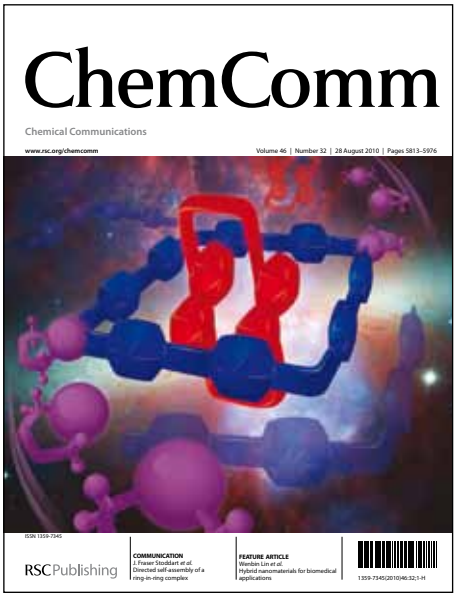
View Article Online
View Journal

ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: K. Bera and I. N. Namboothiri, *Chem. Commun.*, 2013, DOI: 10.1039/C3CC45985C.



This is an *Accepted Manuscript*, which has been through the RSC Publishing peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, which is prior to technical editing, formatting and proof reading. This free service from RSC Publishing allows authors to make their results available to the community, in citable form, before publication of the edited article. This *Accepted Manuscript* will be replaced by the edited and formatted *Advance Article* as soon as this is available.

To cite this manuscript please use its permanent Digital Object Identifier (DOI®), which is identical for all formats of publication.

More information about *Accepted Manuscripts* can be found in the **Information for Authors**.

Please note that technical editing may introduce minor changes to the text and/or graphics contained in the manuscript submitted by the author(s) which may alter content, and that the standard **Terms & Conditions** and the **ethical guidelines** that apply to the journal are still applicable. In no event shall the RSC be held responsible for any errors or omissions in these *Accepted Manuscript* manuscripts or any consequences arising from the use of any information contained in them.

Journal Name ChemComm Dynamic Article Links ►

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

View Article Online
DOI: 10.1039/C3CC45985C
ARTICLE TYPE

Enantioselective Synthesis of α-Nitro-δ-ketosulfones via a Quinine-Squaramide Catalyzed Conjugate Addition of α-Nitrosulfones to Enones

Kalisankar Bera[a] and Irishi N. N. Namboothiri*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

Conjugate Addition of α-nitrosulfones to vinyl ketones in the presence of 0.2 mol % of a quinine-squaramide organocatalyst afforded α-nitro-γ-ketosulfones possessing a tetrasubstituted chiral center in excellent yield and enantioselectivity in most cases. This strategy also offers a facile and convenient entry into γ-sulfonylhydroxamates that are one carbon homologs of potent enzyme inhibitors.

Sulfonylhydroxamic acids are inhibitors of matrix metalla-protease (MMP) and are effective for the treatment of cancer and arthritis.[1] For instance, β-sulfonylhydroxamate **1a**, in which a sulfonyl group is attached to a chiral center, is a potent MMP and PDE (phosphodiesterase) inhibitor.[2-3] The enantiopure compound **1a** displays superior activity as compared to the racemic one and the enantioselective synthesis of **1a** involves the oxidation of enantioenriched thioether precursor.[3] Recently, sulfones attached to a tetrasubstituted chiral center[4-6] received considerable attention due to their wide range of biological activities, for instance, against Alzheimer's (as γ-secretase inhibitor **1b**)[4] and glaucoma.[6]

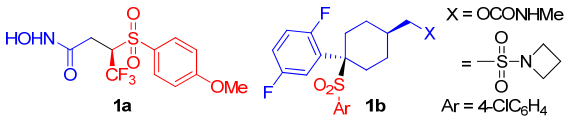


Figure 1 Potent Inhibitors of MMP, PDE and γ-Secretase

The sulfonyl group in organosulfones, viz. active methylene sulfones, vinyl sulfones and other sulfone based nucleophiles and electrophiles, takes part in a variety of synthetic transformations and is an easily removable functional group.[7]

Enantioselective approaches to sulfones include catalytic asymmetric Michael addition of various nucleophiles to β-unsubstituted vinyl sulfones[8] and β-substituted vinyl sulfones,[9] nucleophilic addition of active methylene[10] and methine[11-12] sulfones to various electrophiles, and other miscellaneous methods.[13-14] However, to our knowledge, generation of sulfones attached to a chiral carbon remains scarcely explored under catalytic asymmetric conditions.[12,14]

As part of our ongoing research program to develop novel catalytic methods for the asymmetric synthesis of quaternary carbon centers, we have reported enantioselective synthesis of quaternary α-nitro/aminophosphonates.[15-16] Herein we report an organocatalyzed enantioselective synthesis of quaternary α-nitro-δ-ketosulfones via Michael addition of α-nitrosulfones to enones using an alkaloid derived squaramide catalyst. Transformations of the product to quaternary γ-nitro-γ-sulfonyl hydroxamic acid and γ-nitro-γ-sulfonyl carboxylic acid are also reported here.

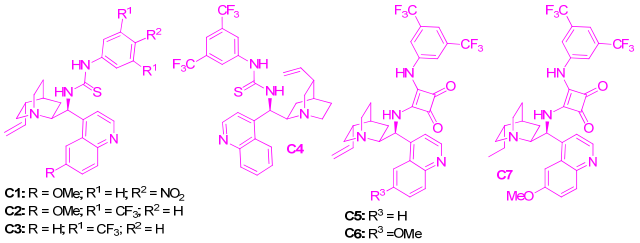


Figure 2 Catalysts Screened

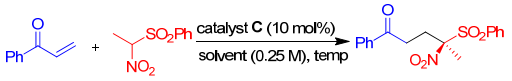
The reaction conditions were optimized by performing Michael addition of nitrosulfone **3a** to phenyl vinyl ketone **2a** using several cinchona-based bifunctional organocatalysts and solvents at different temperatures (Figure 2 and Table 1). At the outset, the quinine-thiourea catalyst **C1**, recently reported from our laboratory,[15] was screened (entry 1). To our delight, the Michael adduct **4a**, a quaternary α-nitrosulfone, was isolated in good yield (96%) and enantioselectivity (90% ee) when 10 mol % of **C1** was employed in mesitylene at rt (entry 1). Other catalysts such as quinine-thiourea **C2**, cinchonidine-thiourea **C3** and cinchonine-thiourea **C4** were also quite effective in providing the Michael adduct **4a** in excellent yield and selectivity (entries 2-4). Encouraged by these results, further improvement in the enantioselectivity was explored by employing bifunctional cinchona-squaramide catalysts **C5-C7** with greater H-bonding capability (entries 5-8).[17] Cinchonidine-squaramide catalyst **C5** provided the product **4a** with lower selectivity (entry 5). However, quinine-squaramide catalyst **C6**[18] furnished the Michael adduct **4a** with improved selectivity (94%) and excellent yield (98%, entry 6). At this juncture, possible enhancement of enantioselectivity by screening various solvents at different temperatures in the presence of 10 mol% of **C6** was investigated (entries 8-17). Thus, toluene was identified as the best solvent which at -60 °C provided Michael adduct **4a** in 98% yield and 99% ee (entry 17). We were amazed to note that high yield (98%) and selectivity (99% ee) were unaffected even when the catalyst loading was gradually reduced to 5, 2 and 0.2 mol % albeit at the expense of reaction rate (entries 18-20).

Published on 26 September 2013. Downloaded by McGill University on 26/09/2013 19:29:42.

Chemical Communications Accepted Manuscript

View Article Online
DOI: 10.1039/C3CC45985C

Table 1 Catalyst Screening and Optimization of Reaction Conditions[a]



2a 3a 4a

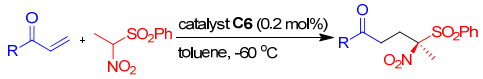
Entry	Cat	solvent	T (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**C1**	mesitylene	rt	1	96	90
2	**C2**	mesitylene	rt	1	94	88
3	**C3**	mesitylene	rt	1	95	91
4	**C4**	mesitylene	rt	1	93	87[d]
5	**C5**	mesitylene	rt	1	95	80
6	**C6**	mesitylene	rt	1	98	94
7	**C7**	mesitylene	rt	1	98	94
8	**C6**	xylene	rt	1	97	93
9	**C6**	toluene	rt	1	97	94
10	**C6**	$PhCF_3$	rt	1	95	88
11	**C6**	CH_2Cl_2	rt	1	86	86
12	**C6**	$(CH_2)_2Cl_2$	rt	1	97	85
13	**C6**	THF	rt	1	91	92
14	**C6**	diethyl ether	rt	1	92	86
15	**C6**	MeCN	rt	1	92	70
16	**C6**	toluene	-20	2	98	96.4
17	**C6**	toluene	-60	4	98	99
18[e]	**C6**	toluene	-60	5	98	98.5
19[f]	**C6**	toluene	-60	8	98	98.6
20[g]	**C6**	toluene	-60	11	98	99

[a] The reactions were performed at 0.2 mmol scale. [b]After silica gel column chromatography. [c] ee's determined by chiral HPLC. [d] opposite enantiomer. [e] 5 mol% catalyst. [f] 2 mol% catalyst. [g] 0.2 mol% catalyst and 0.5 mmol of **3**.

The scope of the above reaction was subsequently investigated by treating α-nitrosulfone **3a** with various enones **2b-o** under the above optimized conditions, i.e. 0.2 mol % catalyst **C6**, in toluene at -60°C (Table 2). It is noteworthy that regardless of the steric and electronic properties and position of substituents on the aromatic ring of enones, the Michael adducts **4a-i** were isolated in excellent yields (97-99%) and selectivities (96-99% ee) over a period of 2-20 h (entries 1-9). However, faster reaction rate was observed in the case of enones possessing electron withdrawing substituents such as NO_2, CN, Br and Cl at unhindered positions (entries 5-7 and 9) when compared to enones possessing electron donating substituents such as Me and OMe (entries 2-4). Polycyclic aromatic enones **2j-k**, heteroaromatic enones **2l-m** and an aliphatic enone **2n** were also well tolerated in terms of the chemical and optical yields of the products (entries 10-14), except that 1-naphthyl vinyl ketone **2k** furnished the Michael adduct **4k** with lower selectivity (72% ee, entry 11). However, since the reaction rate dramatically decreased with aliphatic enone **2n** the reaction had to be conducted at rt with 10 mol% of the catalyst **C6** (entry 14). A dienone **2o** also furnished the Michael adduct **4o** in 98% yield and 97% ee (entry 15). Notably, the reaction is highly regioselective in that α-nitrosulfone **3a** selectively reacted with the β-unsubstituted olefin moiety in the presence of a β-substituted olefin moiety in enone **2o** (entry 15).

Encouraged by the excellent results obtained from the reaction of nitrosulfone **3a** with a variety of enones **2** (Table 2), the scope of the reaction was investigated further with other sterically and electronically different nitrosulfones **3b-g** (Table 3). Thus, various alkyl, allyl and benzyl substituted nitrosulfones **3b-g** were treated with a representative enone **2i** under the optimal reaction conditions (Table 3). In general, the Michael adducts **5a-f** were obtained in excellent yields (90-99%) and enantioselectivities (entries 1-6). The enantioselectivity dropped marginally (to 85% ee) in the case of **5a** (entry 1) and substantially (to 50% ee) when a nitrosulfone **3f** possessing a long alkyl chain was employed (entry 5). This is attributable to the interference of the long, linear and flexible alkyl chain in **3f** in the Michael addition step (see Figure 3, *vide infra*). Since the rate of the reaction was very slow at -60 °C in case of benzyl substituted nitrosulfone **3g,** the reaction was performed at rt (entry 6).

Table 2 Scope of Enones **2**[a]

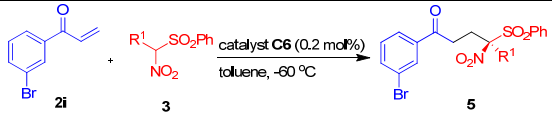


2 3a 4

Entry	R	Time (h)	4	Yield (%)[b]	ee (%)[c]
1	C_6H_5	11	**4a**	98	99
2	4-MeC_6H_4	10	**4b**	99	96
3	4-$OMeC_6H_4$	16	**4c**	98	99
4	3,4-$(OMe)_2C_6H_3$	20	**4d**	99	96
5	4-ClC_6H_4	5	**4e**	98	>99
6	4-CNC_6H_4	3	**4f**	99	>99
7	4-$NO_2C_6H_4$	2	**4g**	99	99
8	2-ClC_6H_4	14	**4h**	97	98
9	3-BrC_6H_4	5	**4i**	99	>99[d]
10	2-naphthyl	14	**4j**	98	99
11	1-naphthyl	15	**4k**	99	72
12	2-furyl	12	**4l**	96	99
13	2-thienyl	7	**4m**	97	97
14[e]	*c*-C_6H_{11}	10	**4n**	86	91
15	PhCH=CH	15	**4o**	98	97

[a] The reactions were performed at 0.5 mmol scale. [b] After silica gel column chromatography. [c] Ee determined by chiral HPLC. [d] This reaction was also performed at larger scale (*vide infra*). [e] Reaction performed at rt.

Table 3 Scope of Nitrosulfones **3** [a]



2i 3 5

Entry	R^1	3	Time (h)	5	Yield (%)[b]	ee (%)[c]
1	Et	**3b**	12	**5a**	96	85
2	allyl	**3c**	10	**5b**	99	>99
3	*n*-Bu	**3d**	14	**5c**	93	95
4	*n*-C_5H_{11}	**3e**	17	**5d**	98	95
5	*n*-C_7H_{15}	**3f**	17	**5e**	90	50
6[d]	benzyl	**3g**	8	**5f**	95	96

[a] The reactions were performed at 0.5 mmol scale. [b] After silica gel column chromatography. [c] Ee determined by chiral HPLC. [d] Reaction performed at rt.

The absolute configuration of the Michael adducts **4-5** was unambiguously assigned as *R* by single crystal X-ray structure analysis of a representative compound **4i** (Figure 3, see also the ESI). The proposed mechanism based on model studies involves deprotonation of nitrosulfone **3** by the quinuclidine moiety of catalyst **C6** and activation of enone **2** by the squaramide moiety (Figure 3). In the favored approach **II**, the squaramide moiety also co-ordinates with the nitro group, and the quinuclidine moiety with the nitro and the sulfonyl groups, to enable *Re*-face approach of the enone **2** towards the nitrosulfone anion affording (*R*)-nitrosulfone **4** or **5**. The alternative approach **I** appears disfavored due to severe steric interactions between the phenyl group of sulfone and the quinuclidine moiety of the catalyst.

Published on 26 September 2013. Downloaded by McGill University on 26/09/2013 19:29:42.

Chemical Communications Accepted Manuscript

This journal is © The Royal Society of Chemistry [year]

View Article Online
DOI: 10.1039/C3CC45985C

Our reaction conditions are suitable for the synthesis of nitrosulfones **4-5** on multi-gram scale without any appreciable drop in the yield or selectivity. This was demonstrated by the synthesis of 2.9 g of **4i** (97%) with 99% ee via Michael addition of 1.5 g of nitrosulfone **3a** to 2.2 g of vinyl ketone **2i** (Table 2, entry 9).

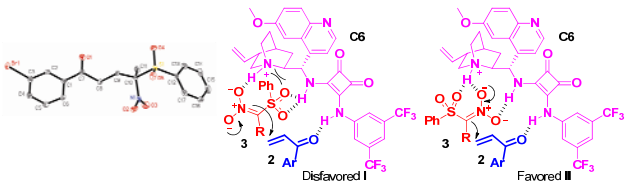
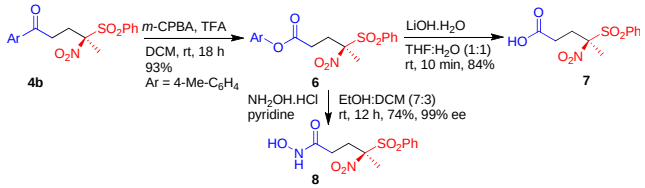


Figure 3. X-ray Structure of **4i** and Proposed Mechanistic Model

Nitrosulfonylketones **4** and **5** in which the carbonyl group is at the δ-position of the nitro and the sulfonyl group are excellent precursors for the enantioselective synthesis of carboxylic acid **7** and hydroxamic acid **8** (Scheme 2). Thus a representative nitrosulfonylketone **4b** was subjected to Baeyer-Villiger oxidation using *m*CPBA-TFA to afford nitrosulfonyl ester **6** in 93% yield. Lithium hydroxide mediated hydrolysis of nitrosulfonyl ester **6** afforded quaternary γ-nitro-γ-sulfonyl carboxylic acid **7** in 84% yield. More importantly, the ester **6** was successfully transformed to hydroxamic acid **8** in 74% yield by treating with hydroxylamine hydrochloride. The ee of the intermediate **6** and the final product **8** matched well with the ee of the starting compound **4b**.



Scheme 1 Enantioselective Synthesis of Hydroxamic Acid

In conclusion, conjugate addition of α-nitrosulfones to vinyl ketones afforded α-nitro-δ-ketosulfones in excellent yield and enantioselectivity in the presence of as low as 0.2 mol% quinine-squaramide organocatalyst. The feasibility of scale up of the enantioselective conjugate addition as well as a practical application of the products in the enantioselective synthesis of carboxylic acids and hydroxamic acids have been successfully demonstrated.

INNN thanks DAE India for financial assistance and KSB thanks CSIR India for a senior research fellowship.

[a] *Department of Chemistry, Indian Institute of Technology Bombay, Mumbai 400 076, India, irishi@iitb.ac.in*

† Electronic Supplementary Information (ESI) available: See DOI: 10.1039/b000000x/

Notes and references

1 B. Lovejoy, A. R. Welch, S. Carr, C. Luong, C. Broka, R. T. Hendricks, J. A. Campbell, K. A. M. Walker, R. Martin, H. Van Wart and M. F. Browner, *Nat. Struct. Biol.*, 1999, **6**, 217.

2 For an article: J. M. Salvino, R. Mathew, T. Kiesow, R. Narensingh, H. J. Mason, A. Dodd, R. Groneberg, C. J. Burns, G. McGeehan, J. Kline, E. Orton, S.-Y. Tang, M. Morrisette and R. Labaudininiere, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1637.

3 (a) X.-Q. Dong, X. Fang, and C.-J. Wang, *Org. Lett.*, 2011, **13**, 4426; (b) M. Sani, G. Candiani, F. Pecker, L. Malpezzia and M. Zandaa, *Tetrahedron Lett.*, 2005, **46,** 2393.

4 I. Churcher, D. Beher, J. D. Best, J. L. Castro, D. J. Gentry, T. Harrison, L. Hitzel, E. Kay, S. Kerrad, H. D. Lewis, P. Morentin-Gutierrez, R. Mortishire-Smith, P. J. Oakley, M. Reilly, D. E. Shaw, M. S. Shearman, M. R. Teall, S. Williams, J. D. J. Wrigley, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 280.

5 For selected recent examples, see: (a) V. Aranapakam, G. T. Grosu, J. M. Davis, B. Hu, J. Ellingboe, J. L. Baker, J. S. Skotnicki, A. Zask, J. F. DiJoseph, A. Sung, M. A. Sharr, L. M. Killar, T. Walter, G. Jin and R. Cowling, *J. Med. Chem.*, 2003, **46**, 2361; (b) M. Fernández and J. Caballero, *Bioorg. Med. Chem.*, 2007, **15**, 6298; (c) D. P. Becker, C. I. Villamil, T. E. Barta, L. J. Bedell, T. L. Boehm, G. A. DeCrescenzo, J. N. Freskos, D. P. Getman, S. Hockerman, R. Heintz, S. C. Howard, M. H. Li, J. J. McDonald, C. P. Carron, C. L. Funckes-Shippy, P. P. Mehta, G. E. Munie, and C. A. Swearingen, *J. Med. Chem.*, 2005, **48**, 6713.

6 M. F. Surgrue, A. Harris and I. Adamsoms, *Drugs Today*, 1997, **33**, 283.

7 Selected books/reviews: (a) T. G. Back, K. N. Clary and D. Gao, *Chem. Rev.*, 2010, **110**, 4498; (b) A. El-Awa, M. N. Noshi, X. M. D. Jourdin and P. L. Fuchs, *Chem. Rev.*, 2009, **109**, 2315; (c) N. S. Simpkins, *Sulfones in Organic Synthesis*, Pergamon, Oxford, 1993; (d) D. A. Alonso and C. Najera, *Org. React.*, 2008, **72**, 367. (e) E. N. Prilezhaeva, *Russ. Chem. Rev.*, 2000, **69**, 367.

8 Selected recent reviews: (a) A. R. Alba, X. Companyo and R. Rios, *Chem. Soc. Rev.*, 2010, **39**, 2018; (b) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixao and K. A. Joergensen, *Angew. Chem., Int. Ed.*, 2010, **49**, 2668.

9 (a) S. Rajkumar, K. Shankland, J. M. Goodman and A. J. A. Cobb, *Org. Lett.*, 2013, **15**, 1386; (b) P. H. Bos, A. J. Minnaard and B. L. Feringa, *Org. Lett.*, 2008, **10**, 4219; (c) P. Mauleón, I. Alonso, M. R. Rivero and J. C. Carretero, *J. Org. Chem.*, 2007, **72**, 9924; (d) J.-N. Desrosiers, W. S. Bechara and A. B. Charette, *Org. Lett.*, 2008, **10**, 2315.

10 (a) J. L. García-Ruano, V. Marcos and J. Alemán, *Chem. Commun.*, 2009, 4435; (b) A.-N. Alba, X. Companyo´, A. Moyano and R. Rios, *Chem. Eur. J.*, 2009, **15**, 11095; (c) A. Landa, A. Puente, J. I. Santos, S. Vera, M. Oiarbide and C. Palomo, *Chem. Eur. J.*, 2009, **15**, 11954; (d) N. Nielsen, C. B. Jacobsen, M. W. Pixao, N. Holub and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2009, **131**, 10581; (e) G. K. Surya Prakash, F. Wang, Z. Zhang, C. Ni, R. Haiges and G. A. Olah, *Org. Lett.*, 2012, **14**, 3260; (f) C. B. Jacobsen, K. L. Jensen, J. Udmark and K. A. Jørgensen, *Org. Lett.*, 2011, **13**, 4790.

11 (a) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura and T. Toru, *J. Am. Chem. Soc.*, 2007, **129**, 6394; (b) T. Furukawa, N. Shibata, S. Mizutana, S. Nakamura, T. Toru and M. Shiro, *Angew. Chem., Int. Ed.*, 2008, **47**, 8051; (c) C. Ni, F. Wang and J. Hu, *Beilstein J. Org. Chem.*, 2008, 4; (d) A.-N. Alba, X. Companyo´, A. Moyano and R. Rios, *Chem. Eur. J.*, 2009, **15**, 7035; (e) S. Zhang, Y. Zhang, Y. Ji, H. Li and W. Wang, *Chem. Commun.*, 2009, 4886; (f) F. Ullah, G.-L. Zhao, L. Deiana, M. Zhu, P. Dziedzic, I. Ibrahem, P. Hammar, J. Sun and A. Córdova, *Chem. Eur. J.*, 2009, **15**, 10013; (g) C. B. Jacobsen, M. Nielsen, D. Worgull, T. Zweifel, E. Fisker and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2011, **133**, 7398.

12 (a) M. B. Cid, J. López-Cantero, S. Duce and J. L. Garcia Ruano, *J. Org. Chem.*, 2009, **74**, 431; (b) G. K. Surya Prakash, F. Wang, T. Stewart, T. Mathew and G. A. Olah, *Proc. Natl. Acad. Sci. U. S. A.*, 2009, **106**, 4090. (c) M. Kamlar, N. Bravo, A. R. Alba, S. Hybelbauerová, I. Císarˇová, J. Veselý, A. Moyano, and R. Rios, *Eur. J. Org. Chem.*, 2010, 5464.

13 (a) Catalytic hydrogenation of unsaturated sulfones: T. Zhou, B. Peters, M. F. Maldonado, T. Govender and P. G. Andersson, *J. Am. Chem. Soc.*, 2012, **134**, 13592; (b) Reduction of β-ketosulfones: X. Wan, Q. Meng, H. Zhang, Y. Sun, W. Fan and Z. Zhang, *Org. Lett.*, 2007, **9**, 5613.

14 (a) Allylation of sodium sulfinate: M. Ueda and J. F. Hartwig, *Org. Lett.*, 2010, **12**, 92; (b) Stereospecific decarboxylative allylation of sulfones**:** J. D. Weaver, B. J. Ka, D. K. Morris, W. Thompson and J. A. Tunge, *J. Am. Chem. Soc.*, 2010, **132**, 12179; (c) Intramolecular

Published on 26 September 2013. Downloaded by McGill University on 26/09/2013 19:29:42.

Chemical Communications Accepted Manuscript

View Article Online
DOI: 10.1039/C3CC45985C

cyclopropanation of α-diazo-β-ketosulfones: M. Honma, T. Sawada, Y. Fujisawa, M. Utsugi, H. Watanabe, A. Umino, T. Matsumura, T. Hagihara, M. Takano and M. Nakada, *J. Am. Chem. Soc*., 2003, **125**, 2860; (d) [3+2] cycloaddition of azomethine ylides with vinyl sulfones**:** (a) T. Llamas, R. G. Arrayás and J. C. Carretero, *Org. Lett*., 2006, **8**, 1795; (b) S.-I. Fukuzawa and H. Oki, *Org. Lett*., 2008, **10**, 1747.

15 K. Bera and I. N. N. Namboothiri, *Org. Lett*., 2012, **14**, 980.

16 K. Bera and I. N. N. Namboothiri, *Adv. Synth. Catal*., 2013, **355**, 1265.

17 (a) J. P. Malerich, K. Hagihara and V. H. Rawal, *J. Am. Chem. Soc*., 2008, **130**, 14416; Review: (b) J. Aleman, A. Parra, H. Jiang and K. A. Jørgensen, *Chem. Eur. J*., 2011, **17**, 6890.

18 W. Yang and D.-M. Du, *Org. Lett.*, 2010, **12**, 5450.

Published on 26 September 2013. Downloaded by McGill University on 26/09/2013 19:29:42.

Chemical Communications Accepted Manuscript

This journal is © The Royal Society of Chemistry [year]