Synthetic Methods

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

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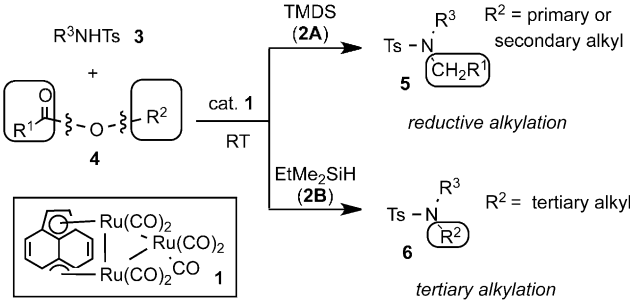
It is well known that alkyl amines are important functional groups in organic chemistry, and exploration of their preparative methods has been a target of current organic synthesis.[1,2] Although nucleophilic substitution reactions of alkyl halides or sulfonate esters by amines are one of the most straightforward 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.

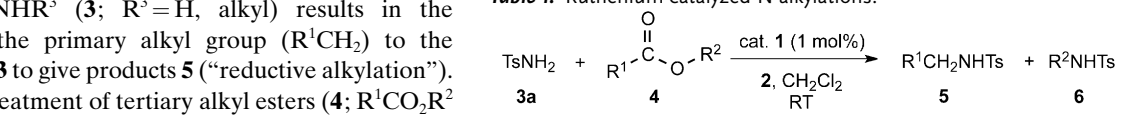
As shown in Scheme 1, the reaction of primary or secondary alkyl esters (**4**; $R^1CO_2R^2$ where R^2 = primary or secondary alkyl) with the combination of a hydrosilane (**2**) and a catalytic amount of the ruthenium complex **1**[14] in the presence of $TsNHR^3$ (**3**; R^3 = H, alkyl) results in the introduction of the primary alkyl group (R^1CH_2) to the nitrogen atom of **3** to give products **5** ("reductive alkylation"). In contrast, the treatment of tertiary alkyl esters (**4**; $R^1CO_2R^2$ where R^2 = tertiary-alkyl) with the same catalyst system under similar reaction conditions results in the cleavage of the O–R^2 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 R^2 group of **4**.



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

Typical examples of reductive alkylation and tertiary alkylation are shown in Table 1 (see details in the Supporting Information). Treatment of **3a** with $Ph(CH_2)_2CO_2Me$ (**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 $Ph(CH_2)_3NHTs$ (**5a**) in 96% yield (entry 1). The ethyl ester **4a** also gave **5a** in high yield without over alkylation (entry 2). The isopropyl ester $Ph(CH_2)_2CO_2iPr$ also behaved as a primary alkyl source, but the yield of **5a** was moderate. Interestingly, the reaction of $Ph(CH_2)_2CO_2tBu$ or $AcOtBu$ under similar reaction conditions gave a mixture of **5a** or EtNHTs (**6a″**) and *t*BuNHTs (**6a**). Optimization of the

Table 1: Ruthenium-catalyzed N alkylations.



Entry	2	R^1	R^2	4	Products (yield [%])[c]	
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*Pr	*t*Bu	**4b**	**5a′** (8)	**6a** (92)
4[b]	**2B**	*i*Pr	*t*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 CH_2Cl_2. [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 CH_2Cl_2. [c] Yield of isolated product.

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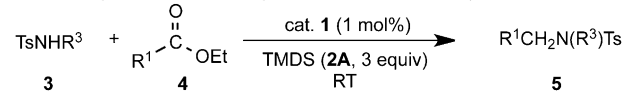
reaction conditions for tertiary alkylation provided the two results shown in entries 3 and 4 in Table 1. Use of iPrCO$_2t$Bu (**4b**) instead of Ph(CH$_2$)$_2$CO$_2t$Bu or AcOtBu resulted in the successful increase of the ratio of **5a′**/**6a** to 8:92 in the reaction with TMDS (entry 3). Selective preparation of **6a** was achieved by changing the silane from **2A** to EtMe$_2$SiH (**2B**) as shown in entry 4.[15]

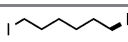
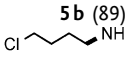
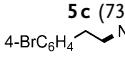
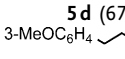
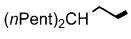
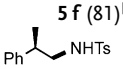
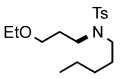
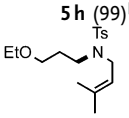
Representative examples for these two reactions under optimized reaction conditions are summarized in Table 2. For reductive alkylation,[16] ethyl esters are generally useful as the primary alkyl source, and the alkylated tosylamides **5b**–**e** were obtained in good yields from the corresponding ethyl esters **4c**–**g** and **3a**. The reaction is tolerant to halogen groups, and no racemization was observed in the reaction of (*R*)-PhCHMeCO$_2$Et (**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(CH$_2$R^1) and the alkylation of TsNH(CH$_2$R^1) (**5**) to give TsN(CH$_2$R^1)$_2$. The exceptions are MeCO$_2$Et and EtO(CH$_2$)$_2$CO$_2$Et (**4i**), which is accompanied by double alkylation to give the corresponding TsN(CH$_2$R^1)$_2$ 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 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 iPrCO$_2$R^2 (R^2 = tertiary alkyl group) with EtMe$_2$SiH 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 TsNHR^2. 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 azacarbocycles are found in a variety of amino acids, alkaloids, and other bioactive molecules, efficient construction of their skeletons is a challenging issue in organic

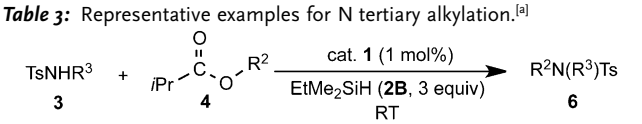
Table 2: Representative examples for reductive N alkylation.[a]

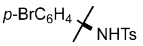
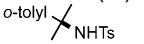
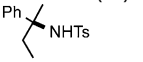
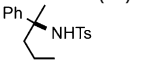
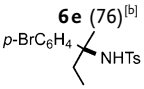
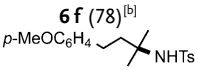
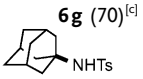
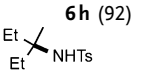
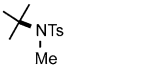
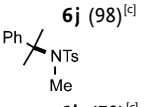


3	R^3	**4**	R^1	Product (yield [%])
3a	H	**4c**	I(CH$_2$)$_5$	 **5b** (89)[b]
3a	H	**4d**	Cl(CH$_2$)$_3$	 **5c** (73)
3a	H	**4e**	4-BrC$_6$H$_4$CH$_2$	 **5d** (67)
3a	H	**4f**	3-MeOC$_6$H$_4$CH$_2$	 **5e** (84)[b]
3a	H	**4g**	(*n*Pent)$_2$CHCH$_2$	 **5f** (81)[c,e]
3a	H	**4h**	(*R*)-Ph(Me)CH	 **5g** (69) (99% *ee*)[c,d]
3c	*n*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 CH$_2$Cl$_2$ (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.

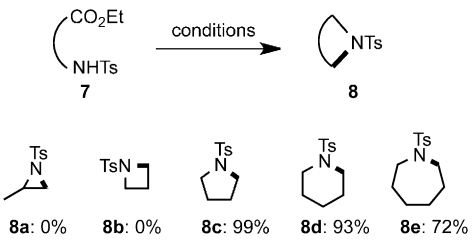
Table 3: Representative examples for N tertiary alkylation.[a]



3	R^3	**4**	R^2	Product (yield [%])
3a	H	**4j**	*p*-BrC$_6$H$_4$Me$_2$C	 **6b** (98)
3a	H	**4k**	(*o*-tolyl)Me$_2$C	 **6c** (73)
3a	H	**4l**	Ph(Me)EtC	 **6d** (80)
3a	H	**4m**	Ph(Me)*n*PrC	 **6e** (76)[b]
3a	H	**4n**	*p*-BrC$_6$H$_4$(Me)EtC	 **6f** (78)[b]
3a	H	**4o**	*p*-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**	*t*Bu	 **6j** (98)[c]
3b	Me	**4r**	PhMe$_2$C	 **6k** (70)[c]

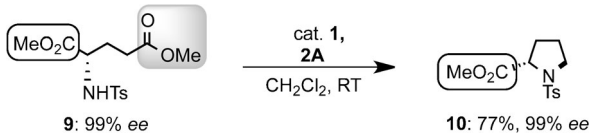
[a] Conducted at RT for 6 h in the presence of **1** (0.0025 mmol), **2B** (0.75 mmol), **3** (0.25 mmol) and **4** (0.5 mmol) in CH$_2$Cl$_2$ (0.1 mL). Less than 5% of the reductive alkylation product **5** was produced. Reported yields are those for the isolated product. [b] Run for 10 h. [c] Run for 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), CH_2Cl_2, 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

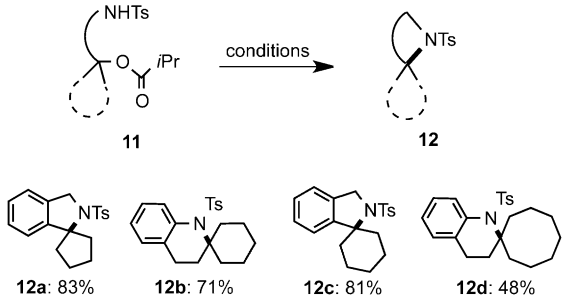


Scheme 3. Chemoselective cyclization of optically active glutamate.

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 azacarbocycles is the construction of the azaspirocycles **12**, which are skeletons often seen in alkaloids.[18] The compounds **12a–d**, which comprise azaspirocycle 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), CH_2Cl_2, reflux, 5 h. See details in the Supporting Information. Reported yields are those for the isolated product.

azacarbocycles. Additional applications and studies into the mechanism[22] are currently underway.

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Keywords: amination · reduction · ruthenium · silanes · synthetic methods

[1] a) S. Patai, *The Chemistry Amino, Nitroso and Related Groups*, Wiley, New York, **1996**; b) R. N. Salvatore, C. H. Toon, K. W. Jung, *Tetrahedron* **2001**, *57*, 7785.
[2] T. Kan, T. Fukuyama, *Chem. Commun.* **2004**, 353.
[3] O. Mitsunobu, *Synthesis* **1981**, 1.
[4] Classical amination reactions via S_N2: a) M. Delépine, *Bull. Soc. Chim. Fr.* **1895**, *13*, S352; b) M. G. Gibson, R. W. Bradshaw, *Angew. Chem.* **1968**, *80*, 986; *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 919.
[5] *Modern Reduction Methods* (Eds.: P. G. Andersson, I. J. Munslow), Wiley-VCH, Weinheim, **2008**.
[6] a) R. F. Borch, A. I. Hassid, *J. Org. Chem.* **1972**, *37*, 1673; b) W. S. Emerson, *Org. React.* **1990**, *14*, 174; c) P. Veeraraghavan Ramachandran, P. D. Gagare, K. Sakavuyi, P. Clark, *Tetrahedron Lett.* **2010**, *51*, 3167; d) T. Gross, A. M. Seayad, M. Ahmad, M. Beller, *Org. Lett.* **2002**, *4*, 2055; e) S. Fleischer, S. Zhou, K. Junge, M. Beller, *Chem. Asian J.* **2011**, *6*, 2240, and references therein.
[7] A Lewis acid promoted S_N1 reaction was reported for the preparation of adamantyl amines: T. Sasaki, A. Nakanishi, M. Ohno, *Chem. Pharm. Bull.* **1982**, *30*, 2051.
[8] J. Clayden, M. Donnard, J. Lefranc, D. J. Tetlow, *Chem. Commun.* **2011**, *47*, 4624.
[9] a) T. Curtius, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 3023; b) T. Curtius, *J. Prakt. Chem.* **1894**, *50*, 275; c) P. A. S. Smith, *Organic Reactions*, *Vol. III*, Wiley, New York, **1946**, p. 337.
[10] Sigmatropic rearrangement leading to tertiary alkylamines: K. C. Majumdar, T. Bhattacharyya, B. Chattopadhyay, B. Sinha, *Synthesis* **2009**, 2117. Also see Ref. [8].
[11] a) J. J. Ritter, P. P. Minieri, *J. Am. Chem. Soc.* **1948**, *70*, 4045; b) L. I. Krimen, D. J. Cota, *Org. React.* **1969**, *17*, 213.
[12] For reviews, see: a) M. Shibasaki, M. Kanai, *Chem. Rev.* **2008**, *108*, 2853; b) S. Kobayashi, H. Ishitani, *Chem. Rev.* **1999**, *99*, 1069.
[13] Csp^3–N bond formation with allylic alcohols as an alkyl source: a) J. Muzart, *Eur. J. Org. Chem.* **2007**, 3077; b) J. He, J. W. Kim, K. Yamaguchi, N. Mizuno, *Angew. Chem.* **2009**, *121*, 10072; *Angew. Chem. Int. Ed.* **2009**, *48*, 9888; c) T. Nishikata, B. H.

Lipshutz, *Org. Lett.* **2009**, *11*, 2377; d) B. Das, P. R. Reddy, C. Sudhakar, M. Lingaiah, *Tetrahedron Lett.* **2011**, *52*, 3521; Csp^3–N bond formation with allylic esters, ethers, carbonates, and nitriles as an alkyl source: e) "Transition Metal Reagents and Catalysts, Innovation": J. Tsuji in *Organic Synthesis*, Wiley, Chichester, **2000**; f) T. Nishikata, B. H. Lipshutz, *Chem. Commun.* **2009**, 6472; g) M. Johannsen, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 1689; h) H. Sajiki, T. Ikawa, K. Hirota, *Org. Lett.* **2004**, *6*, 4977; Hydroaminations of olefins: i) M. Utsunomiya, R. Kuwano, M. Kawatsura, J. F. Hartwig, *J. Am. Chem. Soc.* **2003**, *125*, 5608; Csp^3-H amination: j) S. A. Reed, M. C. White, *J. Am. Chem. Soc.* **2008**, *130*, 3316; k) S. Ueno, R. Shimizu, R. Kuwano, *Angew. Chem.* **2009**, *121*, 4613; *Angew. Chem. Int. Ed.* **2009**, *48*, 4543.

[14] a) K. Matsubara, T. Iura, T. Maki, H. Nagashima, *J. Org. Chem.* **2002**, *67*, 4985; b) S. Hanada, T. Ishida, Y. Motoyama, H. Nagashima, *J. Org. Chem.* **2007**, *72*, 7551; c) H. Nagashima, Y. Kubo, M. Kawamura, T. Nishikata, Y. Motoyama, *Tetrahedron* **2011**, *67*, 7667, and references therein.

[15] O-tertiary butylation: a) H. Liang, S. Ito, M. Yoshifuji, *Org. Lett.* **2005**, *7*, 427; b) A. Procopio, P. Costanzo, M. Curini, M. Nardi, M. Oliverio, R. Paonessa, *Synthesis* **2011**, 73.

[16] For reductive Friedel–Crafts alkylation or acylation with esters, see: a) Y. Nishimoto, S. A. Babu, M. Yasuda, A. Baba, *J. Org. Chem.* **2008**, *73*, 9465; b) N. Sakai, K. Kawana, R. Ikeda, Y. Nakaike, T. Konakahara, *Eur. J. Org. Chem.* **2011**, 3178.

[17] We checked other protecting groups, such as Ns, Ms, Bn, $(PhO)_2P$, and $Ph_2P(O)$, and found that they did not work well. We confirmed that the Ts groups **5a** is easily removed by HBr and AcOH.

[18] For a review, see: J. Dake, *Tetrahedron* **2006**, *62*, 3467.

[19] H.-Y. He, D. J. Faulkner, *J. Org. Chem.* **1991**, *56*, 5369.

[20] L. G. Hamann, R. I. Higuchi, L. Zhi, J. P. Edwards, X.-N. Wang, K. B. Marschke, J. W. Kong, L. J. Farmer, T. K. Jones, *J. Med. Chem.* **1998**, *41*, 623.

[21] A. Palma, J. S. Agredo, C. Carrillo, V. Kouznetsov, E. Stashenko, A. Bashsas, J. Amaro-Luis, *Tetrahedron* **2002**, *58*, 8719.

[22] We currently hypothesize that the reaction mechanism is as follows: We reported earlier the ruthenium-catalyzed hydrosilane reduction of carboxylic acid derivatives in which TMDS is an efficient reducing reagent.[14] The reduction of esters in the presence of 1,3,5-trimethoxybenzene leads to aromatic primary alkylation,[14c] which is explained by electrophilic substitution of intermediary species with the aromatic ring. A similar reaction of electrophilic intermediates with tosyl amides leads to N-primary alkylation. We also reported removal of the *t*Bu esters under reaction conditions similar to those for tertiary alkylation presented in this paper; the heterolytic cleavage of O–*t*Bu is induced by the hydrosilanes activated by **1**. The resulting cationic *t*Bu species is replaced by tosylamide to accomplish tertiary alkylation.[23]

[23] S. Hanada, A. Yuasa, H. Kuroiwa, Y. Motoyama, H. Nagashima, *Eur. J. Org. Chem.* **2010**, 1021.

