

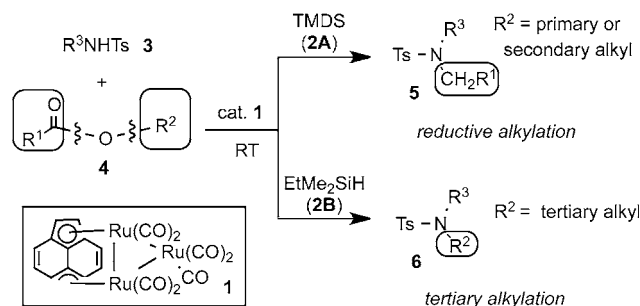
Synthetic Methods

N Alkylation of Tosylamides Using Esters as Primary and Tertiary Alkyl Sources: Mediated by Hydrosilanes Activated by a Ruthenium Catalyst**

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It is well known that alkyl amines are important functional groups in organic chemistry, and exploration of their preparative methods has been a target of current organic synthesis.^[1,2] Although nucleophilic substitution reactions of alkyl halides or sulfonate esters by amines are one of the most straightforward synthetic routes to alkylamines,^[3,4] the alkyl group is often limited to simple primary alkyl groups, and the highly polar nature of the amines causes problematic side reactions, for example, overalkylation and elimination reactions. Two procedures are often used to solve these problems: 1) By using a two-step procedure including N alkylation of amides with alkyl halides or sulfonate esters, with subsequent transformation of the amide function,^[2,5] and 2) the reductive N alkylation of ammonia or amines using ketones or aldehydes as an alkyl source.^[5,6] However, the problem still remains unsolved as described in a recent review by Kan and Fukuyama.^[2] Although preparation of primary and secondary alkyl amines can be achieved by the above procedures, neither nucleophilic substitution nor reductive alkylation provides a general method for the preparation of tertiary alkyl amines.^[7] As summarized in a recent review by Clayden and co-workers,^[8] the rearrangements such as the Curtius rearrangement^[9] and sigmatropic rearrangements^[10] of readily available precursors are practical alternatives, whereas the Ritter reaction,^[11] 1,2-addition of an organometallic reagent to an imine,^[12] and other metal-catalyzed amination reactions^[13] are used for preparation of limited number of amines. Herein we report a unique solution of the problem of N alkylation by using esters as primary and tertiary alkyl sources under mild reaction conditions.

As shown in Scheme 1, the reaction of primary or secondary alkyl esters (**4**; R¹CO₂R² where R² = primary or secondary alkyl) with the combination of a hydrosilane (**2**) and a catalytic amount of the ruthenium complex **1**^[14] in the presence of TsNHR³ (**3**; R³ = H, alkyl) results in the introduction of the primary alkyl group (R¹CH₂) to the nitrogen atom of **3** to give products **5** (“reductive alkylation”). In contrast, the treatment of tertiary alkyl esters (**4**; R¹CO₂R² where R² = tertiary-alkyl) with the same catalyst system



Scheme 1. Two types of N-alkylations with an ester. Ts = 4-toluene-sulfonyl.

under similar reaction conditions results in the cleavage of the O–R² bond of **4**, thus leading to the introduction of the tertiary alkyl group to the nitrogen atom of **3** to give products **6** (“tertiary alkylation”). In other words, introductions of both primary and tertiary alkyl groups to **3** are achieved by simply changing the hydrosilane **2** and the R² group of **4**.

Typical examples of reductive alkylation and tertiary alkylation are shown in Table 1 (see details in the Supporting Information). Treatment of **3a** with Ph(CH₂)₂CO₂Me (**4a'**) in the presence of 1,1,3,3-tetramethyldisiloxane (TMDS; **2A**; 3 equiv) and **1** (1 mol%) at room temperature for 6 hours gave Ph(CH₂)₃NHTs (**5a**) in 96% yield (entry 1). The ethyl ester **4a** also gave **5a** in high yield without over alkylation (entry 2). The isopropyl ester Ph(CH₂)₂CO₂*i*Pr also behaved as a primary alkyl source, but the yield of **5a** was moderate. Interestingly, the reaction of Ph(CH₂)₂CO₂*t*Bu or AcO*t*Bu under similar reaction conditions gave a mixture of **5a** or EtNHTs (**6a''**) and *t*BuNHTs (**6a**). Optimization of the

Table 1: Ruthenium-catalyzed N alkylation.

Entry	TsNH ₂ (3a)		Ester (4)		Products (yield [%]) ^[c]	
	2	R ¹	R ²	4	5	6
1 ^[a]	2A	Ph(CH ₂) ₂	Me	4a'	5a (96)	6a' (0)
2 ^[a]	2A	Ph(CH ₂) ₂	Et	4a	5a (97)	6a'' (0)
3 ^[b]	2B	<i>i</i> Pr	<i>t</i> Bu	4b	5a' (8)	6a (92)
4 ^[b]	2B	<i>i</i> Pr	<i>t</i> Bu	4b	5a' (1)	6a (> 99)

[a] Conducted at RT for 6 h in the presence of **1** (0.0025 mmol), **2A** (0.75 mmol), **3a** (0.25 mmol), and **4a** or **4a'** (0.63 mmol) in CH₂Cl₂.

[b] Conducted at RT for 6 h in the presence of **1** (0.0025 mmol), **2B** (0.75 mmol), **3a** (0.25 mmol), and **4b** (0.5 mmol) in CH₂Cl₂. [c] Yield of isolated product.

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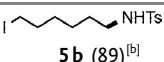
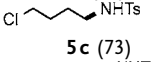
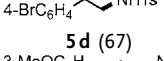
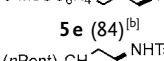
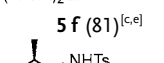
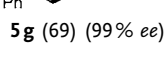
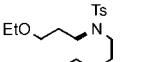
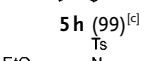
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reaction conditions for tertiary alkylation provided the two results shown in entries 3 and 4 in Table 1. Use of *i*PrCO₂*t*Bu (**4b**) instead of Ph(CH₂)₂CO₂*t*Bu or AcO*t*Bu resulted in the successful increase of the ratio of **5a**/**6a** to 8:92 in the reaction with TMDS (entry 3). Selective preparation of **6a** was achieved by changing the silane from **2A** to EtMe₂SiH (**2B**) as shown in entry 4.^[15]

Representative examples for these two reactions under optimized reaction conditions are summarized in Table 2. For reductive alkylation,^[16] ethyl esters are generally useful as the primary alkyl source, and the alkylated tosylamides **5b–e** were obtained in good yields from the corresponding ethyl esters **4c–g** and **3a**. The reaction is tolerant to halogen groups, and no racemization was observed in the reaction of (*R*)-PhCHMeCO₂Et (**4h**) with **3a**. Selective single alkylation of **3a** was generally accomplished as a result of the significant rate difference between the first alkylation of **3a** to give TsNH(CH₂R¹) and the alkylation of TsNH(CH₂R¹) (**5**) to give TsN(CH₂R¹)₂. The exceptions are MeCO₂Et and EtO(CH₂)₂CO₂Et (**4i**), which is accompanied by double alkylation to give the corresponding TsN(CH₂R¹)₂ as a by-product. Although the rate difference between the first and second alkylations is very large, the high reactivity of **4i** contributes to an increase in the alkylation rate of substituted tosylamides (TsNHR) to the point where the reaction gave two successful

Table 2: Representative examples for reductive N alkylation.^[a]

3	R ³	4	R ¹	Product (yield [%])
3a	H	4c	I(CH ₂) ₅	 5b (89) ^[b]
3a	H	4d	Cl(CH ₂) ₃	 5c (73)
3a	H	4e	4-BrC ₆ H ₄ CH ₂	 5d (67)
3a	H	4f	3-MeOC ₆ H ₄ CH ₂	 5e (84) ^[b]
3a	H	4g	(<i>n</i> Pent) ₂ CHCH ₂	 5f (81) ^[c,e]
3a	H	4h	(<i>R</i>)-Ph(Me)CH	 5g (69) (99% <i>ee</i>) ^[c,d]
3c	<i>n</i> Pent	4i	EtO(CH ₂) ₂	 5h (99) ^[c]
3d	prenyl	4i	EtO(CH ₂) ₂	 5i (99) ^[c]

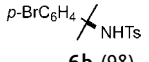
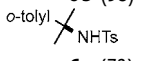
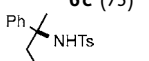
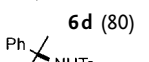
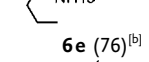
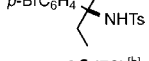
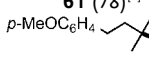
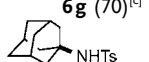
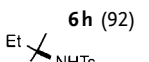
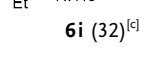
[a] Conducted at RT for 6 h in the presence of **1** (0.0025 mmol), **2A** (0.75 mmol), **3** (0.25 mmol) and **4** (0.63 mmol) in CH₂Cl₂ (0.5 mL). Reported yields are those for the isolated product. [b] Run for 10 h. [c] Run for 20 h. [d] 5 equiv of **4** was used. [e] 2 mol % catalyst was used. See details in the Supporting Information.

examples, that is, the preparation of **5h** and **5i** from the bulky TsNH(*n*Pent) (**3c**) and TsNH(prenyl) (**3d**) substrates, respectively.^[17]

The reaction of *i*PrCO₂R² (R² = tertiary alkyl group) with EtMe₂SiH and **3a** resulted in tertiary alkylations at room temperature as shown in Table 3. The yields of the products are generally high, but the reaction of **4q** gave **6i** in low yield because of the steric bulk, and the E1 reaction of **4q** during the reaction. Steric hindrance of the tertiary alkyl group contributes to the selective single alkylation of **3a** because of the much slower second alkylation of TsNHR². The tosylamide **3b** having a relatively small Me group, however, can be alkylated with **4r** and **4b** under the reaction conditions to give **6k** and **6j**, respectively, in high yields.

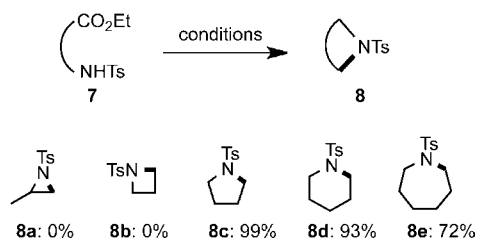
Since azacarboxylic acids are found in a variety of amino acids, alkaloids, and other bioactive molecules, efficient construction of their skeletons is a challenging issue in organic

Table 3: Representative examples for N tertiary alkylation.^[a]

3	R ³	4	R ²	Product (yield [%])
3a	H	4j	<i>p</i> -BrC ₆ H ₄ Me ₂ C	 6b (98)
3a	H	4k	(<i>o</i> -tolyl)Me ₂ C	 6c (73)
3a	H	4l	Ph(Me)EtC	 6d (80)
3a	H	4m	Ph(Me) <i>n</i> PrC	 6e (76) ^[b]
3a	H	4n	<i>p</i> -BrC ₆ H ₄ (Me)EtC	 6f (78) ^[b]
3a	H	4o	<i>p</i> -MeOC ₆ H ₄ (CH ₂) ₂ Me ₂ C	 6g (70) ^[c]
3a	H	4p	adamantyl	 6h (92)
3a	H	4q	Et ₂ MeC	 6i (32) ^[c]
3b	Me	4b	<i>t</i> Bu	 6j (98) ^[c]
3b	Me	4r	PhMe ₂ C	 6k (70) ^[c]

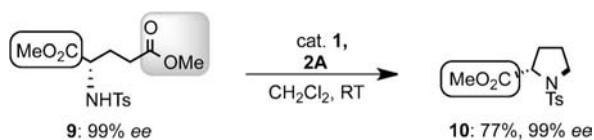
[a] Conducted at RT for 6 h in the presence of **1** (0.0025 mmol), **2B** (0.75 mmol), **3** (0.25 mmol) and **4** (0.5 mmol) in CH₂Cl₂ (0.1 mL). Less than 5% of the reductive alkylation product **5** was produced. Reported yields are those for the isolated product. [b] Run for 10 h. [c] Run for 20 h. See details in the Supporting Information.

synthesis. Intramolecular reductive N alkylation of the amide esters **7** was examined systematically, and five-, six-, and seven-membered azacycles (**8c–e**) were synthesized under the reaction conditions (Scheme 2). Three- and four-membered rings (**8a,b**) could not be formed, even at high temperature.



Scheme 2. Synthesis of azacycloalkanes. Reaction conditions: **1** (0.0025 mmol), **2A** (0.75 mmol), **7** (0.25 mmol), CH₂Cl₂, RT, 20 h. See details in the Supporting Information. Reported yields are those for the isolated product.

One of the interesting applications of intramolecular reductive alkylation is the conversion of the glutamic acid ester **9** into the proline derivative **10** (Scheme 3). To our astonishment, N-tosylated dimethyl glutamate (**9**) easily

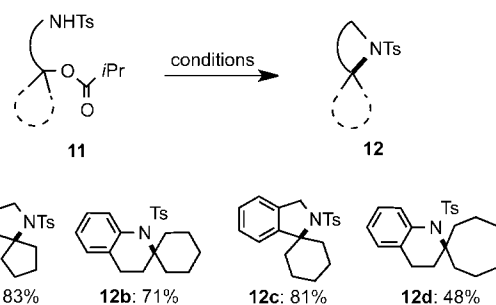


Scheme 3. Chemoselective cyclization of optically active glutamate.

reacts with TMDS in the presence of **1** to give the methyl ester of N-tosylated proline in good yields. No racemization took place during the cyclization. Successful synthesis of the proline derivative is ascribed to the selective reaction of only one of the ester groups with the other remaining intact. It is likely that the ester function very close to N-tosyl group is somehow protected from the reaction towards the ruthenium-catalyzed hydrosilane reduction.

Another challenge for the synthesis of azacarbo-cycles is the construction of the azaspirocycles **12**, which are skeletons often seen in alkaloids.^[18] The compounds **12a–d**, which comprise azaspirocyclic structures, were synthesized in moderate to high yields using **2A** (Scheme 4). These are important skeletons of bioactive compounds.^[19] For example, **12b** is included as a partial structure of a synthetic intermediate for androgen receptor antagonists^[20] and alkaloids such as lilolidine and julolidine derivatives.^[21] Although a number of approaches have been reported for the synthesis of those molecules, the construction of spirocyclic structures from an N-tertiary alkylation reaction with an ester is rare.

In summary, we have developed unique C–N bond-forming reactions by using esters as an alkyl source in the presence of hydrosilanes and a ruthenium catalyst. This reaction is applicable to cyclization reactions producing



Scheme 4. Azaspirocycles. Reaction conditions: **1** (0.005 mmol), **2A** (0.75 mmol), **11** (0.25 mmol), CH₂Cl₂, reflux, 5 h. See details in the Supporting Information. Reported yields are those for the isolated product.

azacarbo-cycles. Additional applications and studies into the mechanism^[22] are currently underway.

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