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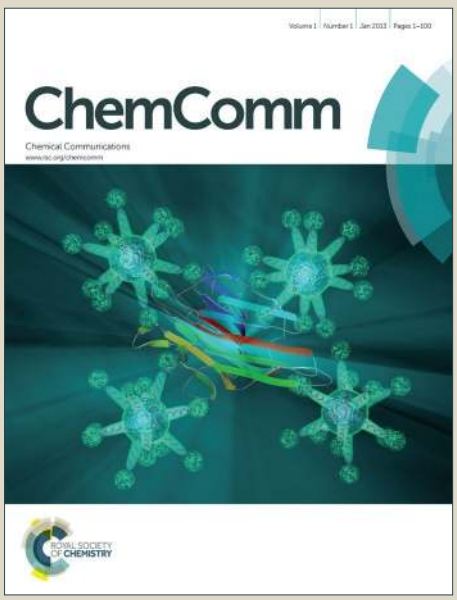

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Brønsted acid mediated N–O bond cleavage for α-amination of ketones through aromatic nitroso aldol reaction

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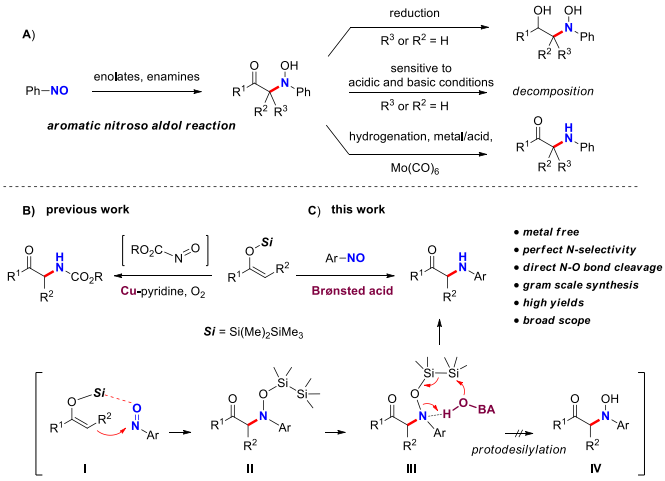
A Brønsted acid mediated N–O bond clevage for α-amination of ketones has been developed through nitroso aldol reaction of less-reactive aromatic nitroso compounds and silyl enol ethers having disilane (-SiMe$_2$TMS) backbone. This transformation is operationally simple and scalable, offering structurally diverse α-amino ketones in high yields (up to 98%) with complete regioselectivity. It represents a mechanistically unique and rare example of metal-free N–O bond clevage process.

The α-amino ketone functionality is a common motif in many classes of bioactive compounds and complex natural products, which has inspired considerable efforts towards the development of efficient synthetic strategies for this high value synthon.[1-3] A conceptually simple and direct way is the electrophilic α-amination of ketones using nitroso compounds.[4,5] Among the various nitroso compounds, nitrosobenze is one of the oldest candidates prepared by Baeyer at the end of nineteenth century.[6] It is bench-stable and many derivatives thereof are also readily prepared. However, the progress of their use in organic synthesis is limited with respect to the choice of nucleophiles, particularly when the nitroso-aldol reaction is considered. This has been rationalized based on the weak reactivity of aromatic nitroso compounds. Consequently, successes have primarily been achieved with more reactive reaction partners such as metal-enolates and enamines both in racemic and asymmetric fashion (Scheme 1A).[7,8] Additionally, nitroso compounds are prototypes of ambient electrophiles and thus, under judicious reaction conditions both the C–N and C–O bonds can be selectively fabricated from a single source. While more examples are known for *O*-selective nitroso aldol reaction with aromatic nitroso compounds, only a handful of reports are available for their *N*-selective nitroso aldol reaction.[9,10] This is likely because *N*-selective aromatic nitroso aldol product is sensitive to water elimination leading to product decomposition. Thus, the reaction is largely restricted for the fully substituted enolates.[8b,9] For other cases, either special precaution was adapted during isolation process or the acidity of the α-hydrogen was altered via *in situ* reduction of carbonyl group to alcohol.[8,11] Furthermore, additional steps were enforced to cleave the N–O bond. Very often metal catalyzed reduction and toxic $Mo(CO)_6$ mediated N–O bond cleavage routes are considered for this purpose, which are unsuitable for the late-stage derivatization of functionalized molecules (Scheme 1A).[4] Therefore, the development of *N*-selective aldol reaction of aromatic nitroso compounds with concomitant N–O bond cleavage without affecting the ketone functionality under mild conditions is highly desirable.



Scheme 1 α-Amination of ketones through nitroso aldol reaction.

In an effect to achieve a solution to the preceding problems, we sought to develop a mechanistically distinct pathway for general *N*-selective aromatic nitroso aldol reaction followed by highly functional group compatible N–O bond cleavage in one-pot manner. Early reports of Sasaki have revealed that reaction of TMS-silyl enol ethers with nitrosobenzene proceeds with *N*-selectivity.[12] However, the

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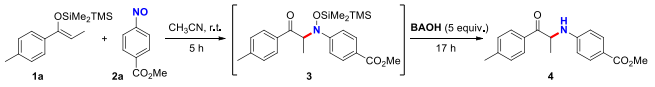
scope of this reaction is very limited and N–O bond cleavage *en route* to α-amino ketones was not addressed. Based on our previous experiences–transition metal catalyzed *N*-selective Mukaiyama nitroso aldol reactions of *in situ* generated nitrosocarbonyl compounds (Scheme 1B)[13]–we have reasoned that ketones derived silyl enol ethers having disilane backbone might react with less reactive aromatic nitroso compounds (Scheme 1C). The Si–Si bond not only increases the reactivity of enol ether by hyperconjugation,[10g] it will also favor the *N*-selectivity by blocking the oxygen center of the nitroso compound through coordination (Scheme 1, below). Further, the product (**II**) thus obtained is also expected to be more stable due the protection of bulky pentamethyldisilanyl group and hence, it is unbiased from decomposition. Now, the presence of a Brønsted acid (BAOH) would selectively trigger the N–O bond cleavage as depicted in Scheme 1, **III**. This is likely because basicity of aromatic amines is high enough to interact with weak Brønsted acid, which stimulates oxophilic silicon for the rearrangement. Consideration of higher Si–O (110 kcal mol^{-1}) bond energy compared to Si–Si (52 kcal mol^{-1}) and N–O (55 kcal mol^{-1}) bond energies also supports this conjecture.[14] Therefore, both the installation of C–N bond and the cleavage of N–O bond can be accomplished in one-pot manner under metal free conditions. However, a decisive choice of Brønsted acids is necessary to nullify the protodesilylation pitfall (Scheme 1, **IV**).

Herein, we describe a Brønsted acid mediated N–O bond cleavage for α-amination of ketones through perfect *N*-selective nitroso aldol reaction of aromatic nitroso compounds and ketones derived silyl enol ethers having disilane backbone. Further, the products are also converted to fully substituted heterocycles, for which limited methods are available.

To prove the viability of this approach, we have intently investigated the reaction of readily available disilane backbone containing silyl enol ether **1a** with nitroso compound **2a** in acetonitrile and the influence of Brønsted acids (BAOH) covering a broad range of p*K*a values in one-pot fashion (Table 1). After the consumption of silyl enol ether (TLC monitored), the Brønsted acid, benzoic acid (p*K*a = 4.20, 5 equiv.), was introduced into the reaction flask at room temperature and we were thrilled to discover the direct formation of α-amino ketone **4** in 81% isolated yield (Table 1, entry 1). It is worth noting that *O*-selective nitroso aldol product was undetected for this reaction. The compound **4** was recrystallized and the X-ray analysis unambiguously demonstrated that the aldol reaction proceeded not only with *N*-selectivity but concomitant N–O bond cleavage also took place selectively.[15] Changing the Brønsted acids to acetic acid (p*K*a = 4.76) and 2,2,2-trifluoroethanol (p*K*a = 12.5) resulted in only trace amount of the product (entries 2,3). Presence of substituted catechol (p*K*a = 9.96) delivered only moderate yield (entry 4). When phenylboronic acid (p*K*a = 8.83) was employed, the reaction was very clean and the desired product was isolated with very high yield (90%, entry 5). Use of stronger acid such as phosphoric acid (p*K*a = 2.12) reduced the yield significantly (entry 6). Considering relatively benign toxicology profile of boronic acids and their importance in organic synthesis,[16] we have selected phenylboronic acid for further reaction optimization. Interestingly, the reaction yield was improved up to 94% when loading of phenylboronic acid was reduced from 5 equivalent to 3 equivalent; however, further lowering the catalyst loading is not fruitful giving diminished yield of the desired product (entries 7-9).

Table 1 Screening of Brønsted acids and optimization of the reaction conditions.[a]



Entry	BAOH	Yield [%][b]
1	$PhCO_2H$	81
2[c]	CH_3CO_2H	< 5
3[c]	CF_3CH_2OH	trace
4	4-tert-Butylcatechol	58
5	$PhB(OH)_2$	90
6	H_3PO_4	42
7	**$PhB(OH)_2$ (3 equiv.)**	**94**
8[d]	$PhB(OH)_2$ (1.5 equiv.)	62
9[d,e]	$PhB(OH)_2$ (1 equiv.), MeOH	46

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.18 mmol), CH_3CN (3 ml), **BAOH** (0.75 mmol). [b] Yield of isolated product. [c] TLC showed the presence of intermediate **3** and its decomposition was not observed with the course of the reaction. [d] Incomplete conversion. [e] Reaction time was 36 h and 100 equiv. of MeOH was used. **BAOH**: Brønsted acid.

Crystal structure of **4**:

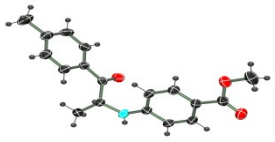
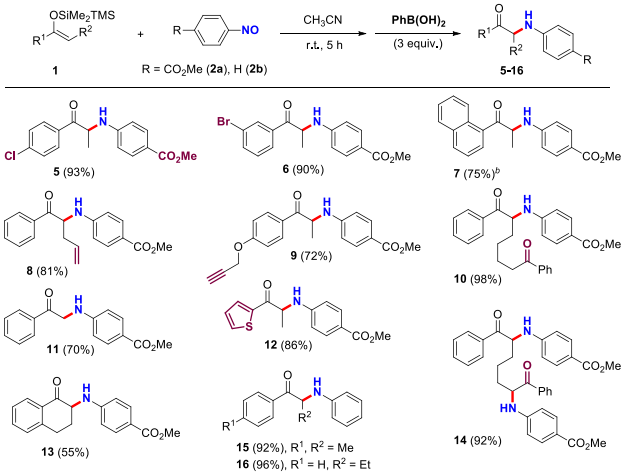


Table 2 Scope of the α-amination reaction.[a]

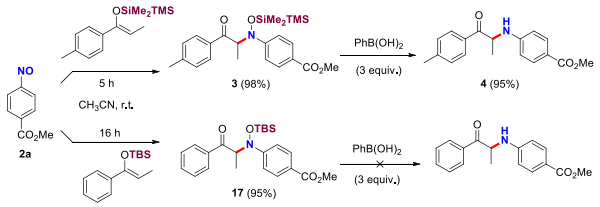


[a] Reaction conditions: **1** (0.15 mmol), **2** (0.18 mmol), CH_3CN (3 ml), $PhB(OH)_2$ (0.45 mmol). Yield of the isolated products are given. [b] Reaction time was 24 h.

Under the optimised conditions, the scope of this metal-free α-amination of ketones has been explored. The reaction proceeded smoothly with various silyl enol ethers delivering the desired products (**5**-**16**) in very high yields (Table 2).[17] The functional group compatibility of this reaction is remarkable; halogens (**5**,**6**), double bond (**8**), triple bond (**9**), ketone (**10**)

and ester substitutions were undisturbed. The silyl enol ether derived from heterocyclic and cyclic ketones are also suitable for this reaction, generating compound **12** and **13** in 86% and 55% isolated yields respectively. The double α-amination reaction furnished synthetically important 1,5-diamine **14** in 92% yield. The reaction is not restricted only for the electron-withdrawing substituted nitroso compound (**2a**); commercially available parent nitrosobenze (**2b**) also gave the desired products (**15**-**16**) in excellent yields (92-96%).

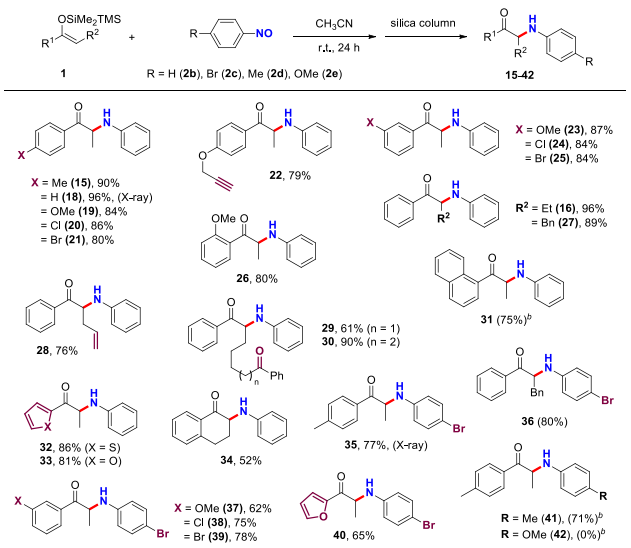
In order to probe the reaction mechanism, we have executed the reaction of TBS- and TMS-Si(Me)$_2$-substituted silyl enol ethers with **2a** (Scheme 2). The reaction was *N*-selective for both the silyl enol ethers and the nitroso aldol products **3** and **17** were isolated as silicon protected in 98% and 95% yields, respectively. When the product **17** was exposed to phenylboronic acid under standard conditions, N–O bond cleavage was not observed even after prolonging the reaction time. In sharp contrast, N–O bond cleavage took place efficiently with product **3** under the identical conditions and the α-amino ketone **4** was isolated in 95% yield, which is comparable to the result obtained for the reaction with boronic acid. These findings suggest that disilane backbone is very important for this strategy.



Scheme 2 Control experiments with TBS- and TMS-Si(Me)$_2$-substituted silyl enol ethers.

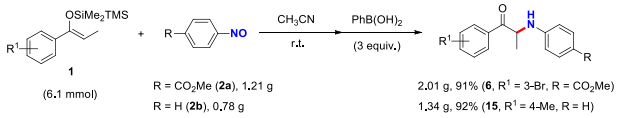
While monitoring the progress of the reaction of silyl enol ether **1a** with nitrosobenzene **2b** by TLC, we have noticed that a new spot was generated in the TLC plate and the R_f–value of this new spot is also identical with the final cleavage product **15**. From this observation, we envisaged that silica gel could also promote this reaction and in that scenario, N–O bond might cleave during the purification by silica gel column chromatography. Accordingly, after the completion of the first aldol step, the crude reaction mixture was loaded directly onto the silica gel column. To our delight, the N–O bond cleavage took place cleanly delivering the α-amino ketone **15** in 90% yield (Table 3). This novel reaction is quite general and a broad spectrum of highly functionalized α-amino ketones including substituted heterocycles (**15**-**34**) were synthesized in very high to excellent yields (up to 96%, Table 3). The reaction also worked well for *p*-bromo and *p*-methyl substituted nitroso compounds producing the α-amino ketones **35**-**41** in high yields (65-80%). However, the aldol step needed longer time for the latter case. For more electron enriched nitroso compound such as **2e** (R = OMe), the aldol reaction did not proceed. Overall, silica gel promoted N–O bond cleavage protocol augurs well as an alternative potent strategy towards α-amino ketone synthesis. However, it is not effective for electron-withdrawing substituted nitroso compounds such as **2a**. The presence of electron withdrawing group reduces the basicity of the aldol product and this disparity in pKa values is possibly the reason of this failure.

Table 3 Silica gel promoted N–O bond cleavage for α-amination of ketones through nitroso aldol reaction.[a]

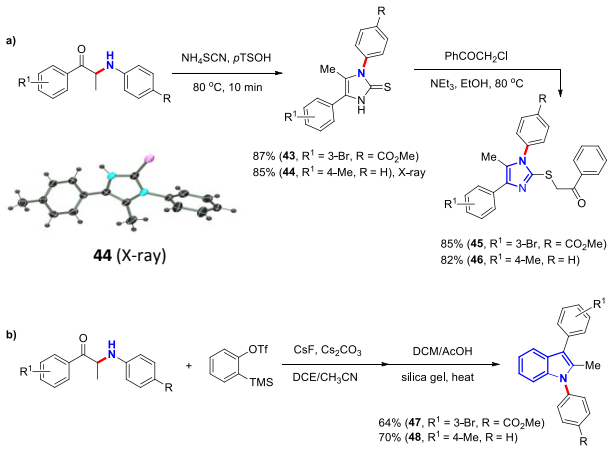


[a] Reaction conditions: **1** (0.15 mmol), **2** (0.18 mmol), CH_3CN (3 ml), Silica gel (Merck 100-200 mesh, 30 g, 30 cm column length). Yield of the isolated products were given. [b] Reaction time was 36 h.

To highlight the synthetic utility of the present protocol, we have executed the reaction of silyl enol ethers **1a** and **1c** with nitroso compound **2** in gram sale (Scheme 3). Gratifyingly, both the amination products were obtained in comparable yields (92 and 91% respectively).



Scheme 3 Scale up of the α-amination reaction.



Scheme 4 Application towards the synthesis of fully substituted imidazoles and indoles.

Given the significance of the heterocycles in medicinal chemistry and as synthetic intermediates, we have also successfully converted the α-amino ketone products to highly substituted heterocycles.[18] Treatment of NH_4SCN under acidic conditions followed by base promoted alkylation delivered fully substituted imidazoles **45**-**46** in high yields (Scheme 4a). Compound **44** was crystalized and X-ray analysis results were used to determine the regioselectivity. Furthermore, substituted indoles **47**-**48** were also synthesized in straightforward manner using [3+2] cycloaddition reaction with benzynes in good yields (Scheme 4b).

In conclusion, we have developed a novel one-pot synthesis of α-amino ketones by integrating nitroso aldol reaction of aromatic nitroso compounds with silyl enol ethers having disilane backbone and a Brønsted acid mediated unprecedented N–O bond cleavage strategy. This protocol is operationally simple, scalable, perfect *N*-selective, and displays a broad substrates scope with high yields (up to 98%). Computational studies to unfold the mechanistic details and investigations towards a catalytic variant of this novel transformation 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; (g). C. Yu, A. Song, F. Zhang and W. Wang, *ChemCatChem,* 2014, **6**, 1863.

3 For selective examples see: (a) S. Saaby, M. Bella and K. A. Jørgensen, *J. Am. Chem. Soc.,* 2004, **126**, 8120; (b) N. Matsuda, K. Hirano, T. Satoh and M. Miura, *Angew. Chem. Int. Ed.,* 2012, **51**, 11827; (c) T. Miura and M. Morimoto, *Org. Lett.,* 2012, **14**, 5214; (d) M. Lamani and K. R. Prabhu, *Chem. Eur. J.,* 2012, **18**, 14638; (e) Y. Wei, S. Lin, and F. Liang, *Org. Lett.,* 2012, **14**, 4202; (f) T. Takeda and M. Terada, *J. Am. Chem. Soc.,* 2013, **135**, 15306; (g) S. Guha, V. Rajeshkumar, S. S. Kotha and G. Sekar, *Org. Lett.,* 2015, **17**, 406. (h) D. Yadagiri and P. Anbarasan, *Chem. Commun.* 2015, ***51***, 14203; (i) X. Yang and F. D. Toste, *J. Am. Chem. Soc.,* 2015, **137**, 3205.

4 For reviews: (a) H. Yamamoto and N. Momiyama, Chem. Commun. 2005, 3514; (b) B. S. Bodnar and M. J. Miller, *Angew. Chem. Int. Ed.,* 2011, **50**, 5630; (c) L. I. Palmer, C. P. Frazier and J. Read de Alaniz, *Synthesis,* 2014, **46**, 269; (d) B. Maji and H. Yamamoto, *Bull. Chem. Soc. Jpn.* 2015, **88**, 753.

5 For selected examples: (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) S. Murru, C. S. Lott, F. R. Fronczek and R. S. Srivastava, *Org. Lett.,* 2015, **17**, 2122. (e) D. J. Fisher, G. L. Burnett, R. Velasco and J. Read de Alaniz, *J. Am. Chem. Soc.,* 2015, **137**, 11614; (f) D. Sandovol, A. V. Samonshin and J. Read de Alaniz, *Org. Lett.,* 2015, **17**, 4514.

6 A. Baeyer, *Chem. Ber.*, 1874, **7**, 1638.

7 Reaction with metal enolates: (a) N. Momiyama and H. Yamamoto, *Org. Lett.,* 2002, **4**, 5360; (b) K. Shen, X. Liu, G. Wang, L. Lin and X. Feng, *Angew. Chem. Int. Ed.,* 2011, **50**, 4684; (c) A. Yanagisawa, T. Fujinami, Y. Oyokawa, T. Sugita and K. Yoshida, *Org. Lett.,* 2012, **14**, 2434.

8 Reaction with enamines: (a) N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.*, 2005, **127**, 1080; (b) H.-M. Guo, L. Cheng, L.-F. Cun, L.-Z. Gong, A.-Q. Mi and Y.-Z. Jiang, *Chem. Commun.*, 2006, 429; (c) C. Palomo, S. Vera, I. Velilla, A. Mielgo and E. Gomez-Bengoga, *Angew. Chem. Int. Ed.*, 2007, **46**, 8054.

9 For *N*-selective aromatic nitroso aldol reactions: (a) J. L. Cantarero, M. B. Cid, T. B. Poulsen, M. Bella, J. L. G. Ruano and K. A. Jørgensen, *J. Org. Chem.*, 2007, **72**, 7062; (b) See also ref. 8.

10 For *O*-selective aromatic nitroso aldol reactions: (a) N. Momiyama and H. Yamamoto, *Angew. Chem. Int. Ed.,* 2002, **41**, 2986; (b) N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.,* 2003, **125**, 6038; (c) S. P. Brown, M. P. Brochu, C. J. Sinz and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2003, **125**, 10808; (d) A. Bøgevig, H. Sunden and A. Cordova, *Angew. Chem. Int. Ed.,* 2004, **43**, 1109; (e) T. Kano, M. Ueda, J. Takai and K. Maruoka, *J. Am. Chem. Soc.*, 2006, **128**, 6046; (f) D. Font, A. Bastero, S. Sayalero, C. Jimeno and M. A. Pericas, *Org. Lett.*, 2007, **9**, 1943; (g) M. Kawasaki, P. Li and H. Yamamoto, *Angew. Chem. Int. Ed.,* 2008, **47**, 3795; (h) M. Lu, Y. Lu, D. Zhu, X. Zeng, X. Li and G. Zhong, *Angew. Chem. Int. Ed.,* 2010, **49**, 1; (i) T. Bui, N. R. Candeias and C. F. Barbas III, *J. Am. Chem. Soc.*, 2010, **132**, 5574; (j) A. Yanagisawa, S. Takeshita, Y. Izumi and K. Yoshida, *J. Am. Chem. Soc.*, 2010, **132**, 5328.

11 See the supporting information of ref. 8a.

12 (a) T. Sasaki, Y. Ishibashi and M. Ohno, *Chem. Lett.,* 1983, 863; (b) T. Sasaki, K. Mori and M. Ohno, *Synthesis,* 1985, 279.

13 I. Ramakrishna, G. S. Grandhi, H. Sahoo and M. Baidya, *Chem. Commun.*, 2015, **51**, 13976.

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

15 CCDC 1440804-1440807 contain the supplementary crystallographic data for compounds **4**, **41**, **33**, and **17** respectively.

16 (a) P. C. Trippier and C. McGuign, *Med. Chem. Commun.*, 2010, **1**, 183; (b) D. Hall, in *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*, Wiley-VCH, Weinheim, 2005.

17 The reaction did not work with the silyl enol ether derived from dialkyl ketone such as cyclohexanone.

18 (a) G. K. Gupta, V. Saini, R. Khare and V. Kumar, *Med. Chem. Res.*, 2014, **23**, 4209; (b) A. Bunescu, C. Piemontesi, Q. Wang and J. Zhu, *Chem. Commun.*, 2013, **49**, 10284.