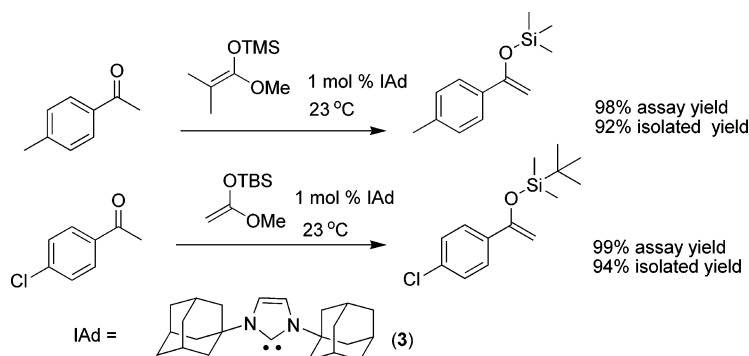


N-Heterocyclic Carbene-Catalyzed Silyl
Enol Ether Formation[†]Jinhua J. Song,* Zhulin Tan, Jonathan T. Reeves, Daniel R. Fandrick,
Nathan K. Yee, and Chris H. SenanayakeDepartment of Chemical Development, Boehringer Ingelheim Pharmaceuticals Inc.,
900 Old Ridgebury Road/P.O. Box 368, Ridgefield, Connecticut 06877-0368

jeff.song@boehringer-ingelheim.com

Received December 17, 2007

ABSTRACT



N-Heterocyclic carbenes (NHCs) were found to catalyze the silyl transfer from trialkylsilyl ketene acetals to ketones. In the presence of a catalytic amount of NHC 3 (IAAd, 0.1 to 5 mol %), a series of enolizable ketones as well as cyclohexanecarboxaldehyde were efficiently converted into the corresponding silyl enol ethers at 23 °C in THF.

In recent years, there has been considerable interest in the use of N-heterocyclic carbenes (NHCs) as organocatalysts and they have been successfully employed to mediate a wide variety of organic reactions.¹ These NHC-catalyzed transformations were made possible by taking advantage of either the strong nucleophilicity (e.g., in Benzoin- and Stetter-type reactions²) or the Brønsted basicity of various NHCs (e.g., in transesterification and acylation reactions^{3,4}).

Recent work from our own laboratories has shown that NHCs are also capable of activating certain silicon–carbon bonds, such as in TMSCN and TMSCF₃, for nucleophilic addition reactions. For example, imidazolylidenes were found to catalyze trifluoromethylation and cyanosilylation of carbonyl compounds at low catalyst loadings (0.01–1 mol

%).^{5–8} The mildness of these conditions was evident by the successful application of this method to the trifluoromethylation of a complex cyclodextrin substrate where the traditional TBAF-mediated protocol failed.⁹ Most recently, we reported that NHCs can catalyze Mukaiyama aldol reactions with catalyst loadings as little as 0.05–0.5 mol %.¹⁰ During

[†] Dedicated to Prof. Li-Cheng Song on the occasion of his election to the Chinese Academy of Sciences.

(1) (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (d) Nair, V.; Bindu, S.; Sreekumar, V. *Angew. Chem., Int. Ed.* **2004**, *43*, 5130.

(2) (a) Enders, D.; Niemeier, O.; Raabe, G. *Synlett* **2006**, 2431. (b) Kerr, M. S.; Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2002**, *124*, 10298. (c) Enders, D.; Breuer, K.; Runsink, J.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1899. (d) Enders, D.; Breuer, K.; Teles, J. H. *Helv. Chim. Acta* **1996**, *79*, 1217. (e) Teles, J. H.; Melder, J.-P.; Ebel, K.; Schneider, R.; Gehrler, E.; Harder, W.; Brode, S.; Enders, D.; Breuer, K.; Raabe, G. *Helv. Chim. Acta* **1996**, *79*, 61. (f) Myers, M. C.; Bharadwaj, A. R.; Milgram, B. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 14675. (g) Kerr, M. S.; Rovis, T. *J. Am. Chem. Soc.* **2004**, *126*, 8876. (h) Chow, K. Y. K.; Bode, J. W. *J. Am. Chem. Soc.* **2004**, *126*, 8126. (i) Mattson, A. E.; Bharadwaj, A. R.; Zuhl, A. M.; Scheidt, K. A. *J. Org. Chem.* **2006**, *71*, 5715. (j) Myers, M. C.; Bharadwaj, A. R.; Milgram, B. C.; Scheidt, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 14675. (k) Enders, D.; Niemeier, O.; Balensiefer, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1463. (l) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. (m) Moore, J. L.; Kerr, M. S.; Rovis, T. *Tetrahedron* **2006**, *62*, 11477. (n) Liu, Q.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 2552. (o) Read de Alaniz, J.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 6284.

this study, it was found that regular ketones, such as *p*-methyl acetophenone (**1a**, Figure 1) did not undergo a Mukaiyama

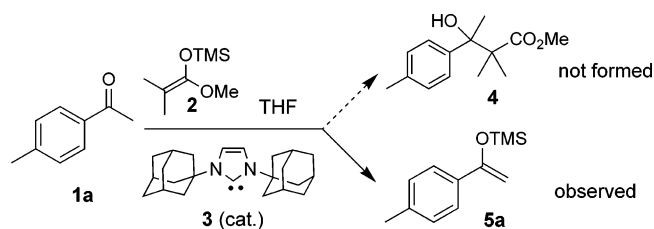


Figure 1. Unexpected silyl enol ether formation

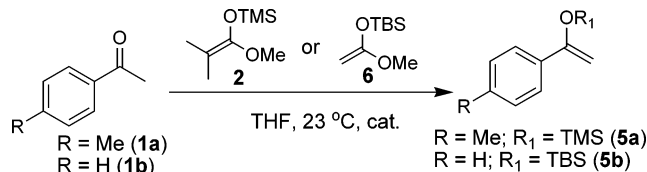
aldol reaction with trimethylsilyl ketene acetal **2** under NHC catalysis in THF. The starting ketone was always recovered from these reactions after aqueous workup. Later, careful analysis of the recovered ketone by ^1H NMR revealed that a very small amount of the unexpected silyl enol ether **5a** was present, indicating that silyl transfer from the silyl ketene acetal **2** to ketone **1a** occurred during these experiments.

We report in this letter that silyl enol ethers¹¹ can be cleanly formed from reactions between enolizable ketones and silyl ketene acetals in good to excellent yields under the catalysis of only 0.1–5 mol % NHC.

Following our initial lead shown in Figure 1, a series of experiments were carried out to define the optimal reaction

conditions for silyl enol ether formation from ketones. With 1 mol % IAd (**3**),¹² the reaction between *p*-methyl acetophenone (**1a**) and trimethylsilyl ketene acetal **2** in THF reached 99% molar conversion within 2.5 h (entry 1, Table 1). Reactions using 0.5 mol % or even 0.1 mol % IAd

Table 1. Defining Reaction Conditions



	starting materials	NHC	loading (mol %)	molar convn (%) ^a			assay yield (%) ^b
				2.5 h	8.5 h	24 h	
1	1a + 2	IAd	1	99	—	—	98
2	1a + 2	IAd	0.5	98	99	—	98
3	1a + 2	IAd	0.1	74	96	99	97
4	1a + 2	<i>t</i> Bu	0.5	82	96	99	95
5	1a + 2	IMes	0.5	44	70	96	91
6	1b + 6	IAd	1	66	85	95	92
7	1b + 6	IAd	0.5	50	71	87	84
8	1a + 2	no	—	—	—	NR	—
9	1b + 6	no	—	—	—	NR	—

^a Molar conversion by HPLC. ^b Assay yield by HPLC.

proceeded smoothly to 99% molar conversions in 8.5 and 24 h, respectively (entries 2–3). *t*Bu-catalyzed reaction was slightly slower, requiring 24 h to achieve 99% molar conversion at 0.5 mol % catalyst level (entry 4). Reaction using IMes (0.5 mol %) progressed to a 96% molar conversion after 24 h (entry 5).

It was found that the much bulkier *tert*-butyldimethylsilyl (TBS) enol ethers could also be formed in a similar manner. Reaction between acetophenone (**1b**) and TBS ketene acetal **6** with 1 mol % IAd gave a 95% molar conversion after 24 h (entry 6). When 0.5 mol % IAd was employed, an 87% molar conversion was achieved after 1 day at 23 °C (entry 7). Finally, control experiments showed that no reaction occurred between **1a** and **2** or **1b** and **6** after 24 h at ambient temperature in the absence of the carbene catalyst (entries 8–9).

The scope of the NHC-catalyzed silyl enol ether formation was explored as summarized in Table 2. On the basis of the results from Table 1, our standard conditions were defined to involve the use of 1 mol % IAd (**3**) in THF at 23 °C, except for two substrates (vide infra). After the reaction was complete (judged by HPLC or GC), the volatiles were directly removed by evaporation without the need for aqueous workup. The residue was then distilled under vacuum to give the desired silyl enol ethers.

In addition to compound **5a** (entry 1, Table 2),¹³ the trimethylsilyl enol ethers of α -tetralone and cyclododecanone

(12) IAd = 1,3-di-(1-adamantyl)imidazol-2-ylidene; *t*Bu = 1,3-di-*tert*-butylimidazol-2-ylidene; IMes = 1,3-di-mesitylimidazol-2-ylidene.

(3) (a) Grasa, G. A.; Guveli, T.; Singh, R.; Nolan, S. P. *J. Org. Chem.* **2003**, *68*, 2812. (b) Singh, R.; Kissling, R. M.; Letellier, M.-A.; Nolan, S. P. *J. Org. Chem.* **2004**, *69*, 209. (c) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583. (d) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587. (e) Nyce, G. W.; Glauser, T.; Connor, E. F.; Mock, A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 3046. (f) Connor, E. F.; Nyce, G. W.; Myers, M.; Mock, A.; Hedrick, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 914. (g) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347. (h) Singh, R.; Nolan, S. P. *Chem. Commun.* **2005**, *43*, 5456. (i) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770.

(4) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453. (5) Song, J. J.; Tan, Z.; Reeves, J. T.; Gallou, F.; Yee, N.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 2193.

(6) Song, J. J.; Gallou, F.; Reeves, J. T.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *J. Org. Chem.* **2006**, *71*, 1273.

(7) (a) Fukuda, Y.; Maeda, Y.; Ishii, S.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 589. (b) Fukuda, Y.; Maeda, Y.; Kondo, K.; Aoyama, T. *Chem. Pharm. Bull.* **2006**, *54*, 397. (c) Fukuda, Y.; Maeda, Y.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 1937. (d) Fukuda, Y.; Kondo, K.; Aoyama, T. *Synthesis* **2006**, 2649. (e) Suzuki, Y.; Abu Bakar, M. D.; Muramatsu, K.; Sato, M. *Tetrahedron* **2006**, *62*, 4227. (f) Kano, T.; Sasaki, K.; Konishi, T.; Mii, H.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 4615.






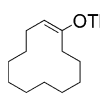

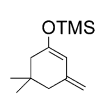

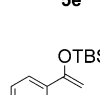
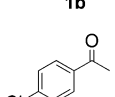
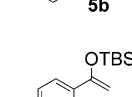
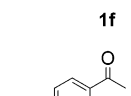
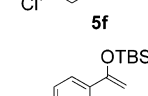

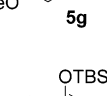







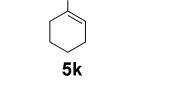
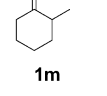
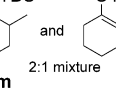
(8) (a) Wu, J.; Sun, X.; Ye, S.; Sun, W. *Tetrahedron Lett.* **2006**, *47*, 4813. (b) For a related aziridine opening reaction with acid anhydride, see: Sun, X.; Ye, S.; Wu, J. *Eur. J. Org. Chem.* **2006**, *21*, 4787.

(9) Bjerre, J.; Fenger, T. H.; Marinescu, L. G.; Bols, M. *Eur. J. Org. Chem.* **2007**, 704.

(10) Song, J. J.; Tan, Z.; Reeves, J. T.; Yee, N.; Senanayake, C. H. *Org. Lett.* **2007**, *9*, 1013.

(11) For representative methods to prepare silyl enol ethers, see: (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462. (b) Kita, Y.; Yasuda, H.; Haruta, J.; Segawa, J.; Tamura, Y. *Synthesis* **1982**, 1089. (c) Tanabe, Y.; Misaki, T.; Kurihara, M.; Iida, A.; Nishii, Y. *Chem. Commun.* **2002**, *15*, 1628. (d) Nakamura, E.; Murofushi, T.; Shimizu, M.; Kuwajima, I. *J. Am. Chem. Soc.* **1976**, *98*, 2346. (e) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 805. (f) Sakurai, H.; Miyoshi, K.; Nakadaira, Y. *Tetrahedron Lett.* **1977**, 2671. (g) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, 2079. (h) Orban, J.; Turner, J. V.; Twitchin, B. *Tetrahedron Lett.* **1984**, *25*, 5099. (i) Takai, K.; Kataoka, Y.; Okazoe, T.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 1065. (j) Davis, F. A.; Lal, G. S.; Wei, J. *Tetrahedron Lett.* **1988**, *29*, 4269.

Table 2. NHC-Catalyzed Silyl Enol Ether Formation

entry	carbonyl compound	cat. loading (mol %)	product	isolated yield (%)
1		1		92
2		1		93
3		1		84
4		1		79
5		1		82
6		1		94
7		1		93
8		1		87
9		5		76
10		1		82
11		1		81
12		4		46
13		1		70

were efficiently prepared (entries 2–3).^{14,15} Silylation of isophorone (**1e**) gave the kinetically favored exocyclic diene

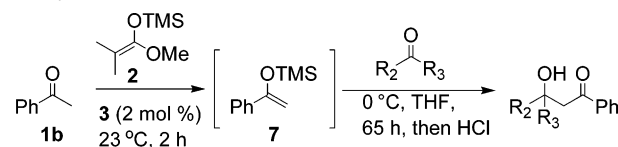






5e in 79% yield (entry 4).¹⁶ Interestingly, the NaH-catalyzed silylation of isophorone was reported to afford the complementary endocyclic diene resulting from the silylation of the thermodynamic enolate.^{11c}

Simple acetophenone derivatives were smoothly converted into the corresponding TBS enol ethers in high yields (entries 5–7).^{17,18} Reaction between TBS ketene acetal **6** and propiophenone **1h** afforded the (*Z*)-silyl enol ether **5h** with >95:5 selectivity (entry 8).¹⁹ This selectivity also held true for reaction with 3-pentanone (*Z/E* = 95:5, 76% yield, entry 9).^{11h} It should be noted that silylation of 3-pentanone using 1 mol % IAd was sluggish and eventually required 5 mol % catalyst and 3 days for complete conversion.

TBS enol ethers of both cyclopentanone and cyclohexanone were obtained uneventfully in high yields under the standard conditions (entries 10–11).^{11h,20} In contrast, methyl cyclohexanone proved to be a challenging substrate (entry 12). The reaction required 4 mol % IAd (**3**) to proceed at a reasonable rate to give a mixture of two isomers (**5m**:**5m'** = 2:1, 46% yield), again favoring the kinetic silyl enol ether **5m**.²¹ Last, cyclohexanecarboxaldehyde was effectively converted into its TBS enol ether **5n** in 70% isolated yield.²²

Since we have previously demonstrated that Mukaiyama aldol reactions with trimethylsilyl enol ether **7** (Table 3)

Table 3. NHC-Catalyzed Tandem Silyl Transfer and Mukaiyama Aldol

			
entry	carbonyl compound	product	isolated yield (%)
1			75
2			65
3			74

could also be catalyzed by IAd (**3**),¹⁰ we investigated the

(13) Van der Vecht, J. R.; Steinberg, H.; De Boer, T. J. *Recl. Trav. Chim. Pays-Bas* **1976**, 95, 149.

(14) Olah, G. A.; Gupta, B. G. B.; Narang, S. C.; Malhotra, R. *J. Org. Chem.* **1979**, 44, 4272.

(15) Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, 43, 2075.

(16) Emde, H.; Gootz, A.; Hofmann, K.; Simchen, G. *Liebigs Ann. Chem.* **1981**, 1643.

(17) Petasis, N. A.; Lu, S.-P. *Tetrahedron Lett.* **1995**, 36, 2393.

(18) Raynolds, P. W.; DeLoach, J. A. *J. Am. Chem. Soc.* **1984**, 106, 4566.

possibility of carrying out the silyl enol ether formation and the subsequent aldol reaction in one pot, thereby using the same catalyst to mediate both transformations. To demonstrate this process, we treated acetophenone with silyl ketene acetal **2** in the presence of 2 mol % IAd (**3**) at 23 °C for 2 h to complete the silyl enol ether formation. Then *p*-tolylaldehyde (**8a**) was added directly into the reaction vessel at 0 °C. After 65 h at that temperature, the reaction mixture was treated with aqueous HCl to give the free aldol product **9a** in 75% yield (entry 1).¹⁰ Two additional examples using *p*-chlorobenzaldehyde (**8b**) and 2,2,2-trifluoroacetophenone (**8c**) were provided in Table 3 to further illustrate this one-pot protocol (entries 2 and 3).¹⁰ This method avoided the need to isolate and handle the potentially labile trimethylsilyl enol ether intermediate.

We propose that, for the silyl enol ether formation reaction, NHC functions like a carbon-centered base.⁴ NHCs are known to possess strong basicities. For example, the pK_a of I^tBu was determined to be 20 in THF and 22.7 in DMSO.²³ The silyl enol ether formation reaction is possibly initiated with NHC deprotonating the ketone to form enolate **A** (Figure 2). Subsequent silyl transfer from the silyl ketene acetal occurs to generate an ester enolate/imidazolium ion pair **B**. The ester enolate, which has a pK_a of ~25, will then deprotonate the imidazolium to regenerate the free carbene and complete the catalytic cycle.

In summary, we have discovered a mild, NHC-catalyzed silyl enol ether formation reaction. A series of enolizable ketones were readily converted into the corresponding silyl enol ethers at room temperature under the influence of a catalytic amount (0.1–5 mol %) of IAd. Formation of the TBS enol ether from cyclohexanecarboxaldehyde was also successful. Furthermore, based on this new method and our previously reported NHC-catalyzed Mukaiyama aldol pro-

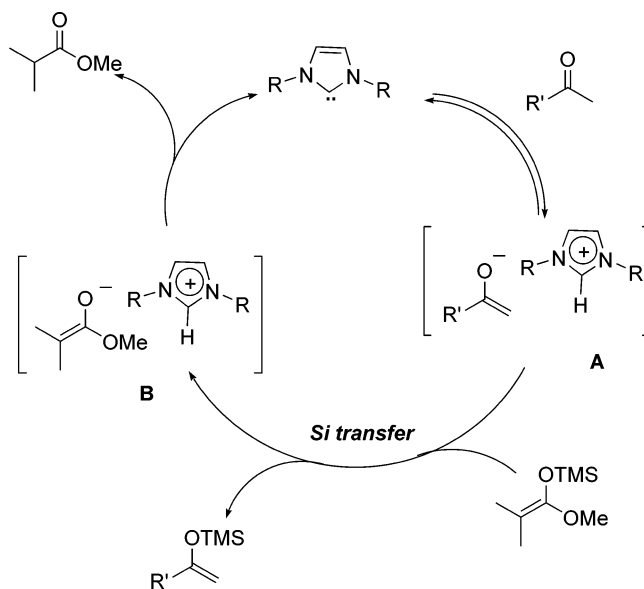


Figure 2. Proposed reaction pathway

tol,¹⁰ a one-pot aldol coupling of acetophenone and aldehydes as well as 2,2,2-trifluoroacetophenone was achieved. These new conditions are metal-free, mild, and operationally simple.²⁴ Considering the broad synthetic utility of silyl enol ethers, we believe that this new methodology will find future applications in organic synthesis. Efforts to further explore potential NHC catalysis for other fundamental organic transformations continue in our laboratories.

Supporting Information Available: Experimental procedures and spectral data for compounds **5a–k**, **5m,n**, and **9a–c**, including copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL703025B

(24) IAd is a nice free-flowing solid and can be easily handled in the laboratory: (a) Arduengo, A. J., III; Harlow, R. L.; Kline, M. *J. Am. Chem. Soc.* **1991**, *113*, 361. (b) IAd, I^tBu, and IMes carbenes are commercially available from Strem Chemicals in Newburyport, MA.

(19) Ohmura, T.; Yamamoto, Y.; Miyaura, N. *Organometallics* **1999**, *18*, 413.

(20) Saraber, F. C. E.; Dratch, S.; Bosselaar, G.; Jansen, B. J. M.; De Groot, A. *Tetrahedron* **2006**, *62*, 1717.

(21) Saraber, F. C. E.; Baranovsky, A.; Jansen, B. J. M.; Posthumus, M. A.; De Groot, A. *Tetrahedron* **2006**, *62*, 1726.

(22) Chenault, H. K.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 4249.

(23) (a) Kim, Y.-J.; Streitwieser, A. *J. Am. Chem. Soc.* **2002**, *124*, 5757.

(b) Magill, A. M.; Cavell, K. J.; Yates, B. F. *J. Am. Chem. Soc.* **2004**, *126*, 871.