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N-Trialkylsilyl Bistrifluoromethanesulfonimides (R_3SiNTf_2) Are Powerful Catalysts for the Highly Efficient α-Amido Alkylation Reactions of Silicon-Based Nucleophiles

Raja Ben Othman, Till Bousquet, Mohamed Othman, and Vincent Dalla*

Unité de Recherche en Chimie Organique et Macromoléculaire, Faculté des Sciences et Techniques de l'Université du Havre, 25 rue Philippe Lebon, BP 540, 76058 Le Havre Cedex, France

vincent.dalla@univ-lehavre.fr

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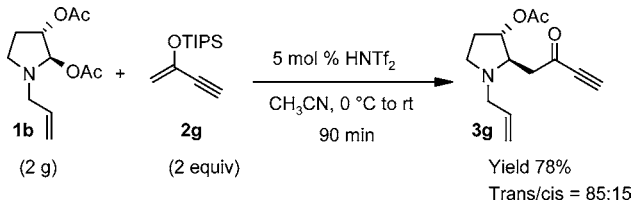
ABSTRACT



In situ formed *N*-trialkylsilyl bistrifluoromethanesulfonimides (R_3SiNTf_2) species have been shown to efficiently catalyze the nucleophilic substitution reactions of chiral 5-oxypyrrolidin-2-ones by silicon-based nucleophiles. The reaction rates were significantly accelerated in comparison to the cases where the usual triflate catalysts are used. Adducts were obtained in high yields and usual stereoselectivities within short reaction times, and the process was compatible with a semipreparative scale.

Recently, the Ghosez and Mikami groups have independently documented the effectiveness of trimethylsilyl bistrifluoromethanesulfonimide (Me_3SiNTf_2) and their trialkylsilyl analogues R_3SiNTf_2 as strong oxophilic Lewis acid catalysts.[1,2] Such reagents, which either can be synthesized before use or prepared in situ by protodesilylation of the precatalyst $HNTf_2$ with a silicon-based olefin, have been recognized to possess substantial better Lewis acidity than their triflate analogues. Subsequently, these reagents appeared to be practical and highly efficient catalysts for various C−C bond forming reactions including 4 + 2 cycloadditions,[1a,2a,b] Mukaiyama aldol[1b,2c,3] and Mukaiyama Michael reactions,[4] 1,2-additions of allylsilanes and alcynylsilanes to aldehydes and acetals,[4] 1,4 additions of allylsilanes to enones,[4,5] C-glycosidation,[4] as well as aromatic electrophilic substitutions[1b] and 2 + 2 cycloadditions between TBS silyl enol ethers and methyl acrylate.[6]

During our continuous research effort in the chemistry of triflates[7] and *N*-acyliminium ions,[8] we have been interested in exploring the competence of the $HNTf_2/R_3SiNTf_2$ systems

(1) (a) Mathieu, B.; Ghosez, L. *Tetrahedron Lett.* **1997**, *38*, 5497. (b) Ishii, A.; Kotera, O.; Saeki, T.; Mikami, K. *Synlett* **1997**, 1145.
(2) (a) Matthieu, B.; Ghosez, L. *Tetrahedron* **2002**, *58*, 8219. (b) Mathieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 9561. (c) Kotera, O.; Motoyama, Y.; Tanaka, Y.; Mikami, K. *Inorg. Chem. Commun.* **1998**, *1*, 10.
(3) Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2001**, 1851.
(4) Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45.
(5) Kuhnert, N.; Peverley, J.; Robertson, J. *Tetrahedron Lett.* **1998**, *39*, 3215.
(6) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2005**, *127*, 3668.
(7) (a) Gasparik, V.; Dalla, V.; Decroix, B. *Synlett* **2002**, 528. (b) Dalla, V.; Decroix, B. *Tetrahedron Lett.* **2002**, *43*, 1657. (c) Tranchant, M.-J.; Dalla, V.; Jabin, I.; Decroix, B. *Tetrahedron* **2002**, *58*, 8425.
(8) (a) Ben Othman, R.; Fousse, A.; Bousquet, T.; Othman, M.; Dalla, V. *Org. Lett.* **2005**, *7*, 2825. (b) Szemes, F.; Fousse, A.; Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. *Synthesis*. In press.

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as catalysts for the α-amido alkylation reactions of weak trialkylsilyl nucleophiles by cyclic *N*-acyliminium ions. Despite the high potential synthetic importance of this process,[9] it is remarkable that the catalytic variant has received so little attention.[8a,10,11] Thus, the development of highly efficient, general, and practical catalytic systems for the α-amido alkylation of silicon-based nucleophiles is greatly desirable, notably for industrial applications. We report herein that R_3SiNTf_2 reagents outperform the catalytic activity of the scarce known catalysts.[8a,10,11] The applicability of this protocol has been demonstrated through the realization of a broad range of reactions, using chiral cyclic *N*-acyliminium ion precursors derived from L-malic acid or succinimide and conventional trialkylsilyl nucleophiles (Figure 1).[12]

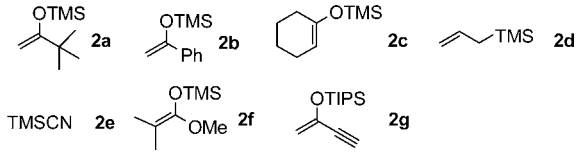
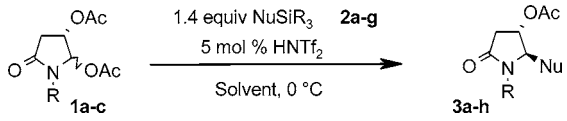


Figure 1. Silicon-based nucleophiles examined throughout this work.

The capacity of Me_3SiNTf_2[12] to efficiently catalyze the nucleophilic substitution reactions of *N*-acyliminium ion precursors was initially investigated through a model reaction between the known diacetoxy lactam **1a**[8b,13] and the trimethylsilyl enol ether derived from pivalone **2a** (Table 1, runs 1−2). Adding 5 mol % of a dichloromethane solution of $HNTf_2$ to a mixture of **1a** and **2a** at 0 °C led to a rapid process to give within 15 min the desired products **3a*t*** and **3a*c*** in good yield and high dr. This reaction could be carried out in either dichloromethane or acetonitrile with equal success (runs 1−2). By direct comparison, the reaction was completed with turnover frequency more than 8 orders of magnitude higher than the TIPSOTf-catalyzed reactions,[8a] confirming that the Lewis acidity of $TMSNTf_2$ outperforms that of the trialkylsilyl triflates.[1a,2a,b,12] Using the optimal conditions (5 mol % $HNTf_2$, $c = 0.25$ M, 0 °C), the reactivity of various trialkylsilyl nucleophiles **2b**−**g** toward 4,5-diacetoxy lactams **1a**−**c** bearing different protecting groups on nitrogen was systematically examined in CH_3CN and CH_2Cl_2 (runs 3−13). Me_3SiNTf_2 showed high applicability and in all circumstances quite better catalytic activity than TIPSOTf.[8a] In general, reactions carried out in CH_2Cl_2 gave higher yields, and equal stereoselectivities, than those performed in CH_3CN (see runs 1 versus 2, 5 versus 6, 7 versus 8, 9 and 12 versus 13) although this trend could be occasionally reversed (runs 10 and 11). For this reason, it is recommended to test both solvents whenever investigating a new reaction with this catalytic system.

The fast transformation achieved even in the reaction of the presumably moderate nucleophile **2g** (runs 10−11) may be the reflection of the higher Lewis acidity of $TIPSNTf_2$ over Me_3SiNTf_2, as previously demonstrated by the Ghosez group.[2b] This R_3SiNTf_2[12] class of catalysts also showed clear advantages in terms of selectivity as no Friedel−Crafts (F−C) adducts were generated in this particular case.[8a] Importantly, the process was compatible with a semipreparative scale, thus opening opportunities for industrial applications. For example, reaction between **1b** and **2g** was successfully achieved on a 2 g scale at 0 °C to provide the

Table 1. α-Amidoalkylations with 4,5-Diacetoxy Lactams **1a**−**c** Derived from L-Malic Acid



run	R	$NuSiR_3$		solvent	time	trans/cis	yield, %[a]
1	Bn	**1a**	**2a**	CH_2Cl_2	15 min	**3a*t*/*c*** >95/5	90
2	Bn	**1a**	**2a**	CH_3CN	30 min	**3a*t*/*c*** >95/5	80
3	Bn	**1a**	**2b**	CH_2Cl_2	15 min	**3b*t*/*c*** 90/10	81
4[b]	Bn	**1a**	**2c**	CH_2Cl_2	1 h	**3c*t*/*c*** >99/1[c]	90
5	Bn	**1a**	**2d**	CH_2Cl_2	15 min	**3d*t*/*c*** 60/40	84
6	Bn	**1a**	**2d**	CH_3CN	15 min	**3d*t*/*c*** 60/40	55
7[d]	Bn	**1a**	**2e**	CH_2Cl_2	15 min	**3e*t*/*c*** 34/66	87
8	Bn	**1a**	**2e**	CH_3CN	15 min		*e*
9[f]	Bn	**1a**	**2f**	CH_2Cl_2	15 min	**3f*t*/*c*** >99/1	86[g]
10[h]	allyl	**1b**	**2g**	CH_3CN	15 min	**3g*t*/*c*** 85/15	82[i]
11[j]	allyl	**1b**	**2g**	CH_3CN	1 h 30	**3g*t*/*c*** 85/15	78
12	PMB	**1c**	**2a**	CH_2Cl_2	15 min	**3h*t*/*c*** >95/5	85
13	PMB	**1c**	**2a**	CH_3CN	15 min	**3h*t*/*c*** >95/5	50

[a] Yield of isolated **3**, after chromatography, from reactions carried out on a 0.4 mmol scale, except for the result in run 11. [b] 1.8 equiv of **2c** was used to guarantee complete conversion. [c] A 3:1 ratio of stereoisomers was formed at the branched enolizable carbon of the cyclic ketone. [d] 2 equiv of **2e** and 9 mol % of $HNTf_2$ were used to guarantee a clean reaction. [e] The hydroxy lactam **4** (not shown) was obtained quantitatively. [f] 9 mol % of catalyst was used to guarantee complete conversion. [g] No reaction in CH_3CN. [h] 2 equiv of **2g** were used to suppress the formation of hydroxy lactam. [i] No reaction in CH_2Cl_2. [j] The reaction was carried out on a 2 g scale.

(9) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.

(10) For recent examples of truly catalytic (catalyst loading <10 mol %) nucleophilic substitution reactions of *N*-acyliminium ion precursors using TMSOTf see: (a) Barrett, A. G. M.; Quayle, P. *J. Chem. Soc., Chem. Commun.* **1981**, 1076. (b) Bernardi, A.; Micheli, F.; Potenza, D.; Scolastico, C.; Villa, R. *Tetrahedron Lett.* **1990**, *31*, 4949. (c) Pilli, R. A.; Dias, L. C. *Synth. Commun.* **1991**, *21*, 2213. (d) Ahman, J.; Somfai, P. *Tetrahedron* **1992**, *48*, 9537. (e) Arndt, H. D.; Polborn, K.; Koert, U. *Tetrahedron Lett.* **1997**, *38*, 3879. (f) D' Oca, M. G. H.; Pilli, R. A.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709. (g) Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477.

(11) Recently, Kobayashi and co-workers reported efficient nucleophilic substitution reactions of methoxy and acetoxy *N*-carbonyl piperidine derivatives by trialkylsilyl nucleophiles catalyzed by 10 mol % of various metal triflates: (a) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989. (b) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809.

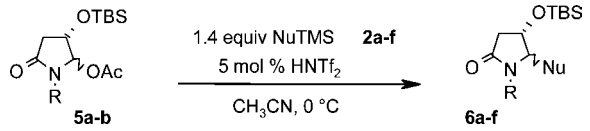
(12) The stepwise formation of Me_3SiNTf_2 by protodesilylation between $HNTf_2$ and either **2b** or **2d** and its subsequent use (5 mol %) to catalyze α-amido alkylations has been realized. The rate and the profile of the reactions compare well with those of the $HNTf_2$ variant (more details are given in the Supporting Information). These results support the occurrence of R_3SiNTf_2 as an active catalyst in the present work, but the possibility that $HNTf_2$ itself also contributes in the mechanism, notably in the first turnover, cannot be ruled out. For similar examples where R_3SiNTf_2 have been claimed to be formed in situ, see refs 1a, 2a, 4, 5, and 6.

(13) Louwrier, S.; Ostendorf, M.; Boom, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1996**, *52*, 2603.

inseparable diastereoadducts **3g*t*** and **3g*c*** in 78% yield (dr = 6:1, run 11). This new α-amido alkylation of a conjugated enolate such as **2g** with chiral *N*-allyl azacycles under catalytic conditions is interesting in its own right and further raises the prospect that combining this process with a ring-closing metathesis could provide a new entry into azabicyclo-[5.3.0]decane scaffolds by entailing two important catalytic reactions as key steps.[14] Finally, this example also demonstrates that the useful allyl protecting group is well tolerated, as also is the PMB group (runs 12−13).[15]

To extend the scope of our process, we next shifted toward examining various 4-*tert*-butyldimethylsilyloxy-5-acetoxy *N*-acyliminium cation precursors **5a**,**b** (Table 2). This more

Table 2. α-Amidoalkylations with 4-*tert*-Butyldimethylsilyloxy-5-diacetoxy Lactams **5a**,**b** Derived from L-Malic Acid



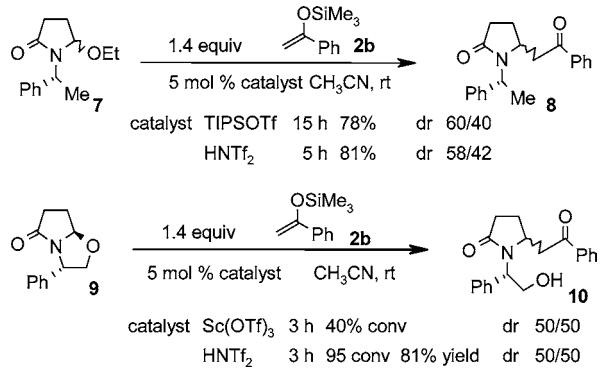
substrate	R	$NuSiR_3$	time, min	yield, %[a]	adduct *trans*/*cis*
5a[b,c]	Bn	**2a**	10	84	**6a*t*** (70), **6a*c*** (14)
5a[b]	Bn	**2c**	30	90	**6b*t*** (76),[d] **6b*c*** (14)[e]
5a	Bn	**2d**	15	82	**6c*t*/*c*** 40/60
5a[f]	Bn	**2e**	15	91	**6d*t*** (33), **6d*c*** (48)
5a	Bn	**2f**	15	55[g]	**6e*t*/*c*** >99/1
5b[b]	PMB	**2a**	15	95	**6f*t*** (75), **6f*c*** (20)

[a] Yield of isolated **6**, after chromatography, from reactions carried out on a 0.4 mmol scale. [b] 10 mol % of catalyst was used and the reaction was carried out in CH_2Cl_2. [c] A complex mixture was obtained in CH_3CN. [d] A 2:1 ratio of stereoisomers was formed at the branched enolizable carbon of the cyclic ketone. [e] A ratio of stereoisomers >95:5 was formed at the branched enolizable carbon of the cyclic ketone. [f] 9 mol % of catalyst and 2.5 equiv of the nucleophile were required to guarantee high yield. [g] This moderate yield was reproducibly obtained although the reaction proceeded cleanly.

hindered class of substrates also displayed high latitude and excellent reactivity toward nucleophiles, as demonstrated by the good yields and short reaction times observed in almost all of the reactions investigated. In contrast to the case of the diacetoxy lactams **1a**−**c**, CH_3CN and CH_2Cl_2 proved complementary solvents with the silyl ethers **5a**,**b**. As previously observed independently by Kobayashi[11b] and us,[8a] no evidence supporting a general substrate enforced stereocontrol was found, and the stereochemical preference of the reaction seems to be mainly governed by the steric demand of the incoming nucleophile.

Finally, the net advantage of the $HNTf_2/Me_3SiNTf_2$ system was clearly demonstrated in the reactions between the weakly reactive pyrrolidinones **7** and **9** bearing chiral auxiliaries at nitrogen[8a] and the trimethylsilyl enol ether derived from acetophenone (Scheme 1). While the reaction of **7** with **2b**

Scheme 1



catalyzed by 5 mol % of TIPSOTf[8a] needed 15 h to reach completion, the Me_3SiNTf_2-catalyzed variant[12] was accelerated by a 3-fold factor to give the expected adduct **8** (two diastereoisomers, 1.5:1 ratio) within 5 h. Also, the bicyclic lactam **9** gave approximately 40% conversion to **10** (two diastereoisomers, 1:1 ratio) after 3 h under guidance of $Sc(OTf)_3$,[11] whereas the amido alkylation catalyzed by Me_3SiNTf_2[12] went almost to completion under the same period of time (see the Supporting Information for more details).

To summarize, we have demonstrated that the $HNTf_2$−R_3SiNTf_2 systems efficiently catalyze the α-amido alkylation of conventional silicon-based nucleophiles by chiral cyclic *N*-acyliminium ion precursors derived from L-malic acid and succinimide. The method also encompasses the presumably weak nucleophilic TIPS enol ether derived from butynone. In terms of catalytic activity, this simple approach outperforms the systems previously known, and harnesses the distinct advantage of trialkylsilyltriflimides to provide a truly practical and environmentally benign class of catalyst for the synthesis of optically enriched azacycles. The high reaction rate displayed by this new amido alkylation procedure is likely to be the result of the outstanding Lewis acidity of R_3SiNTf_2 (and/or Brønsted acidity of $HNTf_2$),[1a,2a,b,12] which contributes to accelerate the *N*-acyliminium ion formation, i.e., the expected rate-limiting step in such reactions.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Such applications have been fully realized in our lab and will be published soon.

(15) The alkylations examined herein afforded comparable stereoselectivities as those catalyzed by TIPSOTf or promoted by conventional Lewis acids; see ref 8a.