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Sequential Reactions of Trimethylsilyldiazomethane with 4-Alkenyl Ketones and Aldehydes Catalyzed by Lewis Bases

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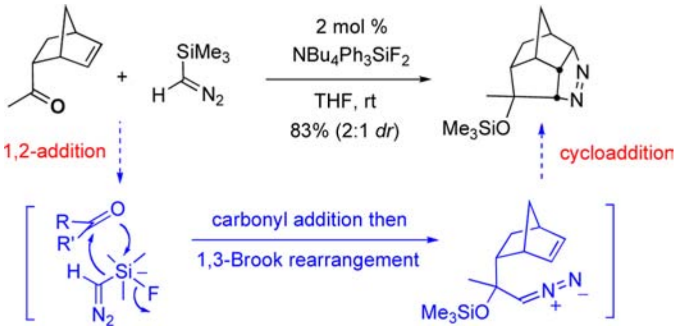
ABSTRACT



A sequence of a carbonyl addition between 4-alkenyl ketones and aldehydes with trimethylsilyldiazomethane followed by a 1,3-Brook rearrangement and an intramolecular 1,3-dipolar cycloaddition was promoted by Lewis bases tetrabutylammonium triphenyldifluorosilicate (TBAT) or potassium *tert*-butoxide (KO-*t*-Bu). Through these concatenated bond-forming processes, a variety of novel bi- and tricyclic Δ^1-pyrazolines were synthesized.

Lewis base-promoted reactions are less thoroughly exploited in organic chemistry compared to the corresponding Lewis acid-promoted transformations. This discrepancy is mainly due to the limited possibilities for valence expansion at carbon centers and the lack of necessary Lewis acidic sites in common organic molecules.[1] The capacity of silicon to attain higher valent states[2] allows various Lewis base-promoted reactions of pronucleophiles associated with silyl groups, and the fluoride[3]- and alkoxide-promoted[4] reactions are their two most prototypic examples. Subsequently, other Lewis bases such as amine oxides and phosphoramides were introduced especially to catalyze or promote asymmetric addition reactions.[5]

In this context, we surmised that trimethylsilyldiazomethane (TMSD)[6] should be an effective donor of the diazomethane anion ($^{-}CHN_2$) in analogy to TMSCN,[7]

[†] Department of Chemistry, Boston College, Boson, MA.

(1) (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (b) Gawronski, J.; Wascinska, N.; Gajewy, J. *Chem. Rev.* **2008**, *108*, 5227.

(2) Reviews: (a) Rendler, S.; Oestreich, M. *Synthesis* **2005**, 1727. (b) Furin, G. G.; Vyazankina, G. A.; Gostevsky, B. A.; Vyazankin, N. S. *Tetrahedron* **1988**, *44*, 2675.

(3) (a) Pharikronburee, V.; Punirun, T.; Soorukram, D.; Kuhakarn, C.; Tuchinda, P.; Reutrakul, V.; Pohmakotr, M. *Org. Biomol. Chem.* **2013**, *11*, 2022. (b) Yoshizawa, K.; Shioiri, T. *Tetrahedron Lett.* **2005**, *46*, 7059. (c) Pilcher, A. S.; DeShong, P. *J. Org. Chem.* **1996**, *61*, 6901. (d) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200.

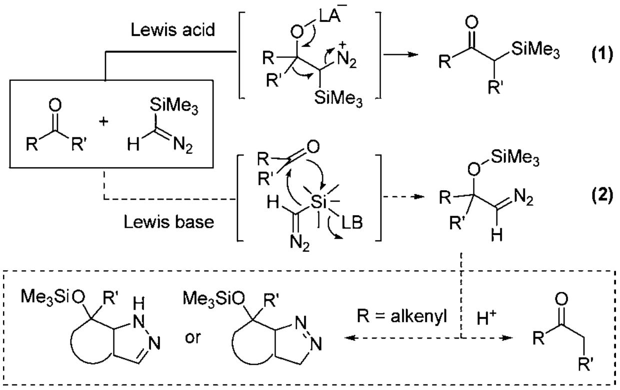
(4) For a perspective of the anion relay chemistry, see: (a) Smith, A. B., III; Wuest, W. M. *Chem. Commun.* **2008**, 5883. (b) Maifeld, S. V.; Lee, D. *Org. Lett.* **2005**, *7*, 4995. (c) Lettan, R. B., II; Scheidt, K. A. *Org. Lett.* **2005**, *7*, 3227.

(5) (a) Wolf, L. M.; Denmark, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 4743. (b) Denmark, S. E.; Wilson, T. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 3236. (c) Weickgenannt, A.; Oestreich, M. *ChemCatChem.* **2011**, 1527. (d) Wadhwa, K.; Chintareddy, V. R.; Verkade, J. G. *J. Org. Chem.* **2009**, *74*, 6681. (e) Denmark, S. E.; Beutner, G. L.; Wynn, T.; Eastgate, M. D. *J. Am. Chem. Soc.* **2005**, *127*, 3774. (f) Denmark, S. E.; Fan, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7825.

(6) (a) For a recent review of TMS-diazomethane, see: Shioiri, T.; Aoyama, T. Trimethylsilyldiazomethane. (First updated by Snowden, T.) In *Reagents for Silicon-Mediated Organic Synthesis*; Fuchs, P. L., Ed.; Wiley: New York, 2011. (b) Podlech, J. *J. Prakt. Chem.* **1998**, *340*, 679. (c) Shioiri, T.; Aoyama, T. In *Encyclopedia of Reagents for Organic Synthesis*; Paquette, L. A., Ed.; Wiley: Chichester, UK, 1995; vol. 7, p 7254.

10.1021/ol401124t

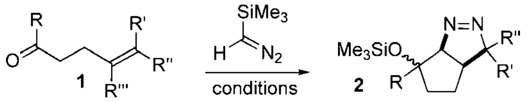
Scheme 1. Lewis Acid- vs Lewis Base-Catalyzed Reaction of TMSD with Carbonyl Compounds

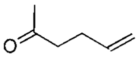
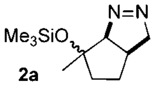
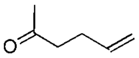
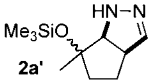
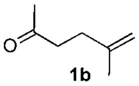
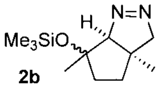
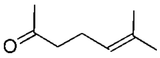
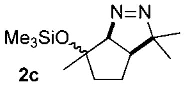
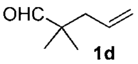
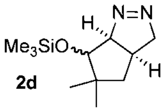
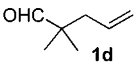
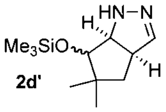
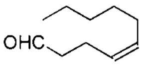
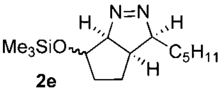
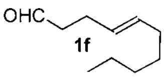
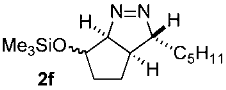


$TMSCF_3$,[8] and $TMSCH_2CN$[9] as the source of the corresponding ^-CN, $^-CF_3$, and $^-CH_2CN$ in the presence of a Lewis base. Although myriad reports are documented for the Lewis acid-promoted addition reactions of TMSD with carbonyl compounds,[10] to the best of our knowledge, the corresponding Lewis base-promoted process has not been reported (Scheme 1).

In Lewis acid-promoted reactions between carbonyl compounds and TMSD, the carbonyl group is activated by Lewis acids, which then reacts with weakly nucleophilic TMSD, thereby generating a one-carbon homologated α-silyl methyl ketone (Scheme 1, eq 1). On the other hand, we surmise that in Lewis base-promoted reactions, the Lewis base will add to the weakly Lewis acidic silicon center of TMSD to activate it as a stronger nucleophile such that it will react with a carbonyl group readily (Scheme 1, eq 2). The resultant intermediate[11] then would undergo various transformations depending on how the diazoalkane moiety is activated. For example, a 1,2-alkyl group shift would occur to give a one-carbon homologated ketone upon protonation.[12]

Table 1. Reactions of Acyclic 4-Alkenyl Aldehydes and Ketones To Form Δ^1-Pyrazolines under Different Conditions



entry	substrate	conditions[a]	product	yield (%)[b]
1	 1a	A	 2a	77 (1.6:1)
2	 1a	B	 2a'	92 (1:1)
3	 1b	A	 2b	72 (1:1)
4	 1c	A B	 2c	62 (1:1) 78 (1:1)
5	 1d	A	 2d	90 (5:1)
6	 1d	B	 2d'	88 (7:1)
7	 1e	A B	 2e	76 (3:1) 65 (2:1)
8	 1f	A B	 2f	37 (2.7:1) 69 (1:0)

[a] Conditions A: 2 mol % of TBAT in THF at rt. Conditions B: 10 mol % of KO-*t*-Bu in THF at rt. [b] Isolated yield.

To expand the utility of the α-silyloxy diazoalkane in eq 2 (Scheme 1), we envision that if one of the alkyl groups contains a suitably positioned double bond, this diazoalkane species would undergo a [3 + 2] dipolar cycloaddition to generate a fused bicyclic pyrazoline.[13] Although typical electron-rich alkenes generally do not undergo [3 + 2] dipolar cycloaddition with diazo alkanes, we expect that the proximity between the diazoalkane moiety and a tethered alkene would have sufficient driving force to react with each other.[14] These sequence of events ultimately will

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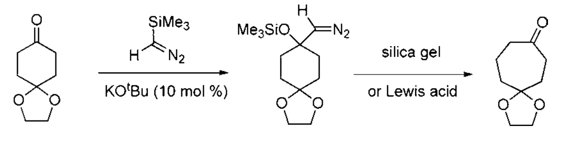
(7) (a) North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147. (b) Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett.* **2000**, *41*, 7457. (c) Holmes, I. P.; Kagan, H. B. *Tetrahedron Lett.* **2000**, *41*, 7453. (d) North, M. *Synlett* **1993**, 807.

(8) (a) Kawano, Y.; Kaneko, N.; Mukaiyama, T. *Chem. Lett.* **2005**, *34*, 1508. (b) Kawano, Y.; Fujisawa, H.; Muyaiyama, T. *Chem. Lett.* **2005**, *34*, 1134. (c) Palomo, C.; Aizpurua, J. M.; López, M. C.; Lecea, B. *J. Chem. Soc., Perkin Trans. 1* **1989**, 1692.

(9) (a) Prakash, G. K. S.; Mogi, R.; Olah, G. A. *Org. Lett.* **2006**, *8*, 3589. (b) Ma, J.-A; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119. (c) Singh, R. P.; Shreeve, J. M. *Tetrahedron* **2000**, *56*, 7613. (d) Prakash, G. K. S.; Yudin, A. K. *Chem. Rev.* **1997**, *97*, 757.

(10) (a) Snyder, S. A.; Wespe, D. A.; von Hof, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 8850. (b) Sletten, E. M.; Nakamura, H.; Jewett, J. C.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 11799. (c) Dabrowski, J. A.; Moebius, D. C.; Wommack, A. J.; Kornahrens, A. F.; Kingsbury, J. S. *Org. Lett.* **2010**, *12*, 3598. (d) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 6614. (e) Youn, J.-H.; Lee, J.; Cha, J. K. *Org. Lett.* **2001**, *3*, 2935. (f) Maruoka, K.; Concepcion, A. B.; Yamamoto, H. *Synthesis* **1994**, 1283.

(11) Such an intermediate was isolated and characterized (ref 12a).



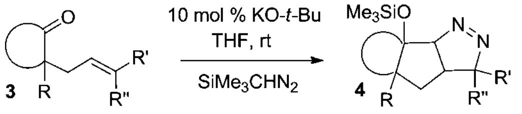
(12) (a) Liu, H.; Sun, C.; Lee, N.-K.; Henry, F. R.; Lee, D. *Chem.—Eur. J.* **2012**, *18*, 11889. (b) Silyl enol ether formation with Rh catalyst: Aggarwal, V. K.; Sheldon, C. G.; Macdonald, G. J.; Martin, W. P. *J. Am. Chem. Soc.* **2002**, *124*, 10300. (c) Zheng, J.-C.; Yun, S. Y.; Sun, C.; Lee, N.-K.; Lee, D. *J. Org. Chem.* **2011**, *76*, 1086.

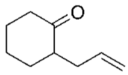
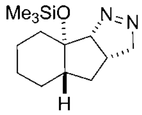
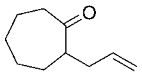
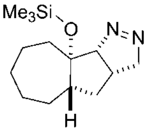
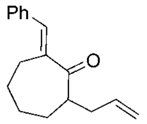
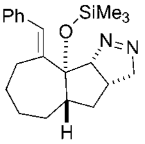
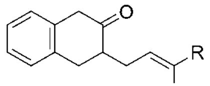
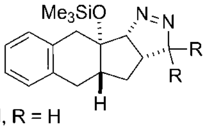
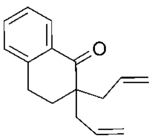
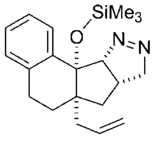
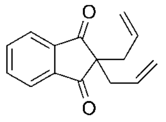
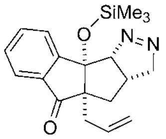
(13) For a related intermolecular process with an activated alkyne, see: Hari, Y.; Tsuchida, S.; Sone, R.; Aoyama, T. *Synthesis* **2007**, *21*, 3371.

lead to cyclic Δ^1-pyrazolines or Δ^2-pyrazolines depending on the substituent pattern and reaction conditions. Herein we describe an effective Lewis base-promoted tandem reaction of TMSD with 4-alkenyl ketones and aldehydes to generate structurally novel bi- and tricyclic Δ^1-pyrazolines.

Our exploration commenced with readily available acyclic 4-alkenyl ketones and aldehydes (Table 1). First, we chose tetrabutylammonium triphenyl difluorosilicate (TBAT) as the catalytic fluoride source because of its availability in an anhydrous form and its solubility in typical organic solvent. When 4-alkenyl ketone **1a** was treated with TMSD in the presence of a catalytic amount of TBAT (2 mol %) in THF at room temperature, a bicyclic Δ^1-pyrazoline **2a** was obtained in 77% yield as a mixture of two diastereomers in a 1:1.6 ratio, which could be easily separated by silica gel chromatography (entry 1).[15] Under these conditions, the corresponding Δ^2-pyrazoline **2a′** was not detected. However, replacing TBAT with KO-*t*-Bu completely changed the product outcome so that Δ^2-pyrazoline **2a′** became the sole product (92% yield, 1:1 dr) (entry 2).[16] Other 4-alkenyl ketones **1b** and **1c** with di- and trimethyl-substituted alkene behaved similarly, affording Δ^1-pyrazolines **2b** and **2c** in 72 and 78% yields with 1:1 diastereomeric ratios (entries 3 and 4). The corresponding 4-alkenyl aldehydes with mono- and disubstituted alkenes provided Δ^1-pyrazolines **1d**–**f** in high yields (entries 5, 7, and 8). Similar to the formation of **2a′** by using KO-*t*-Bu as the catalyst, the reaction of aldehyde **1d** also provided 88% yield of Δ^2-pyrazoline **2d′** as the sole product in much higher (7:1) diastereoselectivity (entry 6).[17] It is worth mentioning that *cis*- and *trans*-4-decenal **1e** and **1f** showed very different stereochemical outcomes where **2e** was obtained as a 3:1 mixture of epimers under both TBAT- and KO-*t*-Bu-catalyzed conditions (entry 7), whereas **2f** was produced as a single isomer under the same conditions (entry 8).

Table 2. Sequential Reactions of Cyclic Ketones with Allyl or Prenyl Substituents



entry	substrate	product	yield (%)[a]
1	**3a** 	**4a** 	81
2	**3b** 	**4b** 	43 82[b]
3	**3c** 	**4c** 	45[c]
4	 **3d**, R = H	 **4d**, R = H	75
5	**3e**, R = Me	**4e**, R = Me	78
6	**3f** 	**4f** 	61
7	**3g** 	**4g** 	56

[a] Isolated yield. [b] Reaction at −10 °C → rt with KO^{t}Bu in THF.

Having seen the high efficiency of bicyclic pyrazoline formation from acyclic ketones and aldehydes, we next explored the reaction of carbonyl substrates containing a cyclic ketone moiety with at least one α-allyl or substituted allyl group (Table 2). Generally, TBAT was found to be less efficient than KO-*t*-Bu for these substrates; therefore, we employed 10 mol % of KO-*t*-Bu in THF as the standard conditions. Under these conditions, α-allyl cyclohexanone **3a** provided a single *trans*-fused tricyclic Δ^1-pyrazoline **4a** in 81% yield (entry1), whereas 2-allylcycloheptanone **3b** afforded only 43% yield of **4b** (entry 2). Suspecting that the strongly exothermic reaction with KO-*t*-Bu at an ambient temperature might cause the low yield, we repeated the reaction at −10 °C under otherwise identical conditions, which gratifyingly resulted in 82% yield of **4b**. The pyrazoline moiety fused to the central 5-membered ring is *syn* to the trimethylsilyloxy substituent at the ring junction. Cycloheptanone derivative **3c** also yielded a single *trans*-ring junction-fused tricyclic Δ^1-pyrazolines **4c** in 45% yield (entry 3). The low yield for this reaction is attibuted to the participation of the benzylidene via 1,4-addition to form an alternative pyrazoline product.[18] The reactions of 2-allyl and 2-prenyl α-tetralone derivatives **3d** and **3e** provided products **4d** and **4e** in similar yields, respectively, where the Δ^1-pyrazoline ring is *syn* to the trimethylsilyloxy group at the 6–5-*trans*-ring junction (entries 4 and 5). The stereochemistry of products **4c** and **4d** were unambiguously confirmed by single crystal X-ray crystallographic analyses. The reactions of *gem*-diallyl-substituted

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(14) (a) Taber, D. F.; Guo, P. *J. Org. Chem.* **2008**, *73*, 9479. (b) Jung, M.; Huang, A. *Org. Lett.* **2000**, *2*, 2659. (c) Padwa, A.; Ku, H. *J. Org. Chem.* **1980**, *45*, 3756.

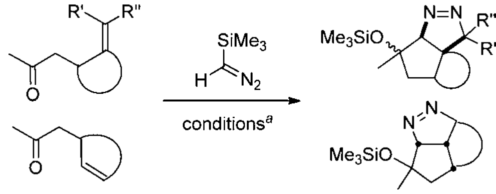
(15) The faster eluting diastereomer was assigned as the *trans*-isomer where the Me$_3$SiO group is *anti* to the pyrazoline ring, which is deduced from the behavior of **6c** and **6d**, the stereochemistry of which was confirmed by X-ray diffraction analysis.

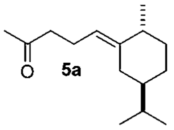
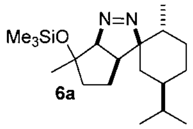
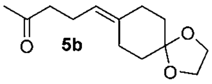
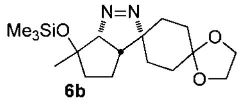
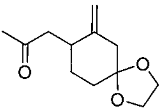
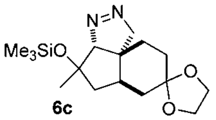
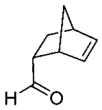
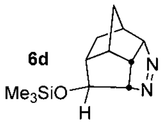
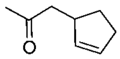
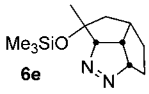
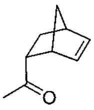
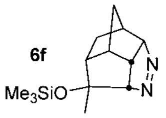
(16) In separate experiments, **2a** was treated with 10, 15, and 20 mol % of KO-*t*-Bu in THF, but **2a** was recovered intact without generating **2a′**.

(17) This assignment is based only on the crude NMR of **2d′** because the purification and full characterization was preempted by its instability on silica gel.

(18) This conclusion is drawn from the spectroscopic data of this byproduct (42% yield); see the Supporting Information.

Table 3. Sequential Reactions of Acyclic Carbonyl in Combination of Exocyclic and Endocyclic Alkenyl Groups



entry	substrate		product		yield (%)[b]
1	**5a**		**6a**		94 (1:1)
2	**5b**		**6b**		90 (1:1)
3	**5c**		**6c**		71 (2.4:1)
4	**5d**		**6d**		74[c] (2:1)
5	**5e**		**6e**		82 (1:1)
6	**5f**		**6f**		83 (2:1)

[a] Conditions: 10 mol % of KO-*t*-Bu in THF at rt. [b] Isolated yield. [c] Reaction under 2 mol % of TBAT in THF at rt.

α-tetralone **3f** afforded a single isomer of tricyclic Δ^1-pyrazolines **4f** in 61% yield (entry 6). The *cis*-ring junction stereochemistry was tentatively assigned on the basis of the generally favorable *cis*-ring junction stereochemistry of 6–5-fused bicycles. The slightly lower yield of **4f** compared to that of monosubstituted counterpart **4d** is most likely due to the steric hindrance of *gem*-disubstitution in **3f** for the initial carbonyl addition. Similarly, substrate **3g** containing two carbonyl groups and *gem*-diallyl substituent provided monoadduct **4g** in 56% yield as a single isomer (entry 7).

We further expanded the reaction scope by employing substrates containing an acyclic carbonyl moiety in combination with either an exocyclic (**5a**–**c**) or an endocyclic (**5d**–**f**) alkene moiety (Table 3). In general, the reactions with these substrates were more efficient than those in Tables 1 and 2 where the tethered alkenes are acyclic, rendering the formation of complex Δ^1-pyrazolines **6a**–**f** in higher yields. Although the diastereoselectivity for the carbonyl addition step could not be controlled, the facial selectivity of the cycloaddition in the next step was found to be high, leading to the formation of only two diastereomers in all cases. Among these pyrazolines, the structures of one of the diastereomers of **6c** and **6d** were confirmed by single-crystal X-ray crystallography (Figure 1).

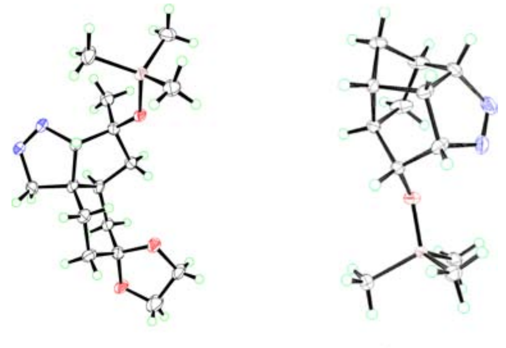

***trans*-6c** ***cis*-6d**

Figure 1. ORTEP of **6c** and **6d**.

In summary, we have disclosed a novel tandem reaction forming structurally diverse Δ^1-pyrazolines through addition of trimethylsilyldiazomethane to ketones and aldehydes followed by a 1,3-Brook rearrangement and subsequent dipolar cycloaddition of the diazoalkane intermediate with the tethered alkene moieties. This sequence of events not only produces structurally novel pyrazoline structures but also uncovers a new mode of unprecedented reactivity of trimethylsilyldiazomethane under Lewis base-catalyzed conditions. The utility of these powerful multiple bond- and ring-forming processes will be further studied in due course.

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

The authors declare no competing financial interest.