

Toward Improving the Chemistry of *N*-Acyliminium Ions: Nucleophilic Substitution Reactions of Pyrrolidinone Derivatives with Trialkylsilyl Nucleophiles Catalyzed by Triisopropylsilyltrifluoromethane Sulfonate (TIPSOTf)

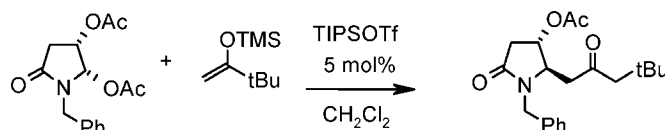
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ABSTRACT



Nucleophilic substitution reactions of racemic and chiral 5-acetoxy-, 5-ethoxy-, and 5-methoxypyrrolidin-2-ones by silicon-based nucleophiles were efficiently catalyzed by TIPSOTf. This process was found to be general and accommodates a broad range of substrate–nucleophile combinations.

Since the discovery by the Speckamp group in the middle of the 1970s that cyclic imides can readily be converted into endocyclic *N*-acyliminium ions,¹ the latter have been involved in an impressive number of synthetic applications, mainly devoted to the synthesis of biologically important nitrogen-containing cyclic compounds.² Of particular interest in this context are the intermolecular nucleophilic substitution reactions of cyclic *N*-acyliminium ion precursors with trialkylsilyl nucleophiles (α -amido alkylations) through activation by a Lewis acid. When classical Lewis acids (BF₃·Et₂O, SnCl₄, TiCl₄, ZnBr₂, ...) are used, stoichiometric

amounts and often more of these reagents are required to achieve synthetically useful results.³ To improve further the potential of these alkylation reactions, the development of processes compatible with the use of reduced amounts of the activator is highly desirable. Trimethylsilyltrifluoromethane sulfonate (TMSOTf) is a peculiar Lewis acid in regard to these nucleophilic substitution reactions of cyclic acyliminium precursors owing to regeneration during the mechanism. Hence, a catalytic version can be envisioned with this promoter. Surprisingly, there have been very few reported examples of such catalytic reactions⁴ since the first report by Barrett and co-workers in 1981.^{4a} Moreover, the

(1) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

(2) (a) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817.
(b) Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem Rev.* **2004**, *104*, 1431.

(3) Acetoxy azetidinones are an exception to this rule and can be alkylated by silicon-based nucleophiles under the catalytic activation of conventional Lewis acids. For a representative example, see: Fuentes, L. M.; Shinkai, I.; Salzmann, T. N. *J. Am. Chem. Soc.* **1986**, *108*, 4675.

Table 1. Effect of Leaving Group^a

run	time	TIPSOTf	yield of 2 (%)	yield of 3 (%)
1	1a 20 min	5 mol %	2a (75)	3a (15) ^b
2 ^c	1a 20 min	5 mol %	2a (75)	3a (15) ^b
3	1a 20 min	2 mol %	2a (75)	3a (17) ^b
4	1b 1 h	5 mol %	2a (75)	3a (17) ^b
5 ^d	1c 12 h	16 mol %	2a (45)	3a (0)
6	1d 20 min	16 mol %	2b (76)	3b (13) ^e

^a Reactions were carried out using **1a** (0.8 mmol) and the silyl enol ether (1.15 equiv), in dichloromethane at 0 °C, unless otherwise noted. ^b The F–C adduct **3b** was obtained as a mixture of either geometrical *Z* and *E* stereoisomers (exclusive *trans* relationship for the substituents located at the C₂–C₃ bond) or as a mixture of *trans* and *cis* stereoisomers (single geometrical isomer for the double bond, *E* or *Z*) in a 4:1 ratio (stereochemistry not determined). ^c The reaction was performed on a 1 g scale. ^d Yield estimated by ¹H NMR spectroscopy on the crude mixture (55% **1c** recovered). ^e The FC adduct **3a** was obtained as a mixture of either geometrical *Z* and *E* stereoisomers (exclusive *trans* relationship for the substituents located at the C₂–C₃ bond) or as a mixture of *trans* and *cis* stereoisomers (single geometrical isomer for the double bond, *E* or *Z*) in a 4:1 ratio (stereochemistry not determined).

number of truly catalytic reactions (≤ 10 mol %) is few.^{4a,c,g–i,l} A landmark contribution has been recently made by the Kobayashi group, who studied the effect of several metal triflates (10 mol %) in such reactions using mainly 2-methoxy and 2-acyloxy piperidine derivatives as acyliminium cation precursors.⁵

On the other hand, TMSOTf is a very air- and moisture-sensitive reagent that must be used freshly distilled. This drawback of the TMSOTf reagent causes a severe limitation from a practical point of view. As a result of its superior stability, we realized that TIPSOTf could be advantageously used in place of its TMS analogue in such catalytic nucleophilic substitution reactions.⁶ This idea capitalizes on recent observations made by Ghosez and co-workers in the

Table 2. Reactions with Various Nucleophiles

run	NuSiR ₃ (equiv)	time (min)	product (2)	yield (%)
1	CH ₂ =C(Ph)(OSiMe ₃)(1.17)	15	2c (Nu = CH ₂ COPh)	89
2	CH ₂ =C(<i>t</i> -Bu)(OSiMe ₃)(1.17)	15	2d (Nu = CH ₂ CO <i>t</i> -Bu)	87
3 ^a	CH ₂ =CHCH ₂ SiMe ₃ (1.2)	30	2e	88
4	NCSiMe ₃ (1.17)	15	2f (Nu = CN)	82
5 ^b	HSiEt ₃ (1.17)	150	2g (Nu = H)	87
6 ^{b,c}	CH ₂ =C(OMe)(OTBS)(1.4) ^{b,c}	40	2h (Nu = CH ₂ CO ₂ Me)	45
7 ^b	Me ₂ C=C(OMe)(OSiMe ₃)(1.4)	720	no reaction	

^a 5 mol % of TIPSOTf was used. ^b The temperature was slightly raised to room temperature. ^c Total consumption of **1a** was achieved; a second product (unidentified) was formed.

context of [4 + 2] cycloaddition reactions of dienes with enoates. They demonstrated that *N*-triisopropylsilyltrifluoromethane sulfonimide ^tPr₃SiNTf₂ exhibits higher Lewis acidity than its trimethylsilyl analogue.⁷ By analogy, we anticipated that the high bulkiness of TIPSOTf would not impede the formation of *N*-acyliminium ions and that low catalyst loading (<10 mol %) may be envisioned regarding its presumed high Lewis acid properties. We report herein efficient nucleophilic substitution reactions of various racemic and optically pure five-membered ring *N*-acyliminium ion precursors using TIPSOTf as a catalyst.⁸ The scope of the process has been demonstrated by the evaluation of a large array of donor–acceptor combinations.

We selected lactam derivatives **1a–d** (Tables 1 and 2), **4a–d** (Table 3), and **7a–d** (Table 4) as acyliminium cation precursors. They were synthesized by conventional methods. 5-Acetoxy lactams **1a** and **4a–d** were prepared using our one-pot reduction-acetylation sequence.⁹

At the outset, we chose the 3,4-fused benzo *N*-allyl-5-acetoxy pyrrolidinone **1a** as one of the simplest acyliminium cation precursors and the triisopropylsilyl enol ether derived from butynone as a nucleophile to verify the competence of TIPSOTf as a catalyst¹⁰ (Table 1).

We were pleased to observe that, in the presence of only 5 mol % of TIPSOTf, **1a** was totally consumed within a

(4) (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) Morimoto, Y.; Nishida, K.; Hayashi, Y.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 5773. (f) Morimoto, Y.; Iwashita, M. *Synlett* **1995**, 1221. (g) Pilli, R. A.; Russowsky, D. *J. Org. Chem.* **1996**, *61*, 3187. (h) Louwrier, S.; Ostendorf, M.; Boom, A.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1996**, *52*, 2603. (i) Arndt, H. D.; Polborn, K.; Koert, U. *Tetrahedron Lett.* **1997**, *38*, 3879. (j) D'Oca, M. G. M.; Pilli, R. A.; Vencato, I. *Tetrahedron Lett.* **2000**, *41*, 9709. (k) Sugiura, M.; Kobayashi, S. *Org. Lett.* **2001**, *3*, 477. (l) Sugiura, M.; Hagio, H.; Hirabayashi, R.; Kobayashi, S. *Synlett* **2001**, 1225. (m) Mikami, K.; Ohmura, H. *Chem. Commun.* **2002**, 2626. (n) El-Nezhawy, A. O. H.; El Diwani, H. I.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 4137. (o) Maldaner, A. O.; Pilli, R. A. *Synlett* **2004**, 1343.

(5) (a) Okitsu, O.; Suzuki, R.; Kobayashi, S. *Synlett* **2000**, 989. (b) Okitsu, O.; Suzuki, R.; Kobayashi, S. *J. Org. Chem.* **2001**, *66*, 809.

(6) When carefully stored under argon at –20 °C, we observed that TIPSOTf could be used with equal success over several months.

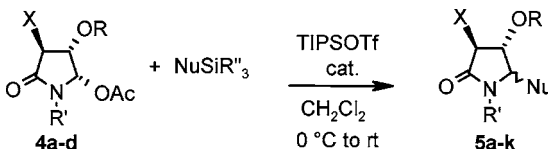
(7) Matthieu, B.; de Fays, L.; Ghosez, L. *Tetrahedron Lett.* **2000**, *41*, 9561.

(8) We are aware of one example of the use of TIPSOTf as catalyst (5 mol %) in a vinylogous Mannich reaction between a highly substituted 2-OTMS-furan derivative and *N*-BOC-2-methoxy proline methyl ester to give the adduct in a poor yield of 32%. See: (a) Martin, S. K.; Barr, K. J. *J. Am. Chem. Soc.* **1996**, *118*, 3299. (b) Martin, S. K.; Barr, K. J.; Smith, D. W.; Bur, S. K. *J. Am. Chem. Soc.* **1999**, *121*, 6990.

(9) Szemes, F.; Fousse, A.; Ben Othman, R.; Bousquet, T.; Othman, M.; Dalla, V. Unpublished results.

(10) Preliminary mechanistic experiments tend to suggest that TIPSOTf does not dissociate and by the way is the real catalyst in the process; more details are given in Supporting Information.

Table 3. Reactions of Enantiopure Acyliminium Cation Precursors. I. 5-Acetoxy Lactams Derived from L-Malic- and L-Tartaric Acids

					
run	NuSiR'3 (equiv)	4	TIPS-OTf (mol %)	time	5 yield % (t/c ^a)
1	CH ₂ =C(Ph)(OSiMe ₃)(1.4)	4a	5	2 h 30	5a 77 (83/17)
2	CH ₂ =C(Ph)(OSiMe ₃)(1.4) ^b	4a	5	2 h 30	5a 64 (90/10)
3	CH ₂ =C(<i>t</i> -Bu)(OSiMe ₃)(1.4)	4a	5	4 h	5b 74 (>97/3)
4	CH ₂ =C(C≡CH)(OSi ⁱ Pr ₃)(1.5) ^c	4b	5	2 h 30	5c 50 (85/15)
5	CH ₂ =C(C≡CH)(OSi ⁱ Pr ₃)(1.5) ^{d,e}	4b	5	1 h	5c 50 (85/15)
6	CH ₂ =CHCH ₂ SiMe ₃ (2)	4a	5	3 h	5d 94 (74/26)
7	CH ₂ =CHCH ₂ SiMe ₃ (2) ^e	4a	5	3 h	5d 77 (63/37)
8	NCSiMe ₃ (1.4)	4a	5	3 h 30	5e 82 (43/57)
9	NCSiMe ₃ (1.4) ^b	4a	5	2 h 30	5e 94 (40/60)
10	Me ₂ C=C(OMe)(OSiMe ₃)(1.4)	4a	5	5 h	5f 74 (>97/3)
11	CH ₂ =C(Ph)(OSiMe ₃)(1.4) ^b	4c	5	4 h 30	5g 80 (87/13)
12	CH ₂ =CHCH ₂ SiMe ₃ (2) ^b	4c	5	4 h 30	5h 67(30/70)
13	CH ₂ =C(Ph)(OSiMe ₃)(1.4)	4d	10	1 h	5i 73 (27/73)
14	CH ₂ =C(C≡CH)(OSi ⁱ Pr ₃)(1.2)	4d	100	0.25h	5j 55 (50/50)

^a *trans/cis* ratio estimated by ¹H NMR spectroscopy and GC–MS analyses. ^b The reaction was carried out in toluene. ^c The F–C adduct **5c'** was also obtained in 13% yield as a mixture of either geometrical *Z* and *E* stereoisomers (exclusive *trans* relationship for the substituents located at the C₂–C₃ bond) or as a mixture of *trans* and *cis* stereoisomers (single geometrical isomer for the double bond, *E* or *Z*) in a 4:1 ratio (stereochemistry not determined). ^d The reaction was carried out in ether. ^e The reaction was carried out in acetonitrile.

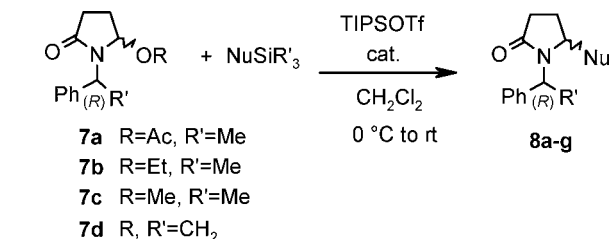
short reaction time to provide the β-aminoketone **2a** in good yield (run 1).¹¹ The Friedel–Crafts (F–C) adduct **3** was also isolated as a mixture of *Z* and *E* stereoisomers in 15% yield.¹²

The reaction could be scaled-up to 1 g of **1a** without alteration of reaction time and yield (run 2). Further

(11) The high reactivity of such a stabilized and bulky TIPS silyl enol ether in catalytic α-amido alkylation reactions is unprecedented. Supporting Information gives additional results for various combinations of TIPS enol ethers and *N*-acyliminium ion precursors to demonstrate further the potential of this new catalytic α-amido alkylation reaction.

(12) Products **3a** and **3b** referred to as F–C adducts by analogy with the mechanism (and nomenclature) proposed by Mikami and co-workers to explain formation of functionalized silyl enol ethers obtained during the course of aldol reactions between simple silyl enol ethers and fluoral (see ref 12b). From a mechanistic point of view, the TIPS silyl enol ether derived from butynone initially condenses onto the iminium cation derived from **1** as a silyl ether nucleophile, which then as a result of the bulkiness of the substituents on silicon fails to give cleavage of the Si–O bond and instead loses a proton to regenerate the double bond. Selective iminium^{12a} and carbonyl^{12b} F–C type reactions of silyl enolates have been developed. The resulting adducts are highly valuable building blocks as a class of functionalized silyl enol ethers readily accessible from simple ones. (a) Wada, M.; Nishihara, Y.; Akiba, K. Y. *Tetrahedron Lett.* **1984**, 25, 5405. (b) Ishii, A.; Kojima, J.; Mikami, K. *Org. Lett.* **1999**, 1, 2013.

Table 4. Reactions of Lactams Bearing Chiral Auxiliaries (Chiral Acyliminium Cation Precursors. II)



run ^a	NuSiR'3 (equiv)	7	TIPSOTf (mol %)	time (h)	8 yield % (de) ^b
1	CH ₂ =C(Ph)(OSiMe ₃)(1.4)	7a	5	15	no reaction
2	CH ₂ =C(Ph)(OSiMe ₃)(1.4)	7b	15	15	8a 42 (50)
3 ^c	CH ₂ =C(Ph)(OSiMe ₃)(1.4)	7b	5	15	8a 78 (20)
4	CH ₂ =C(Ph)(OSiMe ₃)(1.4)	7c	5	15	8a 55 (20)
5 ^c	CH ₂ =C(Ph)(OSiMe ₃)(1.4)	7c	5	15	8a 74 (20)
6	CH ₂ =C(<i>t</i> -Bu)(OSiMe ₃)(1.4)	7c	5	15	8b 30 (26)
7 ^c	CH ₂ =C(<i>t</i> -Bu)(OSiMe ₃)(1.4)	7c	5	15	8b 32 (26)
8	CH ₂ =C(<i>t</i> -Bu)(OSiMe ₃)(1.4)	7c	10 ^d	24	no reaction
9 ^c	Me ₂ C=C(OMe)(OSiMe ₃)(1.4)	7c	5	24	8c 56 (70)
10	CH ₂ =CHCH ₂ SiMe ₃ (1.4)	7c	5	24	no reaction
11	CH ₂ =C(Ph)(OSiMe ₃)(1.4)	7d	5	24	8d 93 (16)
12	CH ₂ =C(<i>t</i> -Bu)(OSiMe ₃)(1.4)	7d	5	24	8e 31 (33)
13	CH ₂ =C(<i>t</i> -Bu)(OSiMe ₃)(2.5)	7d	5	24	8e 34 (33)
14 ^c	CH ₂ =C(<i>t</i> -Bu)(OSiMe ₃)(1.4)	7d	5	24	8e 50 (33)
15 ^c	CH ₂ =C(<i>t</i> -Bu)(OSiMe ₃)(1.4)	7d	10 ^d	24	8e 39 (55)
16 ^c	Me ₂ C=C(OMe)(OSiMe ₃)(1.4)	7d	5	24	8f 89 (20)

^a Unless otherwise noted, reactions were carried out as follows. To a solution of the substrate (0.8 mmol) and the silyl enol ether (1.4 equiv) in dichloromethane (0.8 mL) was added the Lewis acid at 0 °C under an argon atmosphere, and the temperature was slowly raised to room temperature. ^b The stereoisomeric ratio was determined by ¹H NMR spectroscopy and GC–MS analyses. ^c The reaction was carried out in acetonitrile. ^d Sc(OTf)₃ was used as the catalyst.

optimization revealed that the reaction was efficiently catalyzed by 2 mol % of TIPSOTf (run 3). Below this amount of catalyst, the reactivity was significantly lowered.¹³ The ethoxy lactam **1b** was also rapidly consumed using only 5 mol % of TIPSOTf, proving that the nature of the leaving group is not of prime importance (run 4). On the other hand, carrying out the reaction with the hydroxylactam **1c** resulted in an incomplete yet more selective transformation (run 5). Gratifyingly, the present catalytic process also encompassed the unprotected lactam **1d** (run 6). Under the optimal conditions for **1a**, reactions with various silicon-based nucleophiles were also investigated (Table 2). Other silyl enolates, allyltrimethylsilane, trimethylsilyl cyanide, and triethylsilyl hydride reacted smoothly to afford the desired adducts **2c–h** in good yields.

As could be expected, the reactions of trimethylsilyl enol ethers were more selective than that of the less nucleophilic triisopropylsilyl enol ether derived from butynone, with no F–C products being detected (runs 1 and 2). To the best of our knowledge, the formation of lactam **2g** provides the first example of a trialkylsilyltriflate-catalyzed hydroxylactam

(13) A conversion of 76% was observed using 1 mol % of the catalyst.

derivative-lactam conversion, this useful transformation being in most cases effected in the presence of excesses of both a Lewis (or Brønsted) acid and the hydride reagent.¹⁴

Since the relative bulkiness of TIPSOTf could be an impediment to the reaction scope, we next examined enantiopure pyrrolidone derivatives **4a–d** (Table 3) and **7a–d** (Table 4). Unlike **1a**, type **4** acetoxylactams required prolonged reaction time for complete consumption in their reactions with the screened nucleophiles. However, most of the surveyed reactions proceeded well under similar conditions as above (TIPSOTf 5 mol % and 1.4 equiv of nucleophile), except allylation reactions that stopped at a level of ~90% conversion.

Complete reactions were achieved using 2 equiv (not optimized) of allyltrimethylsilane (runs 6, 7, and 12). A key feature of these reactions is provided by the observation that they could also be carried out in toluene (runs 2, 9, 11, and 12) or, in some cases, in ether or acetonitrile (runs 5 and 7).

The compatibility of this catalytic reaction with highly substituted substrates derived from tartaric acid like **4d** when conventional silyl enol ether is used illustrates further its potential (run 13). On the other hand, **4d** impeded the addition of the less nucleophilic triisopropylsilyl enol ether derived from butynone under catalytic conditions, and 1 equiv of TIPSOTf (not optimized) was used to secure a synthetically useful yield for **5j** (run 14).

The alkylations examined herein afforded a comparable level of inherent stereocontrol as related reactions promoted by conventional Lewis acids. Notably, 4,5-diacetoxylactams **4a,b** gave moderate to virtually complete *trans* diastereoselectivity, depending on the size of the nucleophile (runs 1–9),^{4b,g,h,15,16} whereas **4d** afforded adduct **5i** in a *trans/cis* ratio of 2:1 (runs 12 and 13).¹⁵ Allylation of the silyl ether **4c** (run 12) gave a level of stereoselection comparable to that obtained from reactions promoted by InCl₃,¹⁵ TiCl₄ and BF₃·OEt₂.¹⁷ Conversely, the Mannich reaction of **4c** with the silyl enol ether derived from acetophenone gave an opposite stereoselectivity (run 11 versus run 12), with the level of stereoselection paralleling that obtained in the reaction of **4a** (runs 11 versus 1). These results suggest a minimization of the iminium cation stabilizing neighboring group participation by the acetate commonly invoked in related chemistry^{4b,g,h} and support the rationale recently proposed by Kobayashi involving a strong dependence of the stereochemistry upon the nucleophile steric demand.¹⁶

TIPSOTf was also found to efficiently catalyze the alkylation of 5-alkoxylactams bearing chiral auxiliaries with

some silicon-based nucleophiles (Table 4). Steric effects seem to be the major contributory factor in these reactions, as demonstrated by the following results. The acetoxylactam **7a** remained unchanged in the presence of the trimethylsilyl enol ether derived from acetophenone under the standard procedure (run 1). On the other hand, the desired reaction took place when the less crowded, yet intrinsically less electrophilic, alkoxylactams **7b,c** were engaged (runs 2–5). The reaction yield was significantly improved when the steric demand of the substrate was diminished (run 4 versus run 2). The lower yields obtained with the sterically demanding silyl enol ether derived from pivalone provides strong support to the key role of sterics (runs 6–8). In light of these considerations, the fair reactivity between **7c** and the silyl ketene acetal derived from 2-methyl propionic acid methyl ester (run 9) has to be pointed out and suggests that the present reactivity results from a subtle balance between sterics and electronics. Although Meyers's bicyclic lactam **7d** (and related compounds) has previously been demonstrated to be a convenient substrate for allylation,^{18,19} cyanation, or alkylation reactions with organocopper reagents,¹⁸ the results collected in runs 10–14 provide, as far as we are aware, the first examples of their use in a Mannich-type reaction. In general, the yields were able to be improved by carrying out the reactions in CH₃CN (runs 3 versus 2, 5 versus 4, 14 versus 12).

Conversely, neither Sc(OTf)₃^{5a,b} (runs 8 and 15) nor an excess of silyl enol ether (run 13) enhances the yield. Unfortunately, the diastereocontrol remained low in these reactions.

In summary, a broad range of nucleophilic substitution reactions of various 5-alkoxy- and 5-acetoxypyrrolidin-2-ones with silicon-based nucleophiles have been successfully catalyzed using a small amount of TIPSOTf. This catalyst produces rapid reactions and then provides an interesting alternative to the usual TMSOTf reagent regarding the criteria of stability and air and moisture sensitivity. Good to high levels of *trans*-stereoselectivities, *close to those obtained in reactions carried out in the presence of stoichiometric amounts of conventional Lewis acids*, were reached in the reactions of 5-acyloxypyrrolidinones **4a–d**.

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Supporting Information Available: Experimental procedure for the α -amidoalkylation reaction, analytical data, and ¹H NMR spectra for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(16) Recently, Kobayashi and co-workers rationalized the diastereoselectivities observed in nucleophilic substitution reactions of *N*-CBZ 2,3-diacetoxy piperidines as a function of the nucleophile bulkiness. See ref 5b.

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