

論文の内容の要旨

Development of Strong Brønsted Base-catalyzed Carbon–Carbon Bond Forming Reactions Using Alkenes

(強塩基触媒によるアルケンを用いた炭素–炭素結合生成反応の開発)

佐藤 維央

Introduction

Alkenes are an important class of starting materials for carbon–carbon (C–C) bond forming reactions, and many types of the reactions have been developed such as addition reactions to C–C double bond, Heck-type reactions, olefin metathesis, allylic C–H functionalizations, and so on. As for activated alkenes such as α,β -unsaturated carbonyl compounds, there are many efficient reactions reported; however, as for less activated alkenes, harsh reaction conditions, stoichiometric amounts of reagents, by-product formation and using of transition metals as catalysts are normally inevitable; therefore, there is still room to improve the reactions from the view point of efficiency and environmental benefits.

Brønsted base-catalyzed C–C bond forming reactions are one of the most efficient methods, because only proton transfer occurs during the process, thus the reactions essentially show high level of atom economy. However, there are severe limitation of an acidity of hydrogen of pronucleophiles ($pK_a \sim 25$). To conquer this limitation, we have developed a strategy by focusing on the basicity of reaction intermediates (Fig. 1).^[a] In our strategy, the reaction intermediates produced by the addition of carbanions to electrophiles are designed to possess strong basicity. These strongly basic reaction intermediates can regenerate the strong base catalysts or generate the next nucleophilic species *via* deprotonation of the conjugate acids or pronucleophiles, respectively; therefore, the desired reaction can proceed with only a catalytic amount of strong base. Based on the strategy, several catalytic C–C bond forming reactions of weakly acidic pronucleophiles such as amides, esters, and so on have been investigated. However, applicable substrates for these reactions are still limited, and

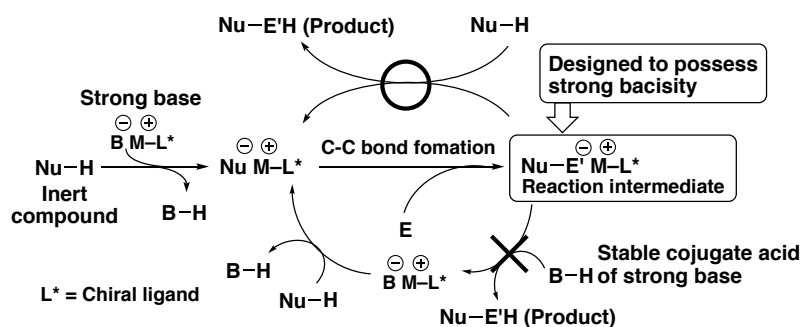


Fig. 1. "Product base" mechanism

Based on the strategy, several catalytic C–C bond forming reactions of weakly acidic pronucleophiles such as amides, esters, and so on have been investigated. However, applicable substrates for these reactions are still limited, and

drastic expansion of this strategy is highly desired to develop efficient catalytic C–C bond forming reactions using less reactive alkenes as starting materials. In my Ph.D. course study, I have developed strong Brønsted base-catalyzed C–C bond forming reactions using less reactive alkenes as both electrophiles and pronucleophiles by newly developed catalytic systems.

1. Catalytic Asymmetric 1,4-Addition Reactions of Amides with α,β -Phosphonates

Although we developed catalytic asymmetric 1,4-addition reactions of several weakly acidic pronucleophiles such as amides, esters, alkyl nitriles, and so on, electrophiles were only limited to α,β -unsaturated amides. On the other hand, phosphonates are often seen in natural products and biologically active compounds, and effective methods for the synthesis of functionalized phosphonates are demanded. After investigations, it was found that α,β -unsaturated phosphonates were attractive and appropriate electrophiles for the catalytic asymmetric 1,4-addition reactions.

(5 年以内に雑誌等に投稿予定のため、該当部分を一部略)

2. Alkyl Potassium-catalyzed Addition Reactions of Alkylarenes with Alkenes

Direct catalytic C–C bond forming reactions of alkylarenes such as toluene and xylene *via* benzylic C–H functionalization is among the most attractive methods for installation of a benzyl moiety into carbon framework, because alkylarenes are generally inexpensive, safe and easy-to-handle compounds, and there is no need of pre-modification of starting materials to more reactive compounds.^[b] However, because of low reactivity of benzylic C–H bond (BDE ~ 90 kcal/mol, $pK_a \sim 43$), these reactions have not been much explored so far. One main approach for the reactions is radical-mediated C–H functionalization of an alkylarene. In this approach, benzylic C–H bond is homolytically cleaved to form a

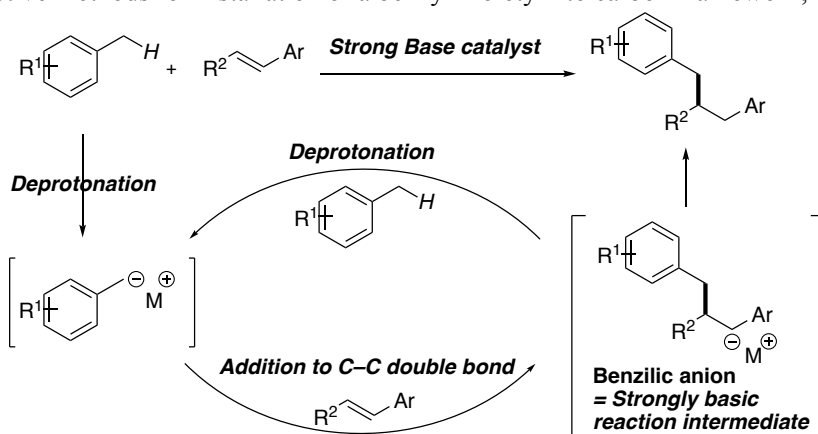
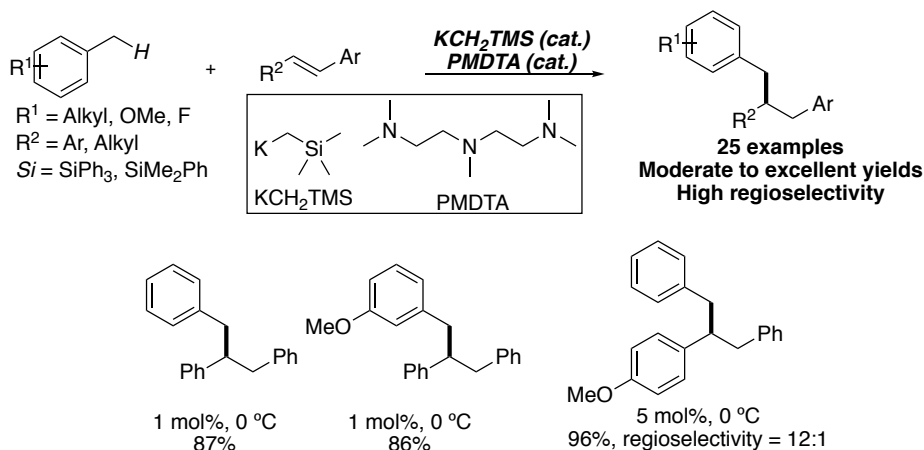


Fig. 2. Catalytic addition reactions of alkylarenes with styrenes

benzylic radical intermediate, then this radical species reacts with an acceptor (normally an electron deficient alkene) to give a product. Recently, combination of this radical intermediate and transition-metal catalysis has been investigated, and also the other approaches such as carbene insertion and Pd- and Ru- catalyzed reactions were reported. However, precious and toxic transition metal and/or harsh reaction conditions are generally required; thus, much milder and efficient reactions are demanded. For this demanding, I hypothesized that strong Brønsted base catalyzed C–C bond forming reactions through benzylic anion intermediates might be a good solution (Fig.2). The key factor for the catalytic reactions was considered that the basicity of the reaction intermediates and the strong Brønsted base catalysts. As for the strongly basic reaction intermediates, quite strong basicity enough to deprotonate less acidic benzylic hydrogens of alkylarenes was considered to be required, then it was assumed that styrene



Scheme 1. Alkyl potassium-catalyzed addition reactions of alkylarenes with alkenes

derivatives could produce such strongly basic intermediates. As for the strong Brønsted base catalysts, it is known that mixture of a KO^tBu/LiTMP (Lithium tetramethylpiperidide) can deprotonate benzylic hydrogen of toluene smoothly at low temperature.^[c] With this hypothesis, the catalytic reaction of toluene with β-phenyl styrene was conducted in the presence of catalytic amounts of KO^tBu/LiTMP to afford the desired product in moderate yield. After intensive investigations, it was found that alkyl potassium as a catalyst minimized the formation of by-products, and I found that, in the presence of a catalytic amount of KCH₂TMS and PMDTA (*N,N,N'*,*N'*,*N'* - pentamethyldiethylenetriamine) as a ligand, the catalytic addition reactions of alkylarenes with β-substituted styrene derivatives proceeded smoothly under mild reaction conditions to afford the target functionalized aromatic compounds in moderate to high yields (Scheme 2). As for nucleophiles, not only toluene, but also several substituted alkylarenes were proper substrates for the reactions. And as for the electrophiles, several unsymmetrical stilbene derivatives showed high yields with high regioselectivities. The lowest catalyst loading was 1 mol% for the reaction of toluene and stilbene, which showed high efficiency of this system.

(5 年以内に雑誌等に投稿予定のため、該当部分を一部略)

3. Catalytic Allylation Reactions of Imines Using Simple Alkenes

(5 年以内に雑誌等に投稿予定のため、非公開)

Conclusion

In my Ph.D. course study, I have developed strong Brønsted base-catalyzed C–C bond forming reactions using less reactive alkenes by focusing on the basicity of reaction intermediates. For the first topic, it was found that α,β-unsaturated phosphonates were appropriate electrophiles for catalytic 1,4-addition reactions of amides. For the second topic, it was revealed that alkyl potassium was an effective catalyst for the catalytic addition reactions of alkylarenes with styrene derivatives to afford the desired functionalized aromatic compounds and silanes in moderate to high yields.

(5 年以内に雑誌等に投稿予定のため、該当部分を一部略)

References

[a] Yamashita, Y.; Kobayashi, S. *Chem. A Eur. J.* **2018**, *24*, 10. [b] Vanjari, R.; Singh, K. N. *Chem. Soc. Rev.* **2015**, *44*, 8062. [c] Fleming, P.; O'Shea, D. F. *J. Am. Chem. Soc.* **2011**, *133*, 1698. [d] Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev.* **2013**, *113*, 5595.