論文の内容の要旨

Development of Novel Carbon-carbon Bond Forming Reactions Utilizing Fluorene Structure

(フルオレン構造を用いた分子活性化法に基づく革新的炭素−炭素結合形成反応の開発)

氏名 松本　正俊

Introduction

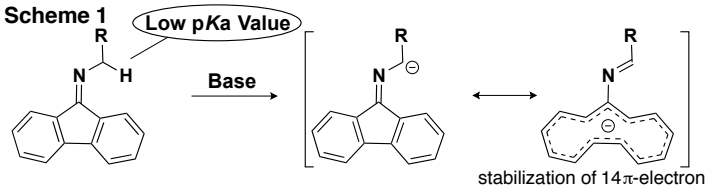
Fluorene, which can be extracted from coal tar, is a molecule possessing fused 6,5,6-ring system. Due to its intriguing features, which include optical and electronic properties, it is expected that fluorene is one of the simplest motifs that can be used as a π-conjugated functional material in industrial and academic researches. Fluorene and its derivatives have been employed as important building blocks in a broad range of materials including light-emitting devices, organic field-effect transistors (OFET), organic photovoltaic cells (OPV), biosensors, etc.　On the other hand, we have focused on the property of the fluorene moiety as a protecting group in organic synthesis.　There are limited reports of synthetic utility, with most literature using the fluorene moiety - 9-fluorenylmethyl carbamate (Fmoc-NR_2) - as a protecting group of amino acids in peptide synthesis.　We expected that this highly conjugated system would show further interesting reactivity, thereby achieving novel organic reactions.

During my Ph.D. studies, I developed new synthetic methods for the functionalization of nitrogen containing compounds.　α-Amino acetonitriles, glycine esters and aldehydes were found to be suitable starting substrates that were protected and activated with the fluorene molecule.

Mannich reactions of α-aminoacetonitriles using fluorenylidene moiety

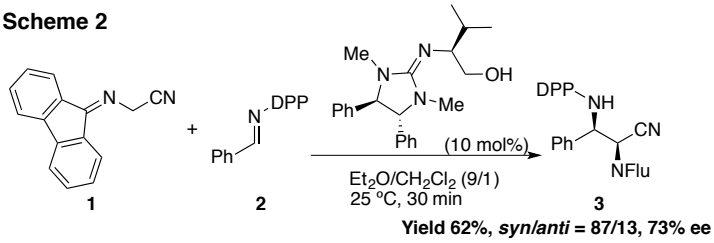
The functionalization of the α-position of α-aminoacetonitriles provides useful compounds in organic synthesis.　The CN functional group can be regard as a synthetic equivalent of amino acid. However, a significant limitation is that the hydrogen on the nitrogen atom is more acidic than that of the desired *α*-position, and so the NH proton is deprotonated preferentially.　Hence, if the reaction is conducted under basic conditions, we cannot utilize the free α-aminoacetonitrile directly.　In order to overcome this issue, I focused on the use of

Scheme 1



9-fluorenylidene as a protecting group of the nitrogen atom and as an activator of the α-position. This is anticipated since the 9-fluorenylidene motif has a great stabilization ability for the corresponding anion by delocalization through the 14π-electron system (**Scheme 1**). We previously developed an efficient synthesis of diamine compounds by Mannich-type reactions of *N*-protected imines, such as *N*-*tert*-butoxycarbonyl (Boc) or N-diphenylphosphinoyl (Dpp) imines[1,2] *via* this activation concept**.** Herein, I described asymmetric Mannich-type reactions using α-aminoacetonitriles with a chiral organobase as a catalyst. I began the optimization process by using fluorenylidene aminonitrile (**1**) with DPP-imine (**2**) in Et_2O/CH_2CH_2 at 25 ºC for 30 min. The reaction proceeded smoothly to provide the desired product in moderate yields with good diastereo- and enantioselectivities (**Scheme 2**). To achieve higher enantioselectivity, many different organobase catalysts were synthesized and tested.

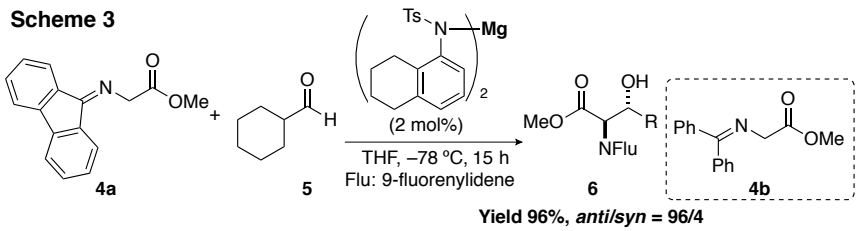
Scheme 2



Aldol reactions of glycine esters using fluorenylidene moiety

The synthesis of *β*-hydroxy-α-amino acids has been widely documented in the literature, and this moiety can be found in numerous natural products. One of the most rapid routes to these products involves the aldol condensation between an *N*-protected glycine and an aldehyde. By using glycine esters, chemists have extensively investigated functionalization methods, especially targeting the α-position, to obtain artificial amino acid core structures. Previous reports from our laboratory using 9-fluorenylidene encouraged us to investigate the direct-type aldol reactions of fluorenylidene-protected glycine Schiff bases. Herein, I describe the development of highly stereoselective aldol reactions using a catalytic amount of base. The reaction proceeded by the addition of an aliphatic aldehyde, cyclohexanecarboxyaldehyde, to a solution of fluorenylidene glycine methyl ester in the presence of 2 mol% base catalyst at –78 ºC for 15 h (**Scheme 3**). When aliphatic aldehydes were utilized, high yields and diastereoselectivities were obtained. Notably, because of the high p*Ka* value of α-hydrogen, the typical glycine Schiff base (**4b**) derived from benzophenone did not work at all under our optimized reaction conditions. This demonstrated that the 9-fluorenylidene moiety showed a higher activation ability than typical protecting groups.

Scheme 3

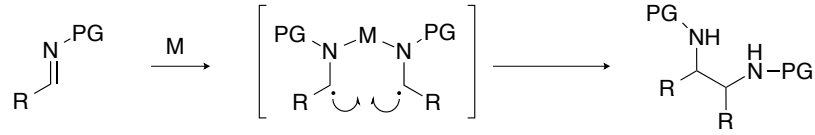


Base catalyzed asymmetric imine-imine coupling reactions using fluorenyl moiety

1,2-Diamines are found as the core framework in numerous chemicals. Due to their incorporation in a huge variety of chemicals and the development of a novel synthetic method to

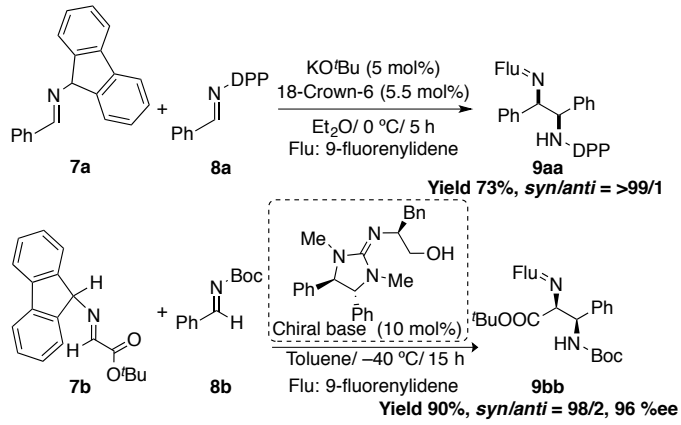
constract the diamine core is important for both academia and industry. Imine-imine coupling is one of the most powerful methods for providing synthetically useful 1,2-diamines in one step. Historically, imine-imine coupling reactions *via* a metal-mediated radical pathway (lanthanide, Al, Ti, Zr, In, Zn-Cu, Mn, Li etc.,) are well-known strategies for the construction of diamines (**Scheme 4**). However, there are several drawbacks; the radical-mediated imine-imine coupling is usually difficult to control, with coupling selectivity between homo-coupling and cross-coupling being poor. This is especially true for selective cross-coupling reactions, where there are only a few successful reports. In all previous cases, more than a stoichiometric amount of the metal species is needed, which is unsatisfactory from an atom-economical point of view, as large amounts of waste metals are produced. Therefore, a highly efficient coupling system is greatly sought after. To achieve this goal, I focused on protecting the nitrogen atom of the imine species, specifically with the fluorene moiety, as I have already demonstrated its utility with several reactions. Once the deprotonation of the fluorenyl imine by a base is achieved, nucleophilic attack of the deprotonated species to its partner imine generates a new carbon-carbon bond, and generates the desired diamine. An interesting point of this system is that the reaction proceeds using only a catalytic amount of base, with selectivity of the coupling being extremely high as a result of the reaction mechanism. In addition, this imine-imine coupling reaction occurs through a base-mediated mechanism, and as such is completely novel. Despite the fact that imines are traditionally regarded as electrophiles, in our system, they behave as nucleophiles. As a preliminary study, fluorenylimine (**7a**) and DPP-imine (**8a**) were employed as coupling partners in the presence of 5 mol% of KO^{t}Bu as base in Et_2O at 0 ºC for 5 h. As expected, the cross-coupling product was obtained in good yield and diastereoselectivity (**Scheme 5**). Upon the success of the racemic reaction, I investigated asymmetric catalysis by using a catalytic amount of chiral organobase which previously was employed in our earlier report. Fortunately, chiral guanidines exhibited remarkable enantioinduction (**Scheme 5**). My imine-imine coupling reaction was applicable to 14 different Boc-imines as coupling partners, giving the desired products in excellent yields, diastereoselectivities and enantioselectivities. Finally, the coupling product was successfully converted into a bioactive monobactam - which has reported for monoamine oxidases (MAO) inhibitory activity in living cells - *via* deprotonation and cyclization in good total yield.

Scheme 4



M = Lanthanide, Al, Ti, Zr, In, Zn-Cu, Mn, Li etc.,

Scheme 5



Conclusion

During the course of my Ph.D. studies, the utility of 9-fluorene moiety was investigated. I demonstrated the utility of the 9-fluorene moiety as a protecting and activating group of primary amines. First, the Mannich-type reactions of fluorenone α-aminoacetonitriles with chiral organobases were achieved. Secondly, the aldol reactions of 9-fluorenylidene glycine Schiff bases with a wide range of aldehydes were demonstrated. The desired aldol products were synthesized in high yields in an *anti*-selective manner. Finally, a novel coupling reactions employing different types of imines were accomplished using only a catalytic amount of chiral source as base. The reaction exhibited broad substrate generality with excellent yields, diastereo- and enantioselectivities.

Reference

1. Kobayashi, S.; Yazaki, R.; Seki, K.; Yamashita, Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 5613.
2. Chen, Y. J.; Seki, K.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 3244.