

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

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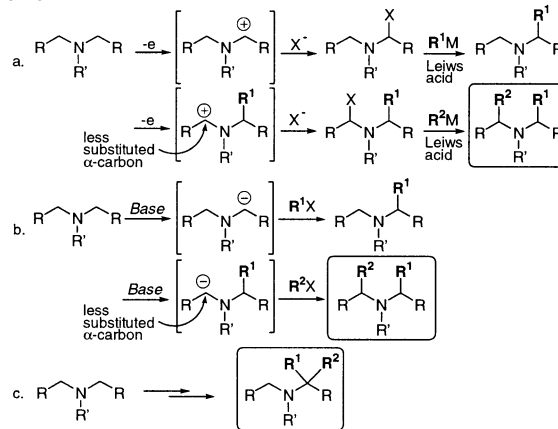
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Selective methods for functionalizing carbons alpha to nitrogen are often central to the synthesis of a variety of nitrogen-containing compounds of biological interest. There are two basic methods to achieve this type of transformation. Oxidative introduction of a hetero nucleophile to the α -position followed by the Lewis acid-promoted generation of an iminium ion and subsequent reaction with a carbon nucleophile (Scheme 1a) is efficient and useful.¹ The electronically inversed method, that is, deprotonation at the α -position followed by reaction with a carbon electrophile (Scheme 1b) is also powerful.² Although these methods are widely utilized in organic synthesis, the introduction of two organic groups on the same α -carbon (Scheme 1c) still remains as a challenging task. The oxidative deprotonation usually takes place at the less substituted α -carbon.¹ Therefore, the second organic group is introduced to the α -carbon different from the carbon to which the first organic group has been introduced (Scheme 1a). The base-promoted deprotonation also takes place at the less substituted α -carbon (Scheme 1b).³ Therefore, the development of a selective method for the introduction of two organic groups on the same carbon is highly called for. We report here a solution to this problem.

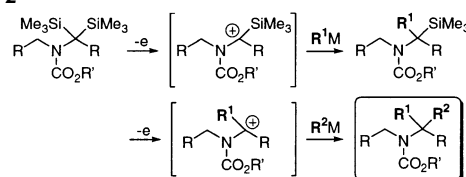
Our approach is based on the concept of an electroauxiliary.⁴ Electroauxiliaries activate substrate molecules toward electrochemical,⁵ photochemical,⁶ and chemical⁷ electron transfer and then control the reaction pathway to bias the formation of desired products. We have already revealed that the preintroduction of an electroauxiliary to a carbon alpha to nitrogen gives rise to selective introduction of a nucleophile on the carbon to which the auxiliary has been attached. In connection with our interest in extending the utility of electroauxiliaries, we have recently expanded our focus to use multiple electroauxiliaries.⁸ Thus, we envisioned that the preintroduction of two electroauxiliaries on one carbon atom alpha to nitrogen would lead to the introduction of two organic groups on the same carbon (Scheme 2). Thus, pyrrolidine carbamate was chosen as an amine derivative for study because many alkaloids of biological interest have the pyrrolidine skeleton. The trimethylsilyl group⁵ 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

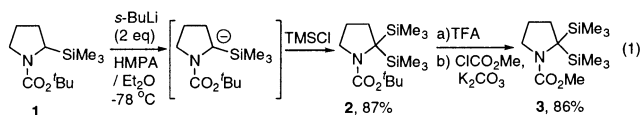
Scheme 1



Scheme 2



by Beak's method⁹ was lithiated selectively at the carbon bearing the silyl group by *sec*-BuLi in Et₂O with HMPA as an additive. The treatment with TMSCl gave *N*-(*tert*-butoxycarbonyl)-2,2-bis-(trimethylsilyl)pyrrolidine **2** in 100% regioselectivity (eq 1).¹⁰ No 2,5-bis(trimethylsilyl)substituted product was obtained. The use of TMEDA in place of HMPA resulted in completely opposite regioselectivity.¹¹ Delicate balance between kinetic (steric) and thermodynamic (stabilization of carbanion by α -silyl group) factors seems to be responsible for these phenomena, although the detailed mechanism is not clear.



Compound **2** was converted into *N*-methoxycarbonyl-2,2-bis-(trimethylsilyl)pyrrolidine **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,¹² 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

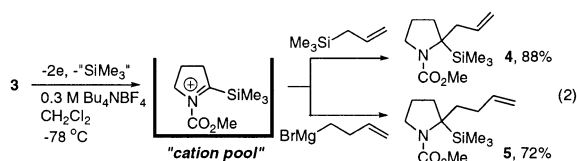
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Table 1. Second Alkylation Using the Cation Pool Method^a and Cyclization Using Metathesis^b

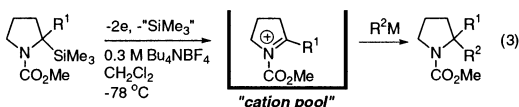
substrate	R ² M	dialkylation product	yield (%)	cyclized product	yield (%)
4	Me ₃ Si-CH=CH ₂		46%		77%
5	Me ₃ Si-CH=CH ₂		67%		86%
5	EtZn-CH=CH(CH ₂) ₃ CH ₃		62%		92%

^a After electrolysis (2.5 F/mol based on the carbamates) at -78°C using a divided cell, to the "cation pool" thus generated was added the carbon nucleophile (2 equiv) to give the product. ^b Reaction was carried out in benzene at room temperature using 5 mol % Grubbs catalyst (bis(tricyclohexylphosphine)benzylideneruthenium (IV) dichloride).^{14a}

that might be otherwise oxidized during an in situ process, such as organo magnesium, zinc, and aluminum reagents can be used without any difficulty.^{12c} Thus, the oxidation of **3** was carried out at -78°C in the absence of a 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).

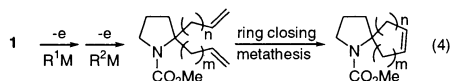


In the next step, **4** and **5** were again oxidized using the "cation pool" method to introduce the second carbon nucleophiles (eq 3, Table 1).



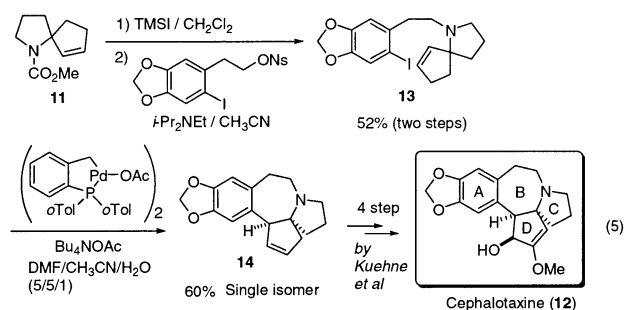
Although it was difficult to introduce the alkenyl group using vinylmagnesium bromide, the use of vinyl zinc reagent¹³ resulted in the satisfactory yield. Lower basicity of the organozinc reagent seems to be responsible for a smooth reaction.^{12c}

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



Ring-closing metathesis¹⁴ is one of the most powerful and reliable approaches to construct a ring system from diolefin. As shown in Table 1, pyrrolidine derivatives having two olefinic groups were successfully converted to spiro compounds using Grubbs 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 (**12**) (eq 5),¹⁵ which is the parent compound of the antileukemic-active harringtonines, a group of uniquely structured pentacyclic alkaloids having a nitrogen-containing spiro system. Thus, the deprotection of compound **11** by TMSI followed by the reaction with 2-(6-iodo-3,4-methylene-dioxyph-



nyl)ethyl 4-nitrobenzenesulfonate^{15d} afforded **13**. Intramolecular Heck-type ring-closing reaction of **13** with palladium catalyst^{15c,16} gave **14** as a single stereoisomer. Because compound **14** is known to be converted to **12** in four steps (75% total yield),¹⁷ a formal total synthesis of **12** was achieved.

In conclusion, the present strategy opens a new aspect of the synthesis of nitrogen-containing compounds having a quaternary carbon center, especially spiro compounds. We are currently expanding our focus to its combinatorial aspects.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data of new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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