

RESEARCH ARTICLE

View Article Online
View Journal | View IssueCite this: *Org. Chem. Front.*, 2016, **3**, 744Received 15th March 2016,
Accepted 10th April 2016

DOI: 10.1039/c6qo00102e

rsc.li/frontiers-organic

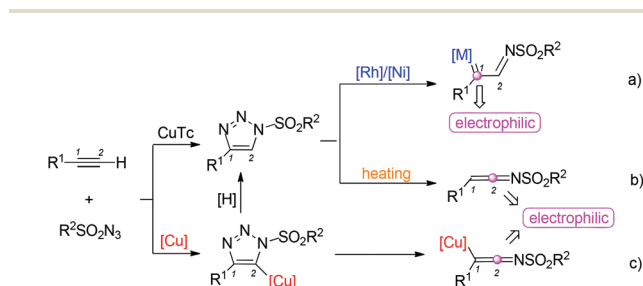
Base-induced synthesis of *N*-dialkylaminomethyl-2*H*-1,2,3-triazoles from *N*-sulfonyl-1,2,3-triazoles†Yu Jiang,^a Qiang Wang,^b Run Sun,^b Xiang-Ying Tang^a and Min Shi^{*a,b}A facile synthetic method to access *N*-dialkylaminomethyl-2*H*-1,2,3-triazoles has been developed via a novel reaction mode from *N*-sulfonyl-1,2,3-triazoles by a base induced reaction. Moreover, 4-phenyl-1*H*-1,2,3-triazoles can also give the same products even in the absence of a base at high temperature.

Introduction

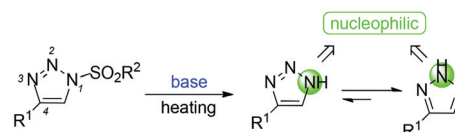
1,2,3-Triazoles are an important class of heterocycles in organic synthesis, medicinal chemistry and materials science.¹ Among them, *N*-sulfonyl-1,2,3-triazoles, which can be easily prepared from copper(i)-catalyzed azide-alkyne cycloadditions,² have attracted much attention of organic chemists because of their potential applications in accessing other heterocycles. Recently, investigation on the reaction types of these compounds has emerged at the forefront of current research. Several different reaction types have been found to date (Scheme 1).

In the presence of Rh/Ni catalysts, *N*-sulfonyl-1,2,3-triazoles will undergo a ring-opening process to afford α -imino metal carbenes.^{3–8} The C1 position with a strong electrophilic ability can be attacked by other nucleophiles.^{4–6} Moreover, a nitrogen atom with an increased nucleophilic ability offers more synthetic flexibility. The α -imino metal carbenes can react with many other compounds to afford useful heterocycles (Scheme 1a).⁷ On the other hand, at high temperature, *N*-sulfonyl-1,2,3-triazoles can also undergo a ring-opening process to afford *N*-sulfonyl ketenimines, which can be attacked by nucleophiles at the C2 position or undergo pericyclic reactions (Scheme 1b).⁹ Indeed, in many reports, *N*-sulfonyl ketenimines were afforded by a one-pot strategy.^{10–12} Cycloaddition between terminal alkynes and sulfonyl azides catalyzed by copper(i) afforded the *N*-sulfonyl triazolyl copper species, which can undergo a ring-opening rearrangement leading to the ketenimine intermediate upon the release of a dinitrogen molecule (Scheme 1c).

However, we recently also found that the sulfonyl group of *N*-sulfonyl-1,2,3-triazoles can undergo elimination to afford 4-phenyl-1*H*-1,2,3-triazoles as nucleophilic intermediates¹³ in the presence of a base at high temperature. Moreover, the intermediates could be converted into more stable 4-phenyl-2*H*-1,2,3-triazoles to trap other electrophiles in the N2-position (Scheme 2).^{14,15} Indeed, bis(dialkylamino)methane was chosen as a reaction partner, which could afford an electrophilic iminium ion.¹⁶ Herein, we would like to report these interesting new findings.

Scheme 1 Formation of α -imino metal carbene and *N*-sulfonyl ketenimines.^aState Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China^bKey Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Meilong Road No. 130, Shanghai, 200237, China. E-mail: mshi@mail.sioc.ac.cn

†Electronic supplementary information (ESI) available: Experimental procedures, characterization data of new compounds. CCDC 1465122. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6qo00102e

Scheme 2 Formation of 4-phenyl-2*H*-1,2,3-triazoles.

Results and discussion

We initially utilized *N*-sulfonyl-1,2,3-triazole **1a** (0.2 mmol) and tetrabenzylmethanediamine **2a** (0.2 mmol) as substrates to examine the reaction outcomes. The results are shown in Table 1. To our delight, in the presence of 1.0 equiv. of K_2CO_3 as an additive, we found that **3aa** was obtained in 39% yield determined by 1H NMR spectroscopy along with the formation of $HNBn_2$ (Table 1, entry 2). Subsequently, solvents were examined (Table 1, entries 3–8). The yield of **3aa** had no obvious improvement when THF or toluene was used (Table 1, entries 3 and 4). While the use of high polar solvents such as DMF and DMSO afforded **3aa** in higher yields (Table 1, entries 5 and 6). Then we turned our attention to identify the best base for this reaction. Both inorganic and organic bases were used in the reaction, and 1,4-diazabicyclo[2,2,2]octane (DABCO) was identified as the best base for the reaction, affording **3aa** in 90% isolated yield. Meanwhile, the corresponding $TsNBn_2$ was also obtained at the same time (Table 1, entry 14). The structure of **3aa** has been unambiguously determined by the X-ray crystal structure of its analogue **3ha** (Fig. 1).¹⁷

With the optimal conditions in hand, we next surveyed the substrate scope of this reaction and the results are shown in Table 2. At first, we synthesized a series of triazoles with different substituents on the aromatic ring and examined their reaction properties. As for substrates **2b–f**, with electron-donating groups on the aromatic ring, the desired products **3** were afforded in 67–72% yields. While for substrates **2g–l**, with electron-withdrawing groups, the corresponding products **3** were afforded in 67–81% yields. These results suggested that the substrates with electron-withdrawing groups on the aromatic

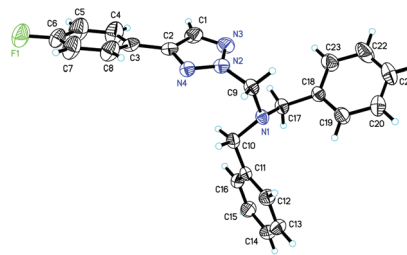


Fig. 1 The ORTEP drawing of **3ha**.

Table 2 Reaction scope: synthesis of triazoles **3** from substrates **1**^a

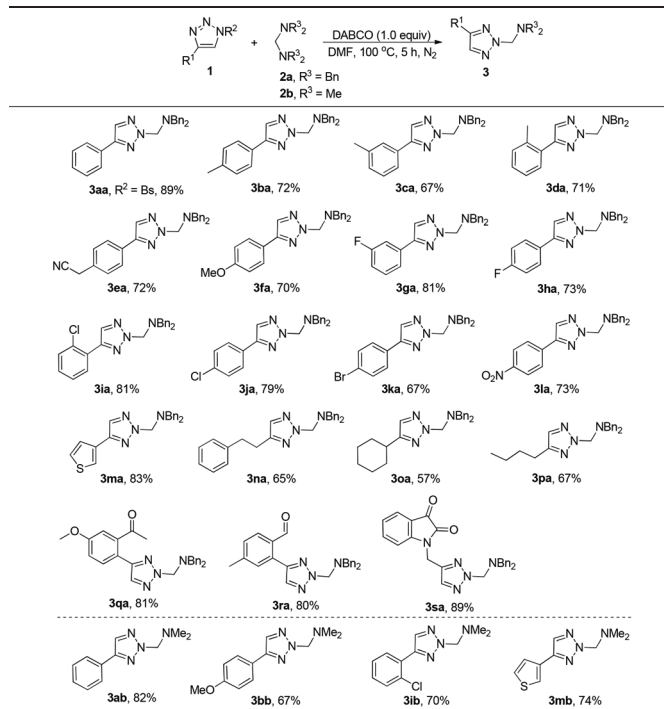
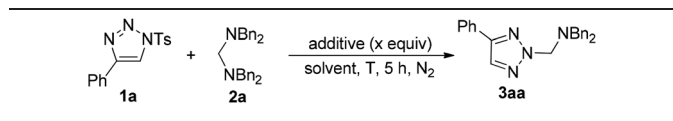


Table 1 Optimization of the reaction conditions



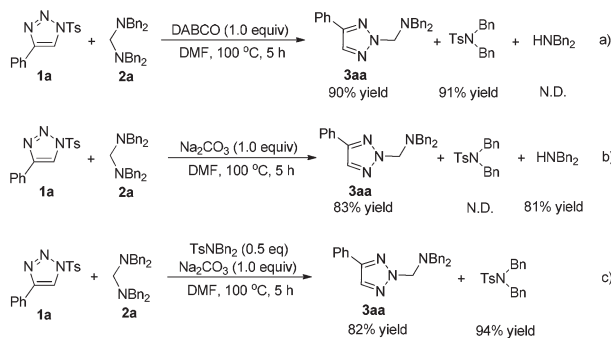
Entry ^a	Additive	X	Solvent	T (°C)	Yield ^b (%)
1	—	—	DCE	100	25
2	K_2CO_3	1.0	DCE	100	39 ^c
3	K_2CO_3	1.0	THF	100	40
4	K_2CO_3	1.0	Toluene	100	51
5	K_2CO_3	1.0	DMF	100	70
6	K_2CO_3	1.0	DMSO	100	68
7	K_2CO_3	1.0	DMF	100	92
8	$NaHCO_3$	1.0	DMF	100	92
9	$NaHCO_3$	1.0	DMF	100	86
10	$NaOH$	1.0	DMF	100	12
11	Et_3N	1.0	DMF	100	11
12	iPr_2NH	1.0	DMF	100	11
13	DBU	1.0	DMF	100	58
14	DABCO	1.0	DMF	100	96 ^d (90 ^e)
15	DMAP	1.0	DMF	100	95

^a Unless otherwise specified, all reactions were performed with **1a** (0.20 mmol), **2a** (0.20 mmol) and additive (0.20 mmol). ^b Yields are determined by 1H NMR using trimethoxybenzene as an internal standard. ^c $HNBn_2$ was obtained in 25% yield. ^d $TsNBn_2$ was obtained in 91% yield. ^e Isolated yield.

^a Conditions: **1** (0.20 mmol), **2** (0.20 mmol) and DABCO (0.20 mmol) were heated in DMF (2.0 ml) at 100 °C for 5 h.

ring may be more conducive to the formation of **3** compared to those of electron-donating ones. When the benzene ring was replaced by the thiophene ring, product **3ma** could also be afforded in good yield. The reaction could also tolerate various triazoles with aliphatic substituents, indicating a broad substrate scope, and giving the desired products **3na**, **3oa** and **3pa** in moderate yields. Furthermore, the substrates bearing functional groups such as a carbonyl group could also afford the corresponding products **3qa**, **3ra** and **3sa** in good yields. When the triazole was protected by the Bs group (4-bromophenylsulfonyl), the reaction also proceeded efficiently, giving the corresponding product **3aa** in 89% yield. Finally, tetramethylmethanediamine **2b** was also used in this reaction, affording the desired products **3ab**, **3bb**, **3ib** and **3mb** in 67–82% yields.

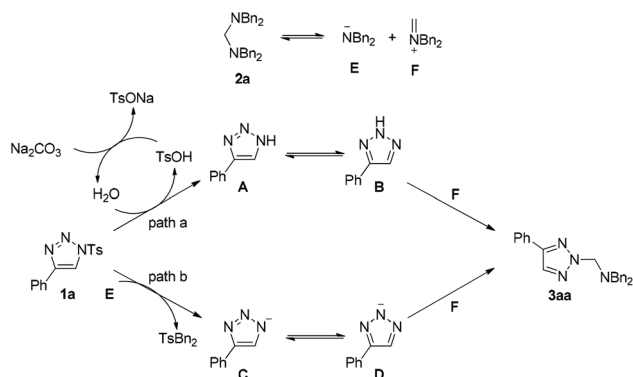
The next experiments mainly focused on the investigation of the mechanism of this reaction. The different by-products



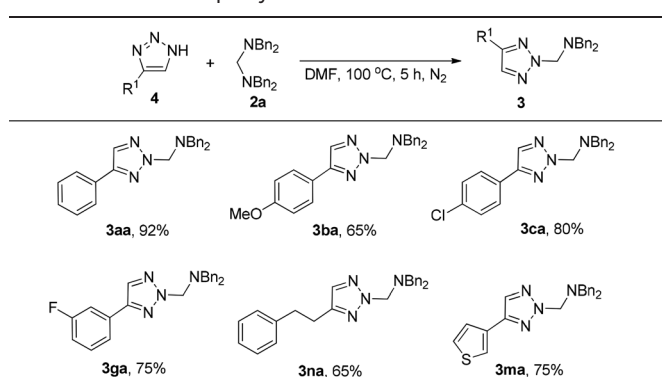
Scheme 3 Control experiments.

of the reaction with different additives caught our attention (Table 1, entries 2 and 14). As shown in Scheme 3, several control experiments were performed. If DABCO was used as the additive, the corresponding TsNBn_2 was obtained in 91% yield along with the product **3aa** in 90% yield (Scheme 3a). However, if Na_2CO_3 was used, HNBn_2 was obtained in 81% yield instead of TsNBn_2 (Scheme 3b). To eliminate the possibility that HNBn_2 is derived from the decomposition of TsNBn_2 , another control experiment was also performed. 0.5 equiv. of TsNBn_2 was added to the Na_2CO_3 -induced reaction, and it could be recovered in 94% yield after 5 h, suggesting that HNBn_2 is not derived from TsNBn_2 (Scheme 3c).

Based on the above results, two possible reaction pathways using substrates **1a** and **2a** as models are outlined in Scheme 4. As for substrate **2a**, it will decompose to give intermediates **E** and **F**. When Na_2CO_3 is used as an additive, substrate **1a** will decompose to form intermediate **A** in the presence of a trace amount of H_2O in the solvent. TsOH is obtained at the same time, which can be neutralized by Na_2CO_3 to deliver H_2O again. Intermediate **A** can be converted into its resonance **B**, which can react with intermediate **F** to give the product **3aa** (path a). If DABCO is used as an additive, substrate **1a** reacts with **E** to give intermediate **C** and TsNBn_2 . Intermediate **D**, derived from **C**, can also react with **F** to give the product **3aa** (path b).



Scheme 4 Plausible reaction mechanisms.

Table 3 Reaction scope: synthesis of triazoles **3** from substrates **4**^a

^a Conditions: **4** (0.20 mmol) and **2** (0.20 mmol) were heated in DMF (2.0 ml) at 100 °C for 5 h.

The investigations on the reaction mechanism suggested that the *in situ* generated 4-phenyl-1*H*-1,2,3-triazole could also react with **2a** to give a similar product. As we expected, substrate **4a** can react with **2a** smoothly even in the absence of DABCO to give the product **3aa** in 92% yield. This result also suggested that intermediate **B** is more stable than **A**. For substrates with electron-donating or -withdrawing groups on the aromatic ring, the reaction proceeded efficiently to give the desired products **3ba**, **3ca** and **3ga** in 65%, 80% and 75% yields, respectively. Meanwhile, for the triazole with an aliphatic substituent, the corresponding product **3na** was formed in 65% yield. In addition, in the case of thiophene-tethered triazole **4m**, the reaction also proceeded smoothly to afford the desired product **3ma** in 75% yield (Table 3).

In summary, a new base-induced reaction mode of *N*-sulfonyl-1,2,3-triazoles has been established, thereby providing a simple procedure for preparation of triazoles bearing dialkylaminomethyl groups. In this reaction, a wide range of substrates can tolerate this reaction. Moreover, 4-phenyl-1*H*-1,2,3-triazoles can also give the same product even in the absence of a base. The potential applications and extension of the substrate scope of this novel synthetic methodology are currently underway in our laboratory.

Acknowledgements

We are grateful for the financial support from the National Basic Research Program of China (973)-2015CB856603 and the National Natural Science Foundation of China (20472096, 21372241, 21361140350, 20672127, 21102166, 21121062, 21302203, 20732008 and 21572052).

Notes and references

- For selected reviews, see: (a) W. Q. Fan and A. R. Katritzky, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, Pergamon Press, Oxford, 1996, vol. 4, p. 1;

- (b) T. Muller and S. Bräse, *Angew. Chem., Int. Ed.*, 2011, **50**, 11844; (c) P. Thirumurugan, D. Matosiuk and K. Jozwiak, *Chem. Rev.*, 2013, **113**, 4905.
- 2 (a) Y. Liu, X. Wang, J. Xu, Q. Zhang, Y. Zhao and Y. Hu, *Tetrahedron*, 2011, **67**, 6294; (b) J. Raushel and V. V. Fokin, *Org. Lett.*, 2010, **12**, 4952; (c) E. J. Yoo, M. Ahlquist, S. H. Kim, I. Bae, V. V. Fokin, K. B. Sharpless and S. Chang, *Angew. Chem., Int. Ed.*, 2007, **46**, 1730.
- 3 For examples on the previous reviews: (a) B. Chattopadhyay and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2012, **51**, 862; (b) A. V. Gulevich and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2013, **52**, 1371; (c) H. M. L. Davies and J. S. Alford, *Chem. Soc. Rev.*, 2014, **43**, 5151; (d) Y. Wang, X. Lei and Y. Tang, *Synlett*, 2015, 2051.
- 4 (a) N. Selander, B. T. Worrell, S. Chuprakov, S. Velaparthi and V. V. Fokin, *J. Am. Chem. Soc.*, 2012, **134**, 14670; (b) J. C. Culhane and V. V. Fokin, *Org. Lett.*, 2011, **13**, 4578; (c) J. S. Alford and H. M. L. Davies, *Org. Lett.*, 2012, **14**, 6020; (d) N. Grimster, L. Zhang and V. V. Fokin, *J. Am. Chem. Soc.*, 2010, **132**, 2510; (e) S. Chuprakov, S. W. Kwok, L. Zhang, L. Lercher and V. V. Fokin, *J. Am. Chem. Soc.*, 2009, **131**, 18034.
- 5 (a) S. Chuprakov, J. A. Malik, M. Zibinsky and V. V. Fokin, *J. Am. Chem. Soc.*, 2011, **133**, 10352; (b) S. Chuprakov, B. T. Worrell, N. Selander, R. K. Sit and V. V. Fokin, *J. Am. Chem. Soc.*, 2014, **136**, 195; (c) T. Miura, T. Tanaka, T. Biyajima, A. Yada and M. Murakami, *Angew. Chem., Int. Ed.*, 2013, **52**, 3883; (d) T. Miura, T. Biyajima, T. Fujii and M. Murakami, *J. Am. Chem. Soc.*, 2012, **134**, 194.
- 6 (a) A. Boyer, *Org. Lett.*, 2014, **16**, 1660; (b) T. Miura, Y. Funakoshi, M. Morimoto, T. Biyajima and M. Murakami, *J. Am. Chem. Soc.*, 2012, **134**, 17440; (c) N. Selander, B. T. Worrell and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2012, **51**, 13054.
- 7 (a) S. Chuprakov, F. W. Hwang and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2007, **46**, 4757; (b) T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 14972; (c) T. Miura, M. Yamauchi and M. Murakami, *Chem. Commun.*, 2009, 1470; (d) B. Chattopadhyay and V. Gevorgyan, *Org. Lett.*, 2011, **13**, 3746; (e) M. Zibinsky and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2013, **52**, 1507; (f) S. Chuprakov, S. W. Kwok and V. V. Fokin, *J. Am. Chem. Soc.*, 2013, **135**, 4652; (g) B. T. Parr, S. A. Green and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 4716; (h) J. E. Spangler and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 6802; (i) Y. Shi and V. Gevorgyan, *Org. Lett.*, 2013, **15**, 5394; (j) T. Miura, T. Tanaka, K. Hiraga, S. G. Stewart and M. Murakami, *J. Am. Chem. Soc.*, 2013, **135**, 13652; (k) B. T. Parr and H. M. L. Davies, *Angew. Chem., Int. Ed.*, 2013, **52**, 10044; (l) T. Miura, T. Tanaka, A. Yada and M. Murakami, *Chem. Lett.*, 2013, **42**, 1308; (m) H. Shang, Y. Wang, Y. Tian, J. Feng and Y. Tang, *Angew. Chem., Int. Ed.*, 2014, **53**, 5662; (n) J. S. Alford and H. M. L. Davies, *J. Am. Chem. Soc.*, 2014, **136**, 10266; (o) D. J. Jung, H. J. Jeon, J. H. Kim, Y. Kim and S. Lee, *Org. Lett.*, 2014, **16**, 2208; (p) C.-E. Kim, S. Park, D. Eom, B. Seo and P. H. Lee, *Org. Lett.*, 2014, **16**, 1900; (q) R.-Q. Ran, J. He, S.-D. Xiu, K.-B. Wang and C.-Y. Li, *Org. Lett.*, 2014, **16**, 3704; (r) T. Miura, Y. Funakoshi, T. Tanaka and M. Murakami, *Org. Lett.*, 2014, **16**, 2760; (s) F. Medina, C. Besnard and J. Lacour, *Org. Lett.*, 2014, **16**, 3232; (t) D. J. Lee, H. S. Han, J. Shin and E. J. Yoo, *J. Am. Chem. Soc.*, 2014, **136**, 11606; (u) X. Ma, S. Pan, H. Wang and W. Chen, *Org. Lett.*, 2014, **16**, 4554; (v) Y.-Z. Zhao, H.-B. Yang, X.-Y. Tang and M. Shi, *Chem. – Eur. J.*, 2015, **21**, 3562; (w) T. Miura, Y. Fujimoto, Y. Funakoshi and M. Murakami, *Angew. Chem., Int. Ed.*, 2015, **54**, 9967.
- 8 (a) J. S. Alford, J. E. Spangler and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 11712; (b) E. E. Schultz and R. Sarpong, *J. Am. Chem. Soc.*, 2013, **135**, 4696; (c) Y. Shi and V. Gevorgyan, *Org. Lett.*, 2013, **15**, 5394; (d) T. Miura, Y. Funakoshi and M. Murakami, *J. Am. Chem. Soc.*, 2014, **136**, 2272; (e) B. Rajagopal, C.-H. Chou, C.-C. Chung and P.-C. Lin, *Org. Lett.*, 2014, **16**, 3752; (f) E. E. Schultz, V. N. G. Lindsay and R. Sarpong, *Angew. Chem., Int. Ed.*, 2014, **53**, 9904; (g) J. Fu, H. Shen, Y. Chang, C. Li, J. Gong and Z. Yang, *Chem. – Eur. J.*, 2014, **20**, 12881; (h) J.-M. Yang, C.-Z. Zhu, X.-Y. Tang and M. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 5142; (i) Y.-S. Zhang, X.-Y. Tang and M. Shi, *Chem. Commun.*, 2014, **50**, 15971; (j) X.-Y. Tang, Y.-S. Zhang, L. He, Y. Wei and M. Shi, *Chem. Commun.*, 2015, **51**, 133; (k) Y. Jiang, X.-Y. Tang and M. Shi, *Chem. Commun.*, 2015, **51**, 2122; (l) Y.-S. Zhang, X.-Y. Tang and M. Shi, *Org. Chem. Front.*, 2015, **2**, 1516; (m) J. He, Y. Shi, W. Cheng, Z. Man, D. Yang and C.-Y. Li, *Angew. Chem., Int. Ed.*, 2016, **55**, 4557; (n) R. Sun, Y. Jiang, X.-Y. Tang and M. Shi, *Chem. – Eur. J.*, 2016, **22**, 5727.
- 9 (a) Y. Jiang, R. Sun, Q. Wang, X.-Y. Tang and M. Shi, *Chem. Commun.*, 2015, **51**, 16968; (b) K. Chen, Z.-Z. Zhu, Y.-S. Zhang, X.-Y. Tang and M. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 6645.
- 10 For recent reviews on *N*-sulfonyl ketenimine chemistry: (a) S. H. Kim, S. H. Park, J. H. Choi and S. Chang, *Chem. – Asian J.*, 2011, **6**, 2618; (b) P. Lu and Y. Wang, *Synlett*, 2010, 165; (c) E. J. Yoo and S. Chang, *Curr. Org. Chem.*, 2009, **13**, 1766; (d) P. Lu and Y. Wang, *Chem. Soc. Rev.*, 2012, **41**, 5687.
- 11 (a) S. H. Cho, E. J. Yoo, I. Bae and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 16046; (b) E. J. Yoo, I. Bae, S. H. Cho, H. Han and S. Chang, *Org. Lett.*, 2006, **8**, 1347; (c) I. Bae, H. Han and S. Chang, *J. Am. Chem. Soc.*, 2005, **127**, 2038; (d) S. L. Cui, J. Wang and Y. Wang, *Org. Lett.*, 2007, **9**, 5023; (e) S. L. Cui, J. Wang and Y. Wang, *Tetrahedron*, 2008, **64**, 487; (f) E. J. Yoo and S. Chang, *Org. Lett.*, 2008, **10**, 1163; (g) S. H. Cho and S. Chang, *Angew. Chem., Int. Ed.*, 2008, **47**, 2836; (h) J. Kim, Y. Lee, J. Lee, Y. Do and S. Chang, *J. Org. Chem.*, 2008, **73**, 9454; (i) J. Y. Kim, S. H. Kim and S. Chang, *Tetrahedron Lett.*, 2008, **49**, 1745; (j) J. She, Z. Jiang and Y. Wang, *Synlett*, 2009, 2023; (k) J. Wang, J. Wang, Y. Zhu, P. Lu and Y. Wang, *Chem. Commun.*, 2011,

- 47, 3275; (l) Z. Chen, D. Zheng and J. Wu, *Org. Lett.*, 2011, **13**, 848; (m) L. Sun, Y. Zhu, P. Lu and Y. Wang, *Org. Lett.*, 2013, **15**, 5894; (n) H.-D. Xu, Z.-J. Jia, K. Xu, M. Han, S.-N. Jiang, J. Cao, J.-C. Wang and M.-H. Shen, *Angew. Chem., Int. Ed.*, 2014, **53**, 9284.
- 12 (a) A. Van Camp, D. Gossens, M. Moya-Portuguez, J. Marchand-Brynaert and L. Ghosez, *Tetrahedron Lett.*, 1980, **21**, 3081; (b) M. Whiting and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, **45**, 3157; (c) W. Lu, W. Z. Song, D. Hong, P. Lu and Y. Wang, *Adv. Synth. Catal.*, 2009, **351**, 1768; (d) S.-Y. Li, Y. Luo and J. Wu, *Org. Lett.*, 2011, **13**, 4312; (e) Y. Xing, H. Zhao, Q. Shang, J. Wang, P. Lu and Y. Wang, *Org. Lett.*, 2013, **15**, 2668; (f) S. Li, Y. Luo and J. Wu, *Org. Lett.*, 2011, **13**, 3190.
- 13 R. Sun, D.-. H. Zhang and M. Shi, *Synlett*, 2014, 2293.
- 14 For the example of base-promoted 1,2-rearrangement of *N*-sulfonyl-1,2,3-triazoles: M. Yamauchi, T. Miura and M. Murakami, *Heterocycles*, 2010, **80**, 177.
- 15 For the example of synthesis of 2-substituted-1,2,3-triazoles: J. Kalisiak, K. B. Sharpless and V. V. Fokin, *Org. Lett.*, 2008, **10**, 3171.
- 16 For several examples on the applications of bis(dialkyl-amino)methane: (a) B. E. Love, *J. Org. Chem.*, 2007, **72**, 630; (b) Y. Xie, J. Hu, Y. Wang, C. Xia and H. Huang, *J. Am. Chem. Soc.*, 2012, **134**, 20613; (c) Y. Xie, J. Hu, P. Xie, B. Qian and H. Huang, *J. Am. Chem. Soc.*, 2013, **135**, 18327; (d) J. Hu, Y. Xie and H. Huang, *Angew. Chem., Int. Ed.*, 2014, **53**, 7272; (e) G. Qin, L. Li, J. Li and H. Huang, *J. Am. Chem. Soc.*, 2015, **137**, 12490.
- 17 The crystal data of **3ha** have been given in CCDC 1465122.