct in excellent yield with excellent diastereo- and enantioselectivities after screening of chiral crown ether, and the system could be applicable to various kind of α,β-unsaturated amide including aliphatic amide with keeping stereoselectivities. In addition, other poorly acidic carbonyl and related compounds, ester and nitrile, was also good pronucleophiles of the catalytic asymmetric 1,4-addition reactions to afford the desired adduct in high yield with good to excellent stereoselectivities. The amide moieties of the desired 1,4-adduct were converted to other functional groups selectively, and the 1,4-adduct was good starting materials of intermediates of natural compounds. The catalyst system could accomplish first example of catalytic asymmetric 1,4-addition reactions of amide.



Scheme 2. Catalytic Asymmetric 1,4-Addition Reactions of Poorly Acidic Carbonyl and Related Nucleophiles

Next, I was interested in the structure of binaphtho-34-crown-10 and KHMDS catalyst system. This catalyst system showed interesting properties about ratio of the binaphtho-34-crown-10 and KHMDS. The catalyst system showed same reactivities and stereoselectivities between 1:1 and 1:2 ratio of binaphtho-34-crown-10 and KHMDS. Judging from these same results, I anticipated the catalyst structure as 1:2 complex of binaphtho-34-crown-10 and KHMDS, and I tried several studies to clarify this expectation. However, results of dynamic ^{1}H

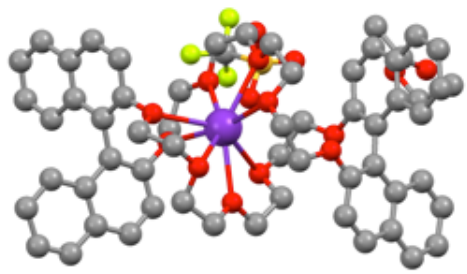


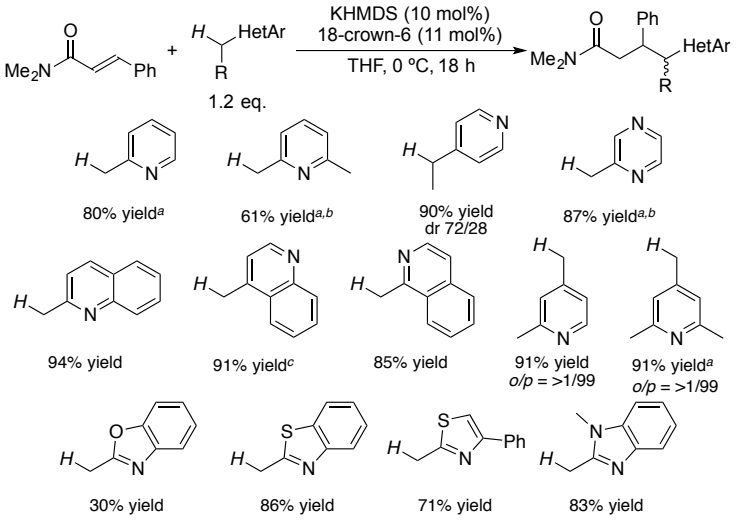
Figure 1. X-ray Crystallographic Structure of KOTf-Binaphtho-34-Crown-10 Complex

NMR and MALDI MS suggested that the structure of the complex be 1:1 complex of binaphtho-34-crown-10 and KHMDS. In addition, crystallographic structure of the 1:2 mixture also indicated 1:1 complex. Thus, the structure of the complex would be 1:1 complex both in solution and crystal.

2. Catalytic 1,4-Addition Reactions of Alkylazaarenes

Azaarenes are one of the most important and versatile structures in alkaloids, and they often shows interesting biological activities *via* coordination of nitrogen atoms into active sites of biomolecules. Therefore, efficient and atom-economical methods to introduce them to complex molecules are highly required. Recently, direct sp^2 C–H activation have been widely developed, and direct introduction of a functional group into azaarenes can be possible *via* cleavage of sp^2 C-H bond of them. However, these methods usually required a stoichiometric amount of an oxidant for completing catalytic cycle. The other method to modify the azaarenes is to use alkylazaarene as a nucleophile *via* activation of a α-hydrogen of the azaarene. In typical methods for the activation of the α-hydrogen, deprotonation of it is common, but the deprotonation always required a stoichiometric amount of strong Brønsted base. Recently, enamine formation of alkylazaarenes by a catalytic amount of Lewis acid have appeared, and this reaction via enamine formation is atom-economical compared to the method of the deprotonation. However, the enamine formation usually requires heating conditions because of high activation energy to cleave the desired sp^3 C–H bond. Thus, we focused on the catalytic reactions using alkylazaarenes in mild conditions with a catalytic amount of a strong Brønsted base catalyst to solve these problems.

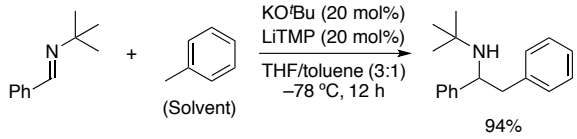
Acidities of alkylazaarenes are almost same as amide and ester, and the catalytic cycle via product base could be achieved in the catalytic 1,4-addition reactions of alkylazaarenes in mild conditions by using similar catalyst system. I found the catalytic reactions using 4-methylpyridine proceeded in the presence of 5 mol% of KHMDS and 18-crown-6, and the catalyst system can be applicable to wide range of α,β-unsaturated amides that had various substituent on the terminal position. The acidities of the alkylazaarenes are the key for the catalytic reactions, and I expected that the catalytic 1,4-addtion reactions using various kinds of alkylazaarenes would be possible, if the acidities of the alkylazaarenes are around 35 in DMSO. Based on this expectation, I started the generality of the nucleophile. Gratifyingly, various kind of alkylazaarenes including benzoxazole, benzothiazole and benzimidazole can work well to afford the desired compound in catalytic manner. The desired 1,4-adduct obtained by the catalytic reaction was easily converted to bioactive compounds by treating under acidic conditions, and the catalytic asymmetric reaction was accomplished by using KHMDS-34-crown-10 catalyst system.



Scheme 3. Catalytic 1,4-Addition Reactions of Alkylazarenes

3. Catalytic Benzylic Additions to Imine Using Alkylarenes

I focused on more poorly acidic nucleophiles in the catalytic reactions than amides, alkylpyridines and so on. Toluene was widely used in organic reactions as a good hydrocarbon solvent and it was inactive in typical reaction conditions. The acidity of benzylic hydrogen of the toluene is ~43 in DMSO and KHMDS and crown ether catalyst system previously I have developed cannot be applicable to the catalytic reactions using toluene. Thus, establishment of very strong Brønsted base is required for the first step of the catalytic reaction. Consequently, I found a mixture of KO^{t}Bu and LiTMP showed very



Scheme 4. Catalytic Benzylic Additions to Imine Using Toluene

strong Brønsted basicity to deprotonate the benzylic hydrogen of toluene after screening of the strong Brønsted bases in stoichiometric reactions. Then, I tried to develop the catalytic reactions using toluene, and I started investigation of electrophiles. *N-tert*-Butyl imine was good electrophiles to show strong basicity in the reaction intermediate, and the basicity of it would be almost same as diisopropylamide and 2,2,6,6-tetramethylpiperazide that was known as very strong Brønsted base. Finally, I succeeded to develop the catalytic benzylic addition using toluene in the presence of a catalytic amount of LiTMP and KO^{t}Bu.

Conclusion

I have developed strong Brønsted base catalyzed reactions using poorly acidic nucleophiles by utilizing the strongly basic reaction intermediates (product base). In the catalytic reactions of carbonyl and related compounds, I accomplished highly stereoselective reactions using binaphtho-34-crown-10 as a chiral ligand. The KHMDS and crown ether catalyst system can be applicable to not only carbonyl compounds but also alkylazaarenes to afford the desired 1,4-adduct in good to high yield in moderate reaction conditions. Finally, I found catalytic benzylic additions using toluene could proceed efficiently in the presence of mix base system of KO^{t}Bu and LiTMP. The product base can broaden the possibility of the catalytic reactions using poorly acidic compounds.