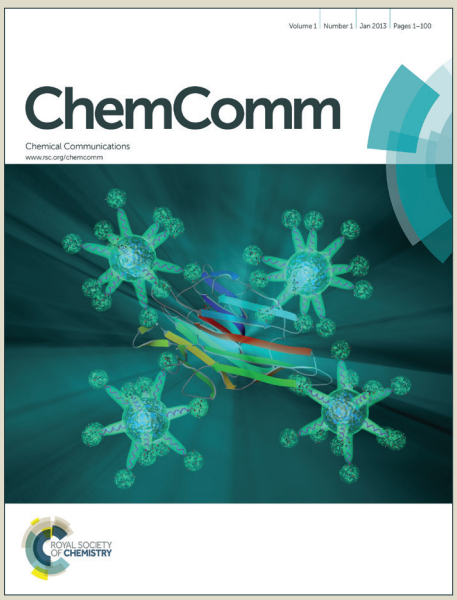
ChemComm

Accepted Manuscript



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

Chem Comm

RSCPublishing

COMMUNICATION

Enantioselective transformation of Na_2SO_3 into allylic sulfonic acids under Pd catalysis

Cite this: DOI: 10.1039/x0xx00000x

Wei Liu, Xiao-ming Zhao*, Hong-bo Zhang, Liang Zhang

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

Pd-catalyzed asymmetric allylic sulfonation of di-aryl-substituted allylic acetates with sodium sulfite (Na_2SO_3) in THF/H_2O at room temperature was described. This method directly provided allylic sulfonic acids in up to excellent yield and enantioselectivity.

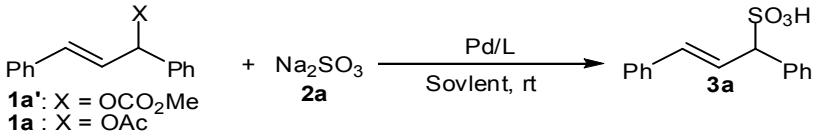
Pd-catalyzed asymmetric allylic substitution has become a useful method for the synthesis of chiral compounds.[1] In this regard, a wide range of nucleophiles such as *C*, *N*, *O*, and SO_2-nucleophile has been explored during the past several decades. Despite Pd-catalyzed allylic substitutions of *S*-nucleophiles to produce achiral allyl sulfur-containing compounds have been extensively studied,[2] only a few enantioselective allylations of *S*-nucleophiles have been described, of which the enantioselectivities and yields varied from poor to excellent depending upon reaction conditions and substrates.[3] Additionally, only sulfinates and more acidic aromatic thiols were effective,[3a,c] and no reactions occurred for other *S*-nucleophiles, probably owing to competitive coordination to the Pd catalysts between these sulphur-containing substrates and chiral ligands.[3a,4] Sulfonic acid (RSO_3H) is of great importance with respect to physiological processes,[5] drug,[6] and resolving agents[7] in pharmaceutical industry. Notably, either *Cefsulodin*[8] or *Sulbenicillin*[9], a semisynthetic cephalosporin antibiotics and a penicillin antibiotic, contains a chiral sulfonic acid. Sulfonic acids with a chiral C–S centre are commonly obtained from the corresponding racemates by resolution technique with chiral amines.[10] A series of enantiomeric α-substituted sulfonic acids was achieved by asymmetric synthesis[11] and "Dutch resolution"[10]. Obviously, a direct method for the formation of allyl sulfonic acid (RSO_3H) is by the allylic sulfanation between allylic substrate and sodium sulfite (Na_2SO_3) under Pd catalysis. To the best of our acknowledgement, such a reaction for the synthesis of sulfonic acids is not yet reported nowadays. Allylic sulfonic acid is not functionalized intermediate but also precursor of sulfonic acid. Herein, we descript Pd-catalyzed allylic sulfanation of allylic acetates with Na_2SO_3, which allows for the synthesis of chiral sulfonic acids.

We began our study by examining a model reaction of (*E*)-1,3-diphenylallyl methyl carbonate (**1a**') with Na_2SO_3 (**2a**) under Pd catalysis (Table 1). The catalyst generated from $[Pd(allyl)Cl]_2$, $Pd(OAc)_2$ and Pd_2dba_3 with (*R*)-BINAP ligand **L1**[12] (see Fig. 1), respectively, was tested in component solvent (THF/H_2O) at room temperature. To our delight, Pd_2dba_3/**L1** led to a formation of allyl sulfonic acid **3a**[13] with 76% ee and no by-product was observed (entries 1–3). Analysis of **1a'** that was recovered upon completion of the reaction in entry 3 by HPLC on a chiral stationary phase illustrated that it is recemic. The effect of structurally various ligands on this allylic sulfonation was further probed. The outcomes revealed that **L1** gave a superior *ee*; both (*R*)-Tol-BINAP **L2**[12] and (*R*)-BisbenzodioxanPhos **L3**[14] resulted in poor to acceptable ee although they are structurally similar to **L1** (entries 4–5). Note that either (*R*,*R*,*Ra*)-Feringa's ligand **L4**[15] or (*S*)-Carreira's ligand **L5**[16] afforded **3a** in 73% and 70% ee, respectively (entries 4–5). Examination of different ligands such as (*S*)-Josiphos, (*S*)-PHOX, (*R*,*R*)-Trost's ligand and (*R*,*R*)-DIOP illustrated that they are ineffective for this reaction. Moreover, leaving group has a considerable impact on the results of this reaction. For example, -OAc led to a higher ee value than that of -OCO_2Me (entry 8 *vs.* entry 3). Analysis of **1a**, which was recovered upon completion of the reaction in entry 8, by HPLC on a chiral stationary phase indicated that it is recemic. Increasing $Pd_2(dba)_3$ from 2.5 to 5.0 mol% led to the considerable improvement of ee value and yield (entries 8–9). Screening the solvents indicated that THF/H_2O 4/1 is the optimum solvents for this reaction, whereas other solvents are ineffective (entries 10–15). We found that the reaction failed in THF without H_2O (Table 1, entry 15). These results suggested that the presence of H_2O is beneficial to the solubility of Na_2SO_3 (**2a**) in this reaction system. Other different *S*-nuceophiles including $NaHSO_3$ (**2b**) and K_2SO_3 (**2c**) were also explored and they gave 88% ee and 89% ee, respectively. Taking into consideration of the economic reason, we chose Na_2SO_3 (**2a**) as the sulfur source. Variation of the ratio of **1a**/**2a** has a significant effect on this reaction (entries 16–18). When both 10% of $Pd_2(dba)_3$ and **1a**/**2a** (5/1) were utilized, the yield of **3a** was somewhat improved but its ee value was slightly decreased (entry 19).

Having established the optimized conditions presented in entry 18 of Table 1, we next explored the scope of the allylic sulfonation of a variety of allylic acetates (**1**) with Na_2SO_3 (**2a**). (*E*)-1,3-Diphenylallyl acetate (**1a**) and the di-aryl-substituted allyl acetates (**1b**–**i**) with either electron-donating (e.g., 3-Me, 3-MeO, and 4-MeO)

or electron-attracting groups (e.g., 3-F, 3-Cl, 3-Br, 4-F and 4-Cl) on the phenyl ring afforded the corresponding sulfonic acids (**3a**–**i**) in fair to excellent yields (40–92%) with acceptable to high enantioselectivities (61–91% ee, Table 2). The sulfonic acid **3f** contains a bromine group on the phenyl ring which can undergo useful transformation. (*E*)-1,3-Di(naphthalen-2-yl)allyl acetate (**1j**) provided (*E*)-1,3-di(naphthalen-

Table 1 Optimization studies for the Pd-catalyzed asymmetric allylic sulfonation of Na_2SO_3 **2a**[a]



Entry	Pd Salt	Cat (mol%)	L	Solvent	X	Time (h)	Yield of **3a** (%)[b]	ee (%)[c]
1	$[Pd(allyl)Cl]_2$	2.5	L1	THF/H_2O = 4/1	OCO_2Me	24	25	32
2	$Pd(OAc)_2$	5.0	L1	THF/H_2O = 4/1	OCO_2Me	24	18	12
3	Pd_2dba_3	2.5	L1	THF/H_2O = 4/1	OCO_2Me	36	23	76
4	Pd_2dba_3	2.5	L2	THF/H_2O = 4/1	OCO_2Me	36	22	37
5	Pd_2dba_3	2.5	L3	THF/H_2O = 4/1	OCO_2Me	36	13	52
6	Pd_2dba_3	2.5	L4	THF/H_2O = 4/1	OCO_2Me	36	20	73
7	Pd_2dba_3	2.5	L5	THF/H_2O = 4/1	OCO_2Me	36	12	70
8	Pd_2dba_3	2.5	L1	THF/H_2O = 4/1	OAc	48	12	89
9	Pd_2dba_3	5.0	L1	THF/H_2O = 4/1	OAc	48	20	90
10	Pd_2dba_3	5.0	L1	Dioxane/H_2O = 4/1	OAc	48	30	78
11	Pd_2dba_3	5.0	L1	Et_2O/H_2O = 4/1	OAc	48	N.R.	-
12	Pd_2dba_3	5.0	L1	THF/H_2O = 2/1	OAc	48	45	74
13	Pd_2dba_3	5.0	L1	THF/H_2O = 1/1	OAc	48	60	40
14	Pd_2dba_3	5.0	L1	THF/H_2O = 9/1	OAc	48	7	89
15	Pd_2dba_3	5.0	L1	THF	OAc	48	N.R.	-
16	Pd_2dba_3	5.0	L1	THF/H_2O = 4/1[d]	OAc	48	22	86
17	Pd_2dba_3	5.0	L1	THF/H_2O = 4/1[e]	OAc	48	10	88
18[f]	Pd_2dba_3	5.0	L1	THF/H_2O = 4/1[e]	OAc	48	60	90
19[f]	Pd_2dba_3	10.0	L1	THF/H_2O = 4/1	OAc	48	65	89

[a] Reagents and conditions: **1a** (or **1a**', 0.20 mmol, 1.0 equiv.), **2a** (0.40 mmol, 2.0 equiv.), organic solvent (2.0 mL)/H_2O(x mL), room temperature under argon; the completion of the reaction is determined by monitoring of TLC. Work-up was performed through a plug of freshly activated acidic ion exchange resin. [b] Calculated yield, for which the weight of H_2O is reduced from the hydrated sulfonic acid based on the integration of the hydrogen of H_2O in ^1H NMR. For the details, see: SI. [c] Determined with the sulfonic acid methyl ester generated by esterification of **3a** with Me_3SiCHN_2 and analysis by HPLC on a chiral stationary phase (Daicel CHIRALPAK AD). [d] THF (4.0 mL)/ H_2O (1.0 mL). [e] THF (1.0 mL)/H_2O (0.25 mL). [f] **1a**/**2a** = 5/1.

Journal Name RSCPublishing

COMMUNICATION

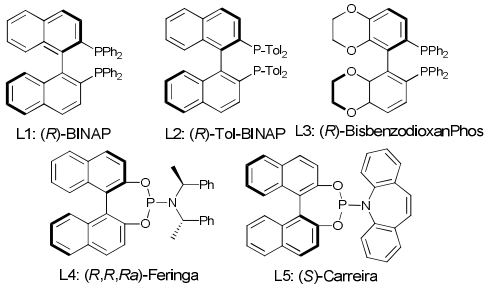


Fig. 1 Ligands used in Pd-catalyzed asymmetric allylic sulfonations.

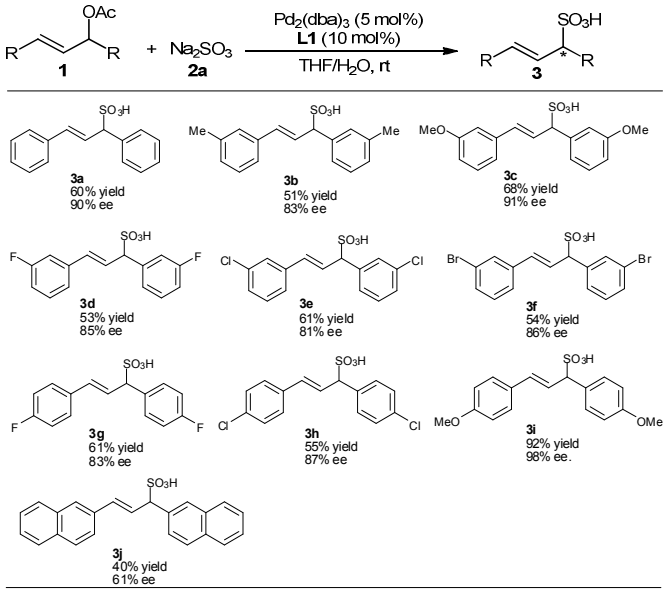
2-yl)prop-2-ene-1-sulfonic acid (**3j**) in 40% yield and 61% ee (Table 2, **3j**). The aliphatic allylic acetates (e.g., R = Me, Et, and cyclohex-2-eneyl) were also examined and the corresponding sulfonation products were not yet observed.

Conclusions

We developed a practical protocol for the construction of allylic sulfonic acids via Pd-catalyzed allylic sulfonation of Na_2SO_3, which afforded the allylic sulfonic acids in moderate yields with a high level of enantioselectivities. This is the first example for the synthesis of chiral allyl sulfonic acids derived from Na_2SO_3.

We gratefully acknowledge the NSFC (21272175 and 20942003) for generous financial support.

Table 2 Scope of the sulfonations of the allylic acetates **1** and Na_2SO_3 **2a**[a,b,c,d]



[a] Reagents and conditions: **1** (1.0 mmol, 5.0 equiv.), **2a** (0.20 mmol, 1.0 equiv.), $Pd_2(dba)_3$(5 mol %)/**L1**(10 mol%), and THF/H_2O = 4/1 at room temperature under argon, monitoring by TLC (~48 h). [b] Calculated yield, for which the weight of H_2O is reduced from the hydrated sulfonic acid based on the integration of the hydrogen of H_2O in ^1H NMR. For the details, see: SI. [c] Determined with the sulfonic acid methyl ester generated by esterification of **3** with Me_3SiCHN_2 and analysis by HPLC on a chiral stationary phase. [d] The ee value of **3i** was determined by HPLC on a chiral stationary phase.

Notes and references

Department of Chemistry, State Key Laboratory of Pollution Control and Resource Reuse, Tongji University, 1239 Siping Road, 200092 Shanghai, P.R. China

† Electronic Supplementary Information (ESI) available: Experimental procedures and analysis data for new compounds. See DOI: 10.1039/c000000x/

1 For the reviews and selective papers, see: (a) A. Saitoh, K. Achiwa, K. Tanaka, T. Morimoto, *J. Org. Chem.* 2000, **65**, 4227; (b) Y. Tamaru, *Eur. J. Org. Chem.* 2005, 2647; (c) B. M. Trost, D. L. Van Vranken, *Chem. Rev.* 1996, **96**, 395; (d) M. Johannsen, K. A. Jørgensen, *Chem. Rev.* 1998, **98**, 1689; (e) T. Hayashi, *J. Organomet. Chem.* 1999, **576**, 195; (f) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* 2000, **33**, 336; (g) L.-X. Dai, T. Tu, S.-L. You, W.-P. Deng, X.-L. Hou, *Acc. Chem. Res.* 2003, **36**, 659; (h) B. M. Trost, M. L. Crawley, *Chem. Rev.* 2003, **103**, 2921; (i) B. M. Trost, *J. Org. Chem.* 2004, **69**, 5813; (j) B. M. Trost, M. R. Machacek, A. Aponick, *Acc. Chem. Res.* 2006, **39**, 747; (k) Z. Lu, S. Ma, *Angew. Chem., Int. Ed.* 2008, **47**, 258; (l) M. Dieguez, O. Pamies, *Acc. Chem. Res.* 2010, **43**, 312; (m) W. Liu, X. M. Zhao, *Synthesis*, 2013, **45**, 2052.

2 (a) T. Kondo, M. Mitsdo, *Chem. Rev.* 2000, **100**, 3205; (b) Eichelmann, H.; Gais, H. J.; *Tetrahedron*: *Asymmetry* 1995, **6**, 643; (c) B. M. Trost, M. J. Krische, R. Radinov, G. Zanoni, *J. Am. Chem. Soc.* 1996, **118**, 6297; (d) B. M. Trost, M. L. Crawley, , C. B. Lee, *J. Am. Chem. Soc.* 2000, **122**, 6120; (e) F. X. Felpin, Y. Landais, *J. Org. Chem.* 2005, **70**, 6441; (f) S. Chandrasekhar, V. Jagadeshwar, B. Saritha, C. Narsihmulu, *J. Org. Chem.* 2005, **70**, 6506; (g) M. Jegelka, B. Plietker, *Org. Lett.* 2009, **11**, 3462; (h) B. Alexey, H. F. Zaitsev, P. S. Caldwell, L. F. V. Pregosin, *Chem. Eur. J.* 2009, **15**, 6468; (i) T. Kondo, Y. Morisaki, S. Uenoyama, K. Wada, T. Mitsudo, *J. Am. Chem. Soc.* 1999, **121**, 8657

3 (a) M. Frank, H. J. Gais, *Tetrahedron*: *Asymmetry*. 1998, **9**, 3353; (b) H. J. Gais, N. Spalthoff, J. Thomas, M. Frank, G. Raabe, *Tetrahedron Lett.*, 2000, **41**, 3809; (c) H. J. Gais, N. Spalthoff, J. Thomas, F. Gerhards, M. Frank, G. Raabe *Chem. Eur. J.* 2003, **9**, 4202; (d) V. N. Tsarev, S. E. Lyubimov, A. A. Shiryaev, S. V. Zheglov, O. G. Bondarev, V. A. Davankov, A. A. Kabro, S. K. Moiseev, V. N. Kalinin, K. N. Gavrilov, *Eur. J. Org. Chem.* 2004, 2214; (e) V. N. Tsarev, S. E. Lyubimov, O. G. Bondarev, A. A. Korlyukov, M. Y. Antipin, P. V. Petrovskii, V. A. Davankov, A. A. Shiryaev, E. B. Benetsky, P. A. Vologzhanin, K. N. Gavrilov, *Eur. J.*

Org. Chem. 2005, 2097; (f) V. N. Tsarev, S. I. Konkin, A. A. Shyryaev, V. A. Davankova, K. N. Gavrilovb, *Tetrahedron: Asymmetry* 2005, **16**, 1737; (g) K. N. Gavrilov, S. E. Lyubimov, S. V. Zheglov, E. B. Benetsky, V. A. Davankov, *J. Mol. Cat. A: Chemical* 2005, **231**, 255; (h) K. N. Gavrilov, V. N. Tsarev, S. I. Konkin, N. M. Loim, P. V. Petrovskii, E. S. Kelbyscheva, A. A. Korlyukov, M. Y. Antipin, V. A. Davankov, *Tetrahedron: Asymmetry* 2005, **16**, 3224; (i) K. N. Gavrilov, S. E. Lyubimov, O. G. Bondarev, M. G. Maksimova, S. V. Zheglov, P. V. Petrovskii, V. A. Davankov, M. T. Reetz, *Adv. Synth. Catal.* 2007, **349**, 609.

4 *S*-Nucleophiles can poison transition metal catalysts, see: (a) Hutton, A. T. *In Comprehensive Coordination Chemistry*; Wilkinson, G., Gillard, R. D., McCleverty, J. A., Eds.; Pergamon: Oxford, U.K., **1984**; Vol. 5, p 1151; (b) Hegedus, L. L.; McCabe, R. W. *Catalyst Poisoning*; Marcel Dekker: New York, **1984**.

5 (a) A. Kalir, H. H. Kalir, in *The Chemistry of Sulfonic Acids, Esters and Their Derivatives*. Chapter 18: Biological Activity of Sulfonic Acid Derivatives (Eds.: S. Patai, Z. Rappoport), John Wiley & Sons, New York, **1991**; (b) R. J. Huxtable, *Physiol. Rev.* 1992, **72**, 101; (c) M. Yoshikawa, S. Yamaguchi, K. Kunimi, H. Matsuda, Y. Okuno, J. Yamahara, N. Murakami, *Chem. Pharm. Bull.* 1994, **42**, 1226.

6 X. Qiu, A. Miles, X. Jiang, X. Sun, N. Yang, *Evidence-Based Complementary and Alternative Medicine*. 2012.

7 (a) P. J. Reider, P. Davis, D. L. Hughes, E. J. J. Grabowski, *J. Org. Chem.* 1987, **52**, 955; (b) R. D. Clark, J. R. Kern, L. J. Kurz, J. T. Nelson, *Heterocycles* 1990, **31**, 353.

8 (a) S. Morimoto, H. Nomura, T. Fugono, T. Azuma, J. Minami, *J. Med. Chem.* 1972, **15**, 1108; (b) S. Morimoto, H. Nomura, T. Ishiguro, T. Fugono, K. Maeda, *J. Med. Chem.* 1972, **15**, 1105.

9 K. Tsuchiya, M. Kondo, *Antimicrob. Agents Chemother.* 1978, **13**, 536.

10 (a) F. A. Davis, P. Zhou, P. J. Carroll, *J. Org. Chem.* 1993, **58**, 4890; (b) D. Enders, C. R. Thomas, G. Raabe, J. Runsink, *Helv. Chim. Acta* 1998, **81**, 1329; (c) C. Huart, L. Ghosez, *Angew. Chem., Int. Ed.* 1997, **36**, 634.

11 (a) R. M. Kellogg, J. W. Nieuwenhuijzen, K. Pouwer, T. R. Vries, Q. B. Broxterman, R. F. P. Grimbergen, B. Kaptein, R. M. La Crois, E. de Wever, K. Zwaagstra, A. C. van der Laan, *Synthesis* 2003, 1626; (b) E. J. Corey, K. A. Cimprich, *Tetrahedron Lett.* 1992, **33**, 4099; (c) D. Enders, N. Vignola, O. M. Berner, J. W. Bats, *Angew. Chem., Int. Ed.* 2002, **41**, 109; (d) D. Enders, O. M. Berner, N. Vignola, W. Harnying, *Synthesis* 2002, 1945; (e) D. Enders, O. M. Berner, N. Vignola, J. W. Bats, *Chem. Commun.* 2001, 2498; (f) M. Moccia, F. Fini, M. Scagnetti, M. F. A. Adamo, *Angew. Chem., Int. Ed.* 2011, **50**, 6893; (g) F. M. Koch, R. Peters, *Chem. Eur. J.* 2011, **17**, 3679.

12 (a) H. Takaya, K. Mashima, K. Koyano, M. Yagi, H. Kumobayashi, T. Taketomi, S. Akutagawa, *J. Org. Chem.* 1986, **51**, 629; (b) R. Noyori, H. Takaya, Acc. *Chem. Res.* 1990, **23**, 345; (c) S. Akutagawa, *Appl. Catal. A: Gen.* 1995, **128**, 171; (d) M. McCarthy, P. J. Guiry, *Tetrahedron* 2001, **57**, 3809; (e) H. Shimizu, I. Nagasaki, T. Saito, *Tetrahedron* 2005, **61**, 5405.

13 The sulfonic acids **3** together with water were obtained after purification, which are inseparable. These outcomes are in agreement with previous works, see: ref:11c,11d,11e and 11f.

14 C.-C. Pai, Y.-M. Li, Z.-Y. Zhou, A. S. C. Chan, *Tetrahedron Lett.* 2002, **43**, 2789.

15 A. W. van Zijl, L. A. Arnold, A. J. Minnaard, B. L. Feringa, *Adv. Synth. Catal.* 2004, **346**, 413.

16 C. Defieber, M. A. Ariger, P. Moriel, E. M . Carreira, *Angew. Chem. Int. Ed.* 2007, **46**, 3139.

