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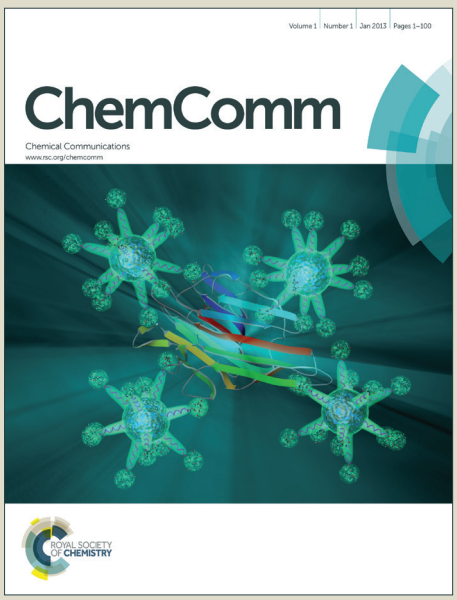

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Mukaiyama aldol reaction of *in situ* generated nitrosocarbonyl compounds: selective C–N bond formation and N–O bond cleavage in one-pot for α-amination of ketones

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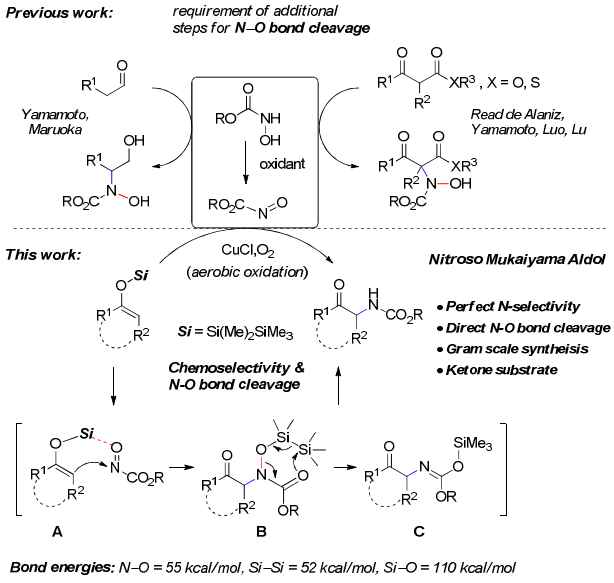
A practical protocol for the α-amination of ketones (up to 99% yield) has been developed via Mukaiyama aldol reaction of *in situ* generated nitrosocarbonyl compounds. The reaction with silyl enol ethers having disilane (-SiMe$_2$TMS) backbone proceeded not only with perfect *N*-selectivity but also concomitant N–O bond cleavage was accomplished. Such cascade of C–N bond formation and N–O bond cleavage in a single step was heretofore unknown in the field of nitrosocarbonyl chemistry. A very high diastereoselectivity (d.r. = 19:1) was accomplished using (-)-menthol derived chiral nitrosocarbonyl compound.

The α-amino ketones constitute a very rapidly developing field of research as molecules containing this functionality are widely represented among pharmaceutically active compounds and complex natural products.[1] The invention of practical synthetic strategies toward this high-value synthon has long been a challenge for organic chemists.[2,3] One straight forward approach is the electrophilic α-amination of ketones.[2] At present various electrophilic aminating agents are available and amongst them the nitrosocarbonyl compounds have gained considerable attention.[4] They can be efficiently generated *in situ* with mild oxidation protocols and more importantly products thus obtained can also be easily manipulated for further transformation.[5] This mitigates the prior limitations such as the difficulty in N–N bond cleavage for azodicarboxylates and burden of N–Ph bond cleavage for nitrosobenzene.[6,7] Despite these advantages the success of synthetically versatile nitrosocarbonyl compounds are still immature, particularly when aldol type reactions are concerned. Nitrosocompounds are prototypes of ambident electrophile and thus, both the C–N and C–O bonds can be constructed from a single source. While more examples are known with excellent *O*-selectivity (*O*-nitroso aldol), reports on high *N*-selective nitrosocarbonyl aldol reactions (*N*-NA) are limited.[8] Current state of the art dictates that breakthrough came, both in asymmetric and racemic versions, only with active methylene type compounds such as β-ketoesters andaldehyde substrates (Scheme 1).[9,10] Heretofore, there is no single report which deals with the α-amination of simple ketones using nitrosocarbonyl compounds. Furthermore, in all the previously reported *N*-NA reactions of nitrosocarbonyl compounds, aldol products were isolated in the form of hydroxylamine (C–N–OH) derivatives and thus, additional steps are obligatory to cleave N–OH bond for further use of the amine moiety.[11] Therefore, development of high *N*-selective nitroso aldol reaction of ketones with concomitant N–O bond cleavage in a single step under mild condition is highly desirable.



Scheme 1 Selective C–N bond formation with nitrosocarbonyl compounds

We envisioned that Mukaiyama aldol reaction of silyl enol ethers having disilane backbone and nitrosocarbonyl

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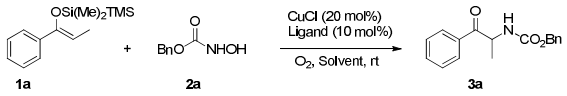
compounds could be a prompt solution of these issues (Scheme 1). The oxophilic nature of silicon will allow coordination of nitrosocarbonyl compound via oxygen center leaving nitrogen center free for the aldol reaction and thus, high *N*-selectivity is expected (Scheme 1, **A**). Furthermore, during this process the silyl group will switch from the oxygen center of silyl enol ether to the oxygen center of nitroso aldol product **B**. Considering the bond energies of N–O (55 kcal/mol), Si–Si (52 kcal/mol), and Si–O (110 kcal/mol) bonds, we also envisaged that product **B** may undergo rearrangement with the cleavage of weak N–O bond *en route* to α-amination of ketones.[12,13] Hence, both the C–N bond formation and N–O bond cleavage can be executed in a single step. However, one should take into account that labile silyl enol ether should not be affected by the oxidation cycle for *in situ* generation of nitrosocarbonyl compounds. Herein, we report an unprecedented Mukaiyama aldol reaction of in situ generated nitrosocarbonyl compounds, which avoids post manipulation of N–O bond cleavage for direct α-amination of ketones.

We commenced our experiment with readily available disilane backbone containing silyl enol ether **1a** as a model substrate and very mild aerobic oxidation technique (CuCl, pyridine, and oxygen) was selected for the *in situ* generation of nitrosocarbonyl compound from commercially available hydroxamic acid **2a** (Table 1). Control experiment revealed that silyl enol ether was fully compatible under this oxidation conditions. To our delight, when **2a** was slowly injected into a THF solution of **1a**, CuCl (20 mol%), and pyridine (10 mol%) under oxygen atmosphere at room temperature, nitrosocarbonyl Mukaiyama aldol reaction proceeded smoothly with perfect *N*-selectivity and concomitant N–O bond cleavage delivering product **3a** in 81% isolated yield (entry 1). The compound **3a** was crystallized and x-ray analysis unambiguously confirmed both the *N*-selectivity and N–O bond cleavage (Table 1, below). The slow addition of **2a** is necessary to avoid condensation between *in situ* formed nitrosocarbonyl species and excess hydroxamic acid **2a**. The changing of solvent from THF to acetonitrile increased the yield significantly and the aldol product **3a** was obtained in 98% yield (entry 2). The reaction seems to be also efficient with other amine ligands. The 2,2-bipyridine and 2-ethyl-2-oxazoline (EtOx) also offered desired product **3a** in 96% and 83% yields respectively, albeit the reaction rate was slow for later case (entries 3,4). The presence of a secondary catalyst such as $Cu(OTf)_2$ gave diminished yield and in this situation considerable desilylation of **1a** was observed (entry 5). The reaction completely failed when MnO_2 was employed as an oxidant for the *in situ* generation of nitrosocarbonyl compound (entry 6).

With the optimal reaction conditions in hand, the substrate scope of this novel *N*-selective nitrosocarbonyl Mukaiyama aldol cascade for the direct production of α-amino ketones was explored and the results are summarized in Table 2.[14] The reaction is quite general for a broad spectrum of silyl enol ethers, cyclic and acyclic, to afford *N*-nitrosocarbonyl aldol products **3** in excellent yields. The silyl enol ethers containing

Table 1 Optimization of Mukaiyama aldol reaction of nitrosocarbonyl compound.[a]

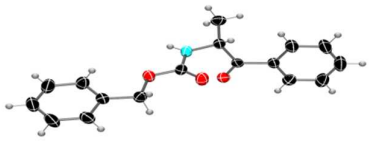


1a **2a** **3a**

Entry	Solvent	Ligand	Yield [%][b]
1	THF	Pyridine	81
2	**CH_3CN**	**Pyridine**	**98**
3	CH_3CN	Bipyridine[c]	96
4	CH_3CN	EtOx[d]	83
5[e]	CH_3CN	Pyridine	66%
6[f]	CH_3CN	Pyridine	N.R.

[a] Reaction Conditions: **1a** (0.15 mmol), **2a** (0.19 mmol), CuCl (0.03 mmol), ligand (0.015 mmol), and oxygen balloon. [b] Yield of isolated product. [c] 2,2′-Bipyridine. [d] EtOx: 2-Ethyl-2-oxazoline, 24 h. [e] In the presence of 10 mol% $Cu(OTf)_2$. [f] MnO_2 as oxidant was used instead of $CuCl/O_2$ combination. Desilylation was observed with the recovery of propiophenone.

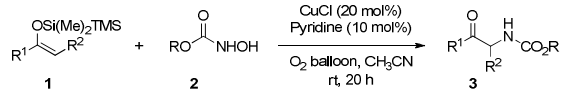
Crystal structure of **3a**:

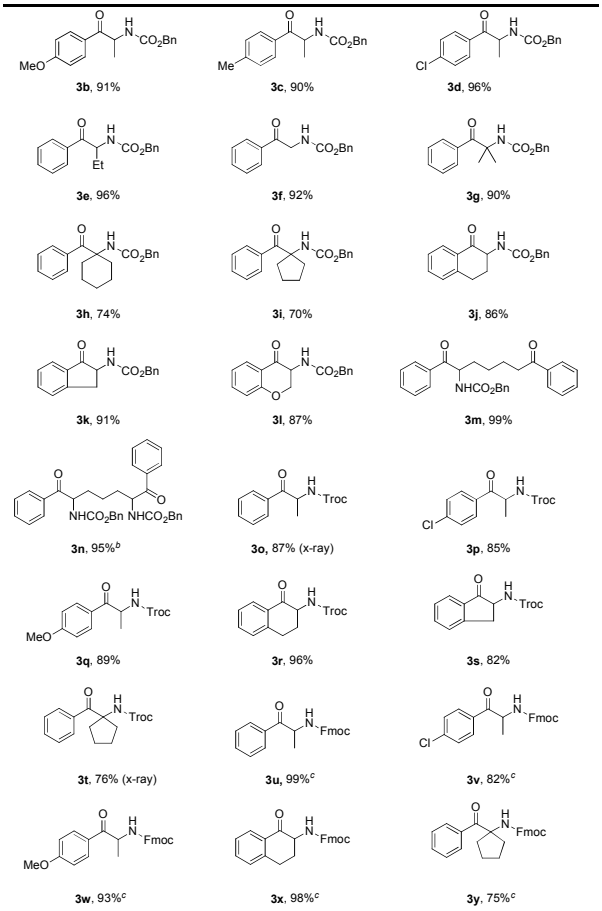


both the electron donating and withdrawing substituents (**1b**-**e**) furnished uniformly excellent yields (90-96%). The reactions with sterically hindered fully-substituted silyl enol ethers (**1g**-**i**) worked equally well and delivered quaternary α-amino ketones **3g**-**i** in high yields (70-90%). The unsubstituted silyl enol ether **1f** was also efficient to yield product **3f** in 92% yield. Double nitrosoaldol reaction gave synthetically important 1,5-diamine in 95% yield (**3m** *vs.* **3n**). The silyl enol ethers derived from 1-tetralone, 1-indanone, and 4-chromanone produced cyclic α-amino ketones (**3j**-**l**) in excellent yield (86-91%). The reaction is not restricted only to the Cbz-protected hydroxamic acid **2a**. Other hydroxamic acids with easily removable protecting group such as Troc-NHOH and Fmoc-NHOH are also efficient for α-amination delivering Troc- and Fmoc-protected α-amino ketones (**3o**-**t** and **3u**-**y**, respectively) in very high to excellent yields (75-99%, Table 2). The reaction was sluggish in case of Boc-protected hydroxamic acid, which can be interpreted with the consideration of steric crowding.

To test the synthetic utility of the present nitrosocarbonyl Mukaiya aldol cascade, we have executed the reaction on a gram scale. With 20 mol% catalyst loading under the optimized reaction conditions, *N*-selective nitroso aldol cascade proceeded smoothly and corresponding α-amino ketone **3a** was obtained in 97% yield (1.11 g, Scheme 2). Thus, the scale up is compatible with this protocol.

Table 2. Scope of the *N*-selective nitrosocarbonyl Mukaiyama aldol reaction.[a]

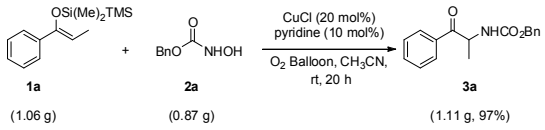




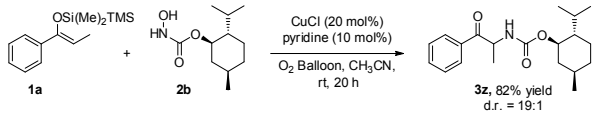
[a] Reaction Conditions: **1** (0.15 mmol), **2** (0.19 mmol), CuCl (0.03 mmol), pyridine (0.015 mmol), and oxygen balloon. Yields of isolated products are given. [b] Reaction time was 36 h. [c] THF (1 mL) was used as co-solvent.

In order to further demonstrate the synthetic utility of this protocol, we have illustrated a representative example of diastereoselective nitrosocarbonyl Mukaiyama aldol cascade using chiral nitrosocarbonyl compound (Scheme 3). When (-)-menthol derived chiral hydroxamic acid **2b** was reacted with silyl enol ether **1a** under the optimized reaction conditions, chiral α-amino ketone **3z** was obtained in very high yield (82%) with excellent diastereoselectivity (d.r. = 19:1).

To support the plausible reaction mechanism, we have performed Mukaiyama aldol reaction of *in situ* generated nitrosocarbonyl compounds with TMS- and TBS-substituted silyl enol ethers under identical reaction conditions (Table 3). When TMS-substituted silyl enol ethers **4** are used, perfect *N*-selectivity was accomplished with Cbz-, Troc-, Fmoc- and Boc-protected hydroxyl amines. However, the concomitant N–O

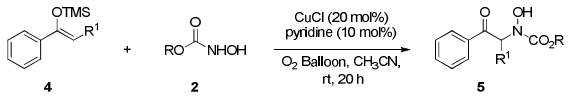


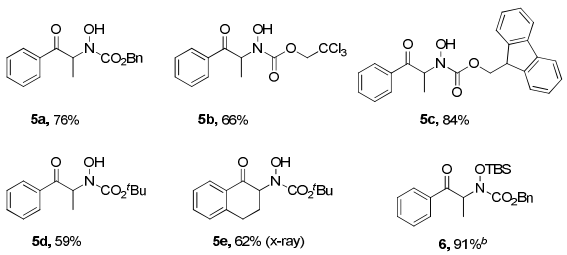
Scheme 2 Scale up of the *N*-selective nitrosocarbonyl Mukaiyama aldol reaction.



Scheme 3 Control of diastereoselectivity with the chiral nitrosocarbonyl compound.

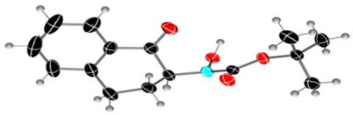
Table 3 N-Selective nitrosocarbonyl Mukaiyama aldol reactions with TMS-substituted silyl enol ethers.[a]





[a] Reaction Conditions: **4** (0.19 mmol), **2** (0.25 mmol), CuCl (0.04 mmol), pyridine (0.019 mmol), and oxygen balloon. Yields of isolated products are given. [b] Reaction was conducted with TBS-substituted silyl enol ether.

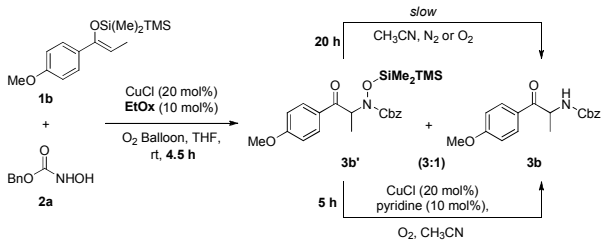
Crystal structure of **5e**:



bond cleavage was not observed and the α-hydroxyamino derivatives **5a-e** were isolated in good yields (59-84%). Compound **5e** was crystalized and x-ray analysis unambiguously sanctioned the presence of N–OH bond (Table 3 below). In case of TBS-protected silyl enol ether, *N*-selective nitroso aldol reaction also took place without N–O bond cleavage and here, *N*-nitrosocarbonyl aldol product **6** was isolated in 91% yield in the form of TBS-protected (Table 3). The product **6** did not undergo N–O bond cleavage even after prolonging the reaction time. For TBS- and TMS-substituted silyl enol ethers, rearrangement via six-membered cyclic intermediate is not feasible and hence, N–O bond cleavage is restricted. These findings suggest that disilane backbone is

very special for this nitrosocarbonyl aldol cascade, which is in agreement with our prior intuition.

Further tuning the reaction conditions revealed that the conversion of the intermediate **3b'** to **3b** is comparatively slow for 2-ethyl-2-oxazoline (EtOx) ligand in THF solvent and a 3:1 mixture of **3b'** and **3b** was isolated by shorting the reaction time to 4.5 h (Scheme 4, ESI page S18). When this mixture was exposed to pure CH_3CN under nitrogen and oxygen separately, **3b'** slowly converted to **3b** in 20 h at room temperature for both the cases. Under our optimized reaction conditions, this conversion took place only in 5 h. Such disparity in reaction rates suggests that the conversation of **3b'** to **3b** is thermally feasible, however, the copper-pyridine complex catalyzes this novel transformation.



Scheme 4 Mechanistic insights.

In conclusion, we have developed unprecedented Mukaiyama aldol reaction of *in situ* generated nitrosocarbonyl compounds with silyl enol ethers having disilane backbone. The reaction is perfect *N*-selective and delivered α-amino ketones in excellent yields with concomitant N–O bond cleavage. Such unique cascade of C–N bond formation and N–O bond cleavage in a single step had not been realized previously in the field of nitrosocarbonyl chemistry. The reaction is scalable and a high diastereoselectivity was observed when chiral nitrosocompound was employed. Studies towards a catalytic asymmetric variant of this novel transformation and computational studies to disclose the mechanistic details are currently ongoing.

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Notes and references

1 (a) F. I. Carroll, B. E. Blough, P. Abraham, A. C. Mills, J. A. Holleman, S. A. Wolckenhauer, A. M. Decker, A. Landavazo, K. T. McElroy, H. A. Navarro, M. B. Gatch and M. J. Forster, *J. Med. Chem.,* 2009, **52**, 6768; (b) P. C. Meltzer, D. Butler, J. R. Deschamps and B. K. Madras, *J. Med. Chem.,* 2006, **49**, 1420; (c) M. C. Myers, J. Wang, J. A. Iera, J.-K. Bang, T. Hara, S. Saito, G. P. Zambetti and D. H. Appella, *J. Am. Chem. Soc.,* 2005, **127**, 6152; (d) R. W. Evans, J. R. Zbieg, S. Zhu, W. Li and D. W. C. MacMillan, *J. Am. Chem. Soc.,* 2013, **135**, 16074.

2 For reviews: (a) J. M. Janey, *Angew. Chem. Int. Ed.,* 2005, **44**, 4292; (b) T. Vilaivan and W. Bhanthumnavin, *Molecules,* 2010, **15**, 917; (c) P. Dembech, G. Seconi and A. Ricci, *Chem. Eur. J.,* 2000, **6**, 1281; (d) A. M. R. Smith and K. K. Hii, *Chem. Rev.,* 2011, **111**, 1637; (e) C. Greck, B. Drouillat and C. Thomassingny, *Eur. J. Org. Chem.,* 2004, 1377; (f) E. Erdik, *Tetrahedron,* 2004, **60**, 8747.

3 (a) N. Matsuda, K. Hirano, T. Satoh and M. Miura, *Angew. Chem. Int. Ed.,* 2012, **51**, 11827; (b) T. Miura and M. Morimoto, *Org. Lett.,* 2012, **14**, 5214; (c) M. Lamani and K. R. Prabhu, *Chem. Eur. J.,* 2012, **18**, 14638; (d) Y. Wei, S. Lin, and F. Liang, *Org. Lett.,* 2012, **14**, 4202; (e) S. Guha, V. Rajeshkumar, S. S. Kotha and G. Sekar, *Org. Lett.,* 2015, **17**, 406.

4 For reviews: (a) B. S. Bodnar and M. J. Miller, *Angew. Chem. Int. Ed.,* 2011, **50**, 5630; (b) M. Baidya and H. Yamamoto, *Synthesis,* 2013, **45**, 1931; (c) L. I. Palmer, C. P. Frazier and J. Read de Alaniz, *Synthesis,* 2014, **46**, 269; (d) G. W. Kirby, *Chem. Soc. Rev.,* 1977, **6**, 1; (e) W. Adam and O. Krebs, *Chem. Soc. Rev.,* 2003, **103**, 4131; (f) S. Iwasa, A. Fakhruddin and H. Nishiyama, *Mini-Rev. Org. Chem.,* 2005, **2**, 157.

5 (a) P. Selig, *Angew. Chem. Int. Ed.,* 2013, **52**, 7080; (b). C. Yu, A. Song, F. Zhang and W. Wang, *ChemCatChem,* 2014, **6**, 1863.

6 Amination with azodicarboxylates: (a) N. Kimaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig and K. A. Jørgensen, *J. Am. Chem. Soc.,* 2002, **124**, 6254; (b) M. Marigo, K. Juhl and K. A. Jørgensen, *Angew. Chem. Int. Ed.,* 2003, **42**, 1367; (c) S. Saaby, M. Bella and K. A. Jørgensen, *J. Am. Chem. Soc.,* 2004, **126**, 8120; (d) T. Takeda and M. Terada, *J. Am. Chem. Soc.,* 2013, **135**, 15306; (e) X. Yang and F. D. Toste, *J. Am. Chem. Soc.,* 2015, **137**, 3205.

7 Amination with nitrosobenzenes: (a) N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.,* **2004**, *126*, 5360; (b) N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.,* 2005, **127**, 1080; (c) T. Kano, M. Ueda, J. Takai and K. Maruoka, *J. Am. Chem. Soc.,* 2006, **128**, 6046; (d) J. L. Cantarero, M. B. Cid, T. B. Poulsen, M. Bella, J. L. G. Ruana and K. A. Jørgensen, *J. Org. Chem.,* 2007, **72**, 7062; (e) C. Palomo, S. Vera, I. Velilla, A. Mielgo and E. G. Bengoa, *Angew. Chem. Int. Ed.,* 2007, **46**, 8054; (f) T. Sasaki, Y. Ishibashi and M. Ohno, *Chem. Lett.,* 1983, 863; (g) T. Sasaki, K. Mori and M. Ohno, *Synthesis,* **1985**, 279.

8 For *O*-nitroso aldol reactions: (a) M. Baidya, K. A. Griffin and H. Yamamoto, *J. Am. Chem. Soc.,* 2012, **134**, 18566; (b) C. P. Frazier, D. Sandoval, L. I. Palmer and J. Read de Alaniz, *Chem. Sci.,* 2013, **4**, 3857; (c) B. Maji and H. Yamamoto, *Angew. Chem. Int. Ed.,* 2014, **53**, 14472; (d) W. Yang, L. Huang, Y. Yu, D. Pflästerer, F. Rominger and A. S. K. Hashmi, *Chem. Eur. J.,* 2014, **20**, 3927; (e) B. Maji and H. Yamamoto, *Synlett,* 2015, DOI: 10.1055/s-0034-1380290.

9 Reactions with β-ketoesters: (a) D. Sandoval, C. P. Frazier, A. Bugarin and J. Read de Alaniz, *J. Am. Chem. Soc.,* 2012, **134**, 18948; (b) C. Xu, L. Zhang and S. Luo, *Angew. Chem. Int. Ed.,* 2014, **53**, 4149; (c) B. Maji, M. Baidya and H. Yamamoto, *Chem. Sci.,* 2014, **5**, 3941; (d) M.–Q. Liang and C.-D. Lu, *Synlett,* 2014, **25**, 991; For computational study, (e) L. Zhang, C. Xu, X. Mi and S. Luo, *Chem. Asian J.,* 2014, **9**, 3565.

10 Reactions with aldehydes: a) T. Kano, F. Shirozu and K. Maruoka, *J. Am. Chem. Soc.,* 2013, **135**, 18036; (b) T. Kano, F. Shirozu and K. Maruoka, *Org. Lett.,* 2014, **16**, 1530; (c) B. Maji and H. Yamamoto, *Angew. Chem. Int. Ed.,* 2014, **53**, 8714.

11 S. Murru, C. S. Lott, F. R. Fronczek and R. S. Srivastava, *Org. Lett.,* 2015, **17**, 2122.

12 R. T. Sanderson, in *Chemical Bonds and Bond Energy*, Academic Press, New York, 1976.

13 For the rearrangement of organosilicon compounds: A. G. Brook, *Acc. Chem. Res.,* 1974, **7**, 77.

14 Reaction did not work with corresponding silyl enol ethers derived from cyclohexanone and cyclopentanone.