Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

COMMUNICATION

Selective Synthesis of 4-(Sulfonyl)-Methyl-1H-Pyrazoles and (*E*)-4,5-Dihydro-1H-Pyrazoles from *N*-Allenic Sulfonylhydrazones

Cite this: DOI: 10.1039/xoxxoooooox

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Yu Zhu, Jun-Jie Hong, Yun-Bin Zhou, Yu-Wei Xiao, Min Lin and Zhuang-Ping Zhan*

Selective synthesis of 4-(sulfonyl)-methyl-1H-pyrazoles and (*E*)-4,5-dihydro-1H-pyrazoles from *N*-allenic sulfonylhydrazones with sulfonyl group migrations has been developed. A key feature of these reactions is that the migrations of the sulfonyl groups to different positions can be controlled by changing Lewis acids.

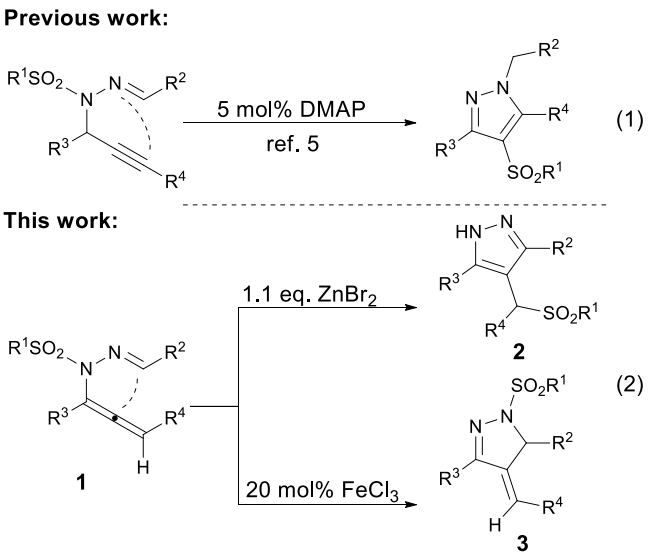
Pyrazoles are found in a variety of biologically active compounds,[1] such as celebrex, zoniporide, and fluzaolate. Owing to their wide applications in pharmaceutical and agrochemical science, substantial attentions of developing efficient strategies for pyrazoles synthesis have been paid.[2] Although conventional approaches for synthesis of pyrazole skeletons involving either modification of pre-existing pyrazole precursors[3] or assembly of new pyrazole rings[4] have been well studied, development of efficient methods to synthesize pyrazole derivatives which could lead to discovery of new bioactive compounds is still a challenge in organic synthesis.

Allenic sulfonamides as a subclass of allenamide[5] have shown impressive synthetic potential in organic chemistry. A diversity of transformations from allenic sulfonamides has been demonstrated which offer versatile entries into a range of fascinating structures.[6]

Recently, our group has reported that Lewis base catalyzed synthesis of multisubstituted 4-sulfonyl-1H-pyrazoles from *N*-propargylic sulfonylhydrazones (Scheme 1, Eq. 1).[7] As a part of our continuing research, we conducted the reactions of *N*-allenic sulfonylhydrazones **1** as a subclass of allenic sulfonamides with Lewis acids. Interestingly, 4-(sulfonyl)-methyl-1H-pyrazoles **2** and (*E*)-4,5-dihydro-1H-pyrazoles **3** were obtained respectively involving regioselective migrations of sulfonyl groups[8] to different positions promoted by different Lewis acids (Scheme 1, Eq. 2).

Department of Chemistry,College of Chemistry and Chemical Engineering Xiamen University, Xiamen, Fujian, People's Republic of China, 361005. E-mail: zpzhan@xmu.edu.cn

† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c000000x/

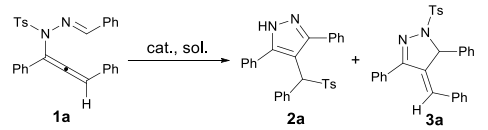


Scheme 1. Cyclization of *N*-allenic sulfonylhydrazone and *N*-propargylic sulfonylhydrazone.

In the initial study, the activity of Lewis acids was screened with *N*-allenic sulfonylhydrazone **1a** as substrate (Table 1). The reaction of **1a** in the presence of 20 mol% $FeCl_3$ in DCM at room temperature gave **3a** in 83% yield. The single product **3a** was isolated in 44% and 34% yields using Lewis acids $BF_3{\cdot}Et_2O$ and AgOTf, respectively (Table 1, entries 2 and 3). The rate of the reaction decreased dramatically catalyzed by 10 mol% $FeCl_3$ and a lower yield of **3a** was achieved (Table 1, entry 4). In the presence of 110 mol% $FeCl_3$, the reaction produced a 34:28 mixture of **2a** and **3a** (Table 1, entry 5). Prolonging the reaction time would not change the ratio of **2a** and **3a**. Subsequently, the reactions of **1a** were investigated with zinc salts. Interestingly, 20 mol% Lewis acid of $ZnCl_2$ and $ZnBr_2$ failed to promote those transformations (Table 1, entries 6 and 15). Nevertheless, the unique product **2a** was observed

in 75% yield promoted by 1.1 equiv of $ZnCl_2$ (Table 1, entry 7). To our delight, $ZnBr_2$ performed better in the formation of **2a** (Table 1, entry 8). Other metal Lewis acids, such as $AlCl_3$, $BiCl_3$ and $InCl_3$, were also screened. No reaction happened when 20 mol% catalysts used, while increasing the amount of Lewis acids to 1.1 equiv led to **3a** in comparatively low yields (Table 1, entries 9-14). The reaction took place in a less effective manner when using solvents such as CH_3CN, THF and DCE. Thus, the most suitable conditions for the synthesis of **2a** and **3a** were established (Table 1, entries 1 and 8).

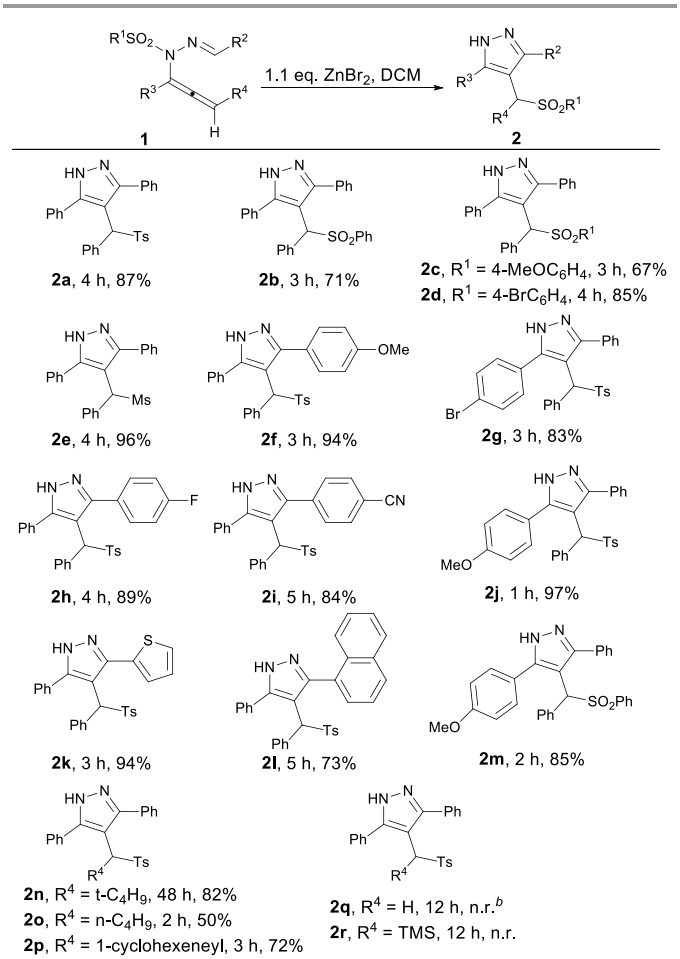
Table 1. Screening for the reaction conditions [a]



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

entry	catalyst (mol%)	time	temp.	yield(**2a**/**3a**) [b]
1	**$FeCl_3$ (20)**	**5min**	**r.t.** [c]	**0/83%**
2	$BF_3{\cdot}Et_2O$ (110)	5min	0 °C	0/44%
3	AgOTf (20)	24h	r.t.	0/34%
4	$FeCl_3$ (10)	10h	r.t.	trace/24%
5	$FeCl_3$ (110)	5min	r.t.	34%/28%
6	$ZnCl_2$ (20)	12h	r.t.	0/0 [d]
7	$ZnCl_2$ (110)	4h	r.t.	75%/0
8	**$ZnBr_2$ (110)**	**4h**	**r.t.**	**87%/0**
9	$AlCl_3$ (20)	12h	r.t.	0/trace [d]
10	$AlCl_3$ (110)	2h	r.t.	trace/36%
11	$BiCl_3$ (20)	12h	r.t.	0/trace [d]
12	$BiCl_3$ (110)	2h	r.t.	5%/30%
13	$InCl_3$ (20)	12h	r.t.	0/0 [d]
14	$InCl_3$ (110)	2h	r.t.	10%/65%
15	$ZnBr_2$ (20)	12h	r.t.	0/0 [d]

[a] Reaction conditions: **1a** (232mg, 0.5 mmol), DCM (5 mL). [b] isolated yield. [c] r.t. = room temperature. [d] Recovery of subtrate**1a**.

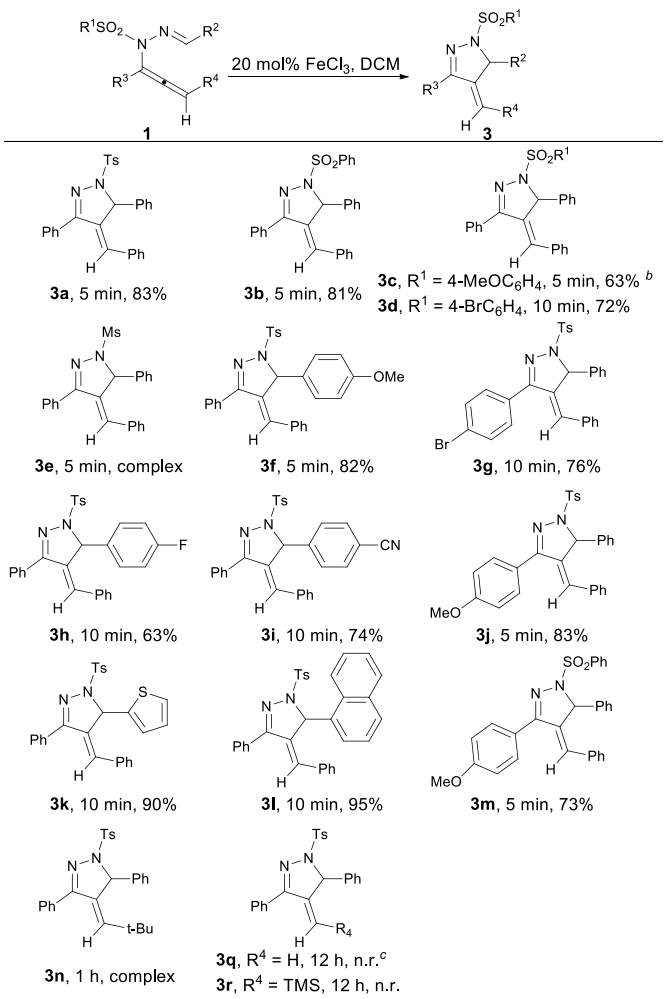


Scheme 2. Synthesis of 4-(sulfonyl)-methyl-(1H)-pyazole [a]. [a] Reaction conditions: substrate **1** (0.5 mmol), DCM (5 mL), $ZnBr_2$ (123 mg, 0.55 mmol), room temperature. [b] n.r. = no reaction.

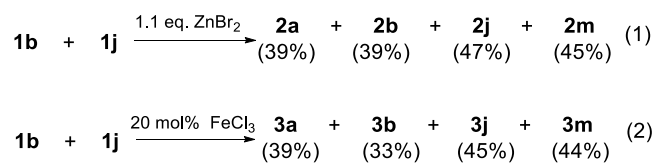
With the optimized reaction conditions in hand, the scope and generality of this zinc-promoted reaction was studied and the results are summarized in Scheme 2. The substrates **1a** (R^1 = 4-MeC_6H_4) and **1b** (R^1 = Ph) gave **2a** and **2b** in 87% and 71% yields, respectively. **1c** (R^1 = 4-$MeOC_6H_4$) and **1d** (R^1 = 4-BrC_6H_4) reacted smoothly affording the desired products **2c** and **2d** in 67% and 85% yields, respectively. **1e** was also successfully employed in the reaction to give corresponding product **2e** in excellent yield (96%). Electron-neutral, electron-deficient, and electron-rich aromatic groups (R^2 and R^3) on the substrates **1** (**1f-j** and **1m**) were all well tolerated, and the desired products (**2f-j** and **2m**) were obtained in moderate to excellent yields (83-97%). The substrates **1k** and **1l** bearing a thiophene ring or a fused ring were also well suitable for those transformations (**2k** and **2l**, 94% and 73% yields). Additionally, internal alkyne substrates **1n-p** (R^4 = t-C_4H_9, n-C_4H_9 and 1-cyclohexeneyl) readily underwent those reactions to afford **2n-p** in moderate to good yields (50%-82%). The results suggested that **1q** (R^4 = H) and **1r** (R^4 = TMS) failed to form **2q** and **2r**.

Next, we investigated the reactions of *N*-allenic sulfonylhydrazones **1a**–**r** using 20 mol% $FeCl_3$ as catalyst. The results are summarized in Scheme 3. **1a-d** were converted into the **3a-d** in moderate to good yields (63-83%), while the reaction of **1e** led to a mixture. *N*-allenic sulfonylhydrazones **1f-j** and **1m** bearing electron-deficient or electron-rich aromatic ring produced (*E*)-4,5-dihydro-1H-pyrazoles **3f-j** and **3m** in moderate to good yields (63-83%). The reactions of substrates **1k** and **1l** containing a 2-thiophenyl or 1-naphthyl group afforded desired products **3k** and **3l** in excellent yields (90% and 95%), respectively. Internal alkyne **1n** (R^4 = t-C_4H_9) failed in this transformation. No reaction of substrates **1q** (R^4 = H) and **1r** (R^4 = TMS) occurred under optimized conditions. Structure of **3l** was unambiguously demonstrated by X-ray diffraction analysis (See the supporting information). [9]

We performed a crossover experiment between equimolar amounts of *N*-allenic sulfonylhydrazones **1b** and **1j** in the presence of 1.1 equiv of $ZnBr_2$ which yielded the corresponding pyrazoles **2b** and **2j** in 39% and 47% yields, respectively, and the crossover products **2a** and **2m** in 39% and 45% yields, respectively (Scheme 4 Eq. 1, determined by HPLC). Furthermore, the $FeCl_3$-catalyzed reaction of a 1:1 mixture of **1b** and **1j** afforded the corresponding pyrazoles **3b** and **3j** in 33% and 45% yields, respectively, and the crossover products **3a** and **3m** in 39% and 44% yields, respectively (Scheme 4 Eq. 2, determined by HPLC). These results clearly indicated that both migrations of sulfonyl group proceeded in intermolecular manners.

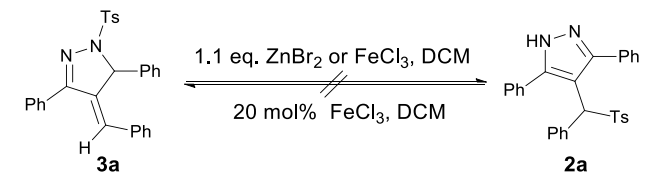


Scheme 3. Synthesis of (*E*)-4,5-dihydro-(1H)-pyrazole [a]. [a] Reaction conditions: substrates **1** (0.5 mmol, 232 mg), DCM (5 mL), $FeCl_3$ (16 mg, 0.1 mmol), room temperature. [b] 50 mol% $FeCl_3$ was used. [c] n.r. = no reaction.



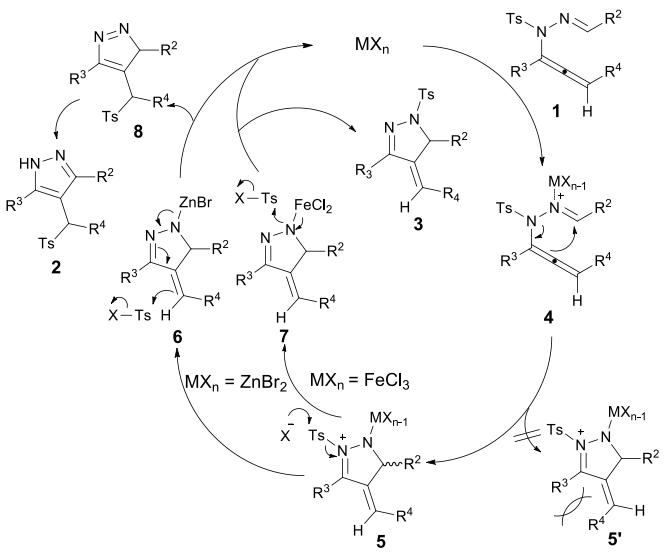
Scheme 4. Crossover reactions of **1b** and **1j**.

The product **2a** or **3a** remained unchanged in the presence of $ZnBr_2$ or $FeCl_3$ in DCM at room temperature for 12 hours, thereby suggesting that interconversion between **2** and **3** does not take place under the optimized reaction conditions (Scheme 5).



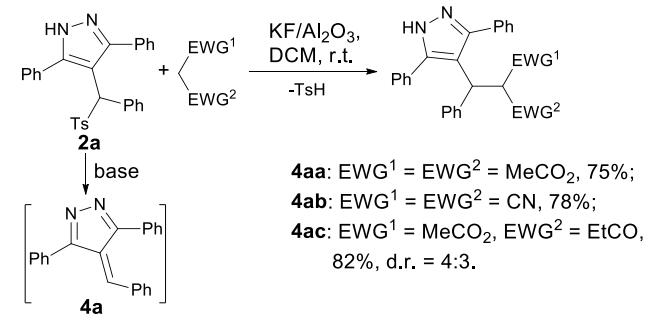
Scheme 5. Interconversion reactions between **2a** and **3a**.

The above experimental results led us to propose the mechanism for the cyclization of **1**. Lewis-acidic transition metal coordinates to nitrogen atom of **1** to form complex **4**. The nitrogen atom donates its lone pair electrons toward allenic moiety followed by the addition of the central *sp* carbon to the azomethine carbon atom. The spatial arrangement of R^3 and R^4 are coplanar in intermediate **5** and **5'**. The small sterically hindered effect avails formation of (*E*)-configuration intermediate **5**. Halide ion promotes *N-S* bond of **5** cleavage to give intermediate **6** or **7**. For zinc-promoted (MX_n = $ZnBr_2$) reaction of the substrates **1**, along with the departure of $ZnBr_2$ from **6**, electrons transfer to exocyclic double bond to render sufonylation reaction and intermediate **8** is formed. Finally, **8** rearranges to pyrazole **2** *via* 1,5-H shift and tautomerization. In iron-catalyzed (MX_n = $FeCl_3$) reaction, elimination of $FeCl_3$ on intermediate **7** and new *N-S* bond formed gives (*E*)-4,5-dihydro-1H-pyrazole **3**. The strength of M-N bond might play a crucial role in selectively producing **2** and **3**. With such simple substrates, the real role of each catalyst for the different selectivity remains a puzzle.



Scheme 6. Proposed mechanism

The ready availability of pyrazoles **2** bearing a sulfonyl moiety opens a new synthetic opportunity for suitable transformation. Pyrazole derivative **4aa** was prepared from **2a** and dimethyl malonate in 75% yield. Malononitrile reacted with **2a** leading to the



Scheme 7. KF on basic alumina-promoted additions of active methylene compounds to pyrazole **2a**.

corresponding product **4ab** in 78% yield. Ethyl acetoacetate and **2a** reacted under basic conditions leading to the mixture **4ac** of two corresponding diastereoisomers in 82% yield. According to the above results, we presumed that under basic conditions pyrazole **2a** underwent elimination of arenesulfinic acid leading to an intermediate vinylogous imine **4a** which added with nucleophile reagents affording 4-substituted pyrazole derivatives.[10]

Conclusions

In summary, selective synthesis of 4-(sulfonyl)-methyl-1H-pyrazoles and (*E*)-4,5-dihydro-1H-pyrazoles from *N*-allenic sulfonylhydrazones has been developed. A key feature of those reactions is that the migration of the sulfonyl groups to different positions can be controlled. Employing inexpensive zinc or iron salt, operational simplicity, mild reaction conditions and no byproduct generation would be beneficial for their large-scale use. Studies aiming at exploring mechanistic aspects of these reactions and developing further transformations of *N*-allenic sulfonylhydrazones are ongoing.

Acknowledgements

Financial support from National Natural Science Foundation of China (No. 21272190), PCSIRT in University and NFFTBS (No. J1210014) is gratefully acknowledged.

Notes and references

1 For selected examples see: (*a*) T. de Paulis, K. Hemstapat, Y. Chen, Y. Zhang, S. Saleh, D. Alagille, R. M. Baldwin, G. D. Tamagnan and P. J. Conn, *J. Med. Chem.*, 2006, **49**, 3332; (*b*) C. E. Mowbray, C. Burt, R. Corbau, S. Gayton, M. Hawes, M. Perros, I. Tran, D. A. Price, F. J. Quinton and M. D. Selby, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 5857; (*c*) F. Chimenti, R. Fioravanti, A. Bolasco, F. Manna, P. Chimenti, D. Secci, O. Befani, P. Turini, F. Ortuso and S. Alcaro, *J. Med. Chem.*, 2007, **50**, 425; (*d*) S. Okuno, A. Saito, T. Hayashi and P. H. Chan, *J. Neurosci.*, 2004, **24**, 7879; (*e*) C. Wasylyk, H. Zheng, C. Castell, L. Debussche, M.-C Multon and B. Wasylyk, *Cancer Res.*, 2008, **68**, 1275.

2 For recent reviews, see: (*a*) S. Fustero, M. a. Sánchez-Roselló, P. Barrio and A. Simón-Fuentes, *Chem. Rev.*, 2011, **111**, 6984; (*b*) Y. L. Janin, *Chem. Rev.*, 2012, **112**, 3924; (*c*) S. Dadiboyena and A. Nefzi, *Eur. J. Med. Chem.*, 2011, **46**, 5258; (*d*) J. Svete, *Arkivoc*, 2006, **7**, 35; (*e*) H. Anwar and M. Elnagdi, *Arkivoc*, 2009, **1**, 198; (*f*) K. Makino, H. S. Kim and Y. Kurasawa, *J. Heterocyclic Chem.*, 1998, **35**, 489; (*g*) K. Makino, H. S. Kim and Y. Kurasawa, *J. Heterocyclic Chem.*, 1999, **36**, 321.

3 For selected examples see: (*a*) R. Goikhman, T. L. Jacques and D. Sames, *J. Am. Chem. Soc.*, 2009, **131**, 3042; (*b*) M. Ye, A. J. Edmunds, J. A. Morris, D. Sale, Y. Zhang and J.-Q. Yu, *Chem. Sci.*, 2013, **4**, 2374; (*c*) S. Grosse, C. Pillard, S. Massip, J. M. Léger, C. Jarry, S. Bourg, P. Bernard and G. Guillaumet, *Chem. Eur. J.*, 2012, **18**, 14943; (*d*) T. Yan, L. Chen, C. Bruneau, P. H. Dixneuf and H. Doucet, *J. Org. Chem.*, 2012, **77**, 7659; (*e*) M. Bhanuchandra, M. R. Kuram and A. K. Sahoo, *Org. Biomol. Chem.*, 2012, **10**, 3538; (*f*) D. L. Browne, J. B. Taylor, A. Plant and J. P. Harrity, *J. Org. Chem.*, 2009, **75**, 984; (*g*) D. Enders, A. Grossmann, B. Gieraths, M. Düzdemir and C. Merkens, *Org. Lett.*, 2012, **14**, 4254.

4 For selected examples see: (*a*) L. Hao, J. J. Hong, J. Zhu and Z. P. Zhan, *Chem. Eur. J.*, 2013, **19**, 5715; (*b*) J. J. Neumann, M. Suri and F. Glorius, *Angew. Chem. Int. Ed.*, 2010, **49**, 7790; (*c*) X. Qi and J. M. Ready, *Angew. Chem. Int. Ed.*, 2007, **46**, 3242; (*d*) R. Kinjo, B. Donnadieu and G. Bertrand, *Angew. Chem. Int. Ed.*, 2011, **50**, 5560; (*e*) A. A. Dissanayake and A. L. Odom, *Chem. Commun.*, 2012, **48**, 440; (*f*) Y. Zhu, S. Wen, G. Yin, D. Hong, P. Lu and Y. Wang, *Org. Lett.*, 2011, **13**, 3553; (*g*) L. Wang, J. Huang, X. Gong and J. Wang, *Chem. Eur. J.*, 2013, **19**, 7555; (*h*) R. S. Foster, H. Jakobi and J. P. Harrity, *Org. Lett.*, 2012, **14**, 4858; (*i*) M. C. Pérez-Aguilar and C. Valdés, *Angew. Chem. Int. Ed.*, 2013, **52**, 7219.

5 For recent reviews, see: (*a*) L.-l. Wei, H. Xiong and R. P. Hsung, *Acc. Chem. Res.*, 2003, **36**, 773; (*b*) T. Lu, Z. Lu, Z.-X. Ma, Y. Zhang and R. P. Hsung, *Chem. Rev.*, 2013, **113**, 4862.

6 For selected examples see: (*a*) S. Suarez-Pantiga, C. Hernández-Díaz, M. Piedrafita, E. Rubio and J. M. Gonzalez, *Adv. Synth. Catal.*, 2012, **354**, 1651; (*b*) A. K. Persson and J. E. Bäckvall, *Angew. Chem. Int. Ed.*, 2010, **122**, 4728; (*c*) S. Suárez-Pantiga, C. Hernández-Díaz, E. Rubio and J. M. González, *Angew. Chem. Int. Ed.*, 2012, **51**, 11552; (*d*) Z. Chen, W. Zhou, X.-X. Li, G.-H. Li and Y. Wu, *Chem. Comm.*, 2013, **49**, 3552; (*e*) J. Brioche, C. Meyer and J. Cossy, *Org. Lett.*, 2013, **15**, 1626; (*f*) A. G. Lohse and R. P. Hsung, *Org. Lett.*, 2009, **11**, 3430; (*g*) X.-X. Li, L.-L. Zhu, W. Zhou and Z. Chen, *Org. Lett.*, 2011, **14**, 436; (*h*) Z.-X. Ma, S. He, W. Song and R. P. Hsung, *Org. Lett.*, 2012, **14**, 5736.

7 Y. Zhu, W.-T. Lu, H.-C. Sun and Z.-P. Zhan, *Org. Lett.*, 2013, **15**, 4146.

8 For selected examples of sulfonyl group shift, see: (*a*) Y. Horino, M. Kimura, Y. Wakamiya, T. Okajima and Y. Tamaru, *Angew. Chem. Int. Ed.*, 1999, **38**, 121; (*b*) H. S. Yeom, E. So and S. Shin, *Chem. Eur. J.*, 2011, **17**, 1764; (*c*) I. Nakamura, U. Yamagishi, D. Song, S. Konta and Y. Yamamoto, *Angew. Chem. Int. Ed.*, 2007, **47**, 2284; (*d*) M. Kimura, Y. Horino, M. Mori and Y. Tamaru, *Chem. Eur. J.*, 2007, **13**, 9686; (*e*) G. RamaâKrishna, C. MallaâReddy and G. SinghâDeora, *Chem. Commun.*, 2012, **48**, 10434; (*f*) X. Xin, D. Wang, X. Li and B. Wan, *Angew. Chem. Int. Ed.*, 2012, **51**, 1693; (*g*) Y. Zhu, H. T. Tang and Z. P. Zhan, *Adv. Synth. Catal.*, 2013, **355**, 1291.

9 CCDC 960118 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

10 (*a*) R. Ballini, A. Palmieri, M. Petrini and R. R. Shaikh, *Adv. Synth. Catal.*, 2008, **350**, 129; (*b*) M. Fochi, L. Gramigna, A. Mazzanti, S. Duce, S. Fantini, A. Palmieri, M. Petrini and L. Bernardi, *Adv. Synth. Catal.*, 2012, **354**, 1373; (*c*) F. Martinelli, A. Palmieri and M. Petrini, *Chem. Eur. J.*, 2011, **17**, 7183; (*d*) R. R. Shaikh, A. Mazzanti, M. Petrini, G. Bartoli and P. Melchiorre, *Angew. Chem. Int. Ed.*, 2008, **47**, 8707; (*e*) L. Jing, J. Wei, L. Zhou, Z. Huang, Z. Li, D. Wu, H. Xiang and X. Zhou, *Chem. Eur. J.*, 2010, **16**, 10955; (*f*) L. L. Cao, Z. S. Ye, G. F. Jiang and Y. G. Zhou, *Adv. Synth. Catal.*, 2011, **353**, 3352; (*g*) A. Palmieri and M. Petrini, *J. Org. Chem.*, 2007, **72**, 1863; (*h*) R. Ballini, A. Palmieri, M. Petrini and E. Torregiani, *Org. Lett.*, 2006, **8**, 4093.

