Electroauxiliary-Assisted Sequential Introduction of Two Carbon Nucloephiles on the Same α-Carbon of Nitrogen: Application to the Synthesis of Spiro Compounds

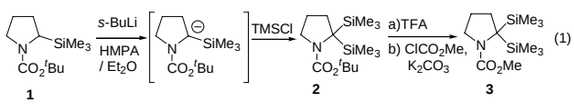
Jun-ichi Yoshida*, Mitsuru Watanabe, and Seiji Suga

Department of Synthetic Chemistry & Biological Chemistry, Graduate School of Engineering, Kyoto University, Kyoto 606-8501

Selective methods for the introduction of organic groups into α-carbon are often central to the synthesis of variety of nitrogen-containing compounds of biological interest. We wish to report a new selective method for the introduction of two organic groups on the same carbon.

Our approach is based on the concept of electroauxiliary.[1] We envisioned that the pre-introduction of two electroauxiliaries on one carbon atom α to nitrogen would lead to the introduction of two organic groups on the same carbon. Thus, pyrrolidine carbamate was chosen as an amine derivative for study because many alkaloids of biological interest have the pyrrolidine skeleton. The trimethylsilyl group was chosen as an electroauxiliary because it is stable and easy to handle. We envisioned that the oxidation of pyrrolidine carbamate having two silyl groups on the same α carbon gives rise to the cleavage of one C-Si bond and the introduction of an organic group. The second oxidation would lead to the cleavage of the second C-Si bond and the introduction of the second organic group on the same α carbon.

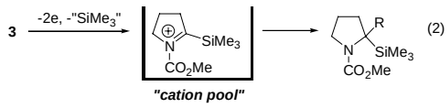
We initiated our study by searching for a straightforward method to introduce two silyl groups on the same α carbon of pyrrolidine skeleton. During extensive screening, we were delighted to find that *N*-*tert*-butoxycarbonyl-2-trimethylsilyl-pyrrolidine **1** prepared by Beak's method was lithiated selectively at the carbon bearing the silyl group by *s*-BuLi in Et_2O with HMPA as an additive. The treatment with TMSCl gave *N*-*tert*-butoxycarbonyl-2,2-bis(trimethylsilyl)pyrrolidine **2** in 100% regioselectivity (eq. 1). No 2,5-bis(trimethylsilyl)-substituted product was obtained. The use of TMEDA in place of HMPA resulted in completely opposite regioselectivity.



(1)

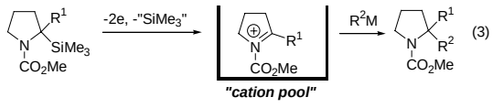
Compound **2** was converted into *N*-methoxycarbonyl- 2,2-bis(trimethylsilyl)pyrrolidin **3**, which is more suitable for the electrochemical oxidation, by the deprotection using TFA and the reaction with methyl chloroformate.

Sequential introduction of two carbon nucleophiles to **3** was studied using the electrochemical method. We employed the "cation pool" method,[2] which involves generation and accumulation of *N*-acyliminium ion at low temperature and subsequent direct reaction with carbon nucleophiles. This one-pot method has an advantage over the conventional processes because nucleophiles that might be otherwise oxidized during an in situ process, such as organo magnesium, zinc, and aluminum reagents can be used without any difficulty. Thus, the oxidation of **3** was carried out at -78 °C in the absence of nucleophile and the resulting 2-silylpyrrolidinium ion was allowed to react with nucleophiles, such as allyltrimethylsilane or homoallylmagnesium bromide to obtain the corresponding coupling products (eq. 2).



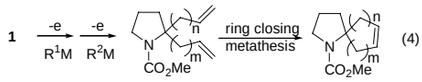
(2)

In the next step, coupling products were again oxidized using "cation pool" method to introduce the second carbon nucleophiles (eq. 3). Although it was difficult to introduce alkenyl group using vinyl magnesium bromide, the use of vinyl zinc reagent resulted in the satisfactory yield. Lower basicity of organozinc reagent seems to be responsible for smooth reaction.



(3)

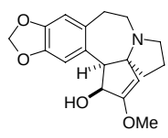
In order to demonstrate the synthetic potential of this strategy, we combined the present sequential transformation with ring closing metathesis[3] to synthesize of nitrogen containing spiro compounds having pyrrolidine skeleton (eq. 4).



(4)

Ring closing metathesis is one of the most powerful and reliable approaches to construct a ring system from diolefin. Pyrrolidine derivatives having two olefinic groups were successfully converted to spiro compounds using Grubbs's catalyst in high yields. Thus, the sequential transformation of **3** followed by ring closing metathesis proved to be a powerful and straightforward access to nitrogen-containing spiro compounds.

The present approach has been successfully applied to the synthesis of cephalotaxine,[4] which is the parent compound of the antileukemicactive harringtonines, a group of uniquely structured pentacyclic alkaloids having a nitrogen containing spiro system.



Cephalotaxine

1. Yoshida, J.; Nishiwaki, K. *J. Chem. Soc., Dalton Trans.* **1998**, 2589
2. Yoshida, J.; Suga, S. *Chem. Eur. J.* **2002**, *8*, 2650.
3. Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413.
4. Tietze, L. F.; Schirok, H.; Wöhrmann, M. *Chem. Eur. J.* **2000**, *6*, 510.