ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Jacobsen Protocols for Large-Scale Epoxidation of Cyclic Dienyl Sulfones: Application to the (+)-Pretazettine Core

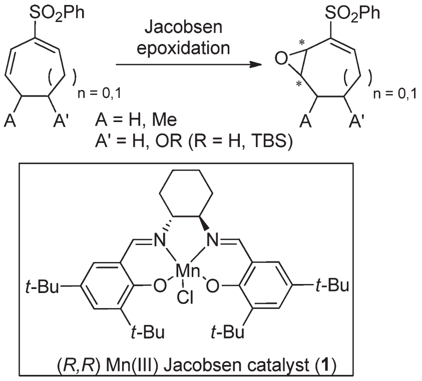
G. Reza Ebrahimian, Xavier Mollat du Jourdin, and Philip L. Fuchs*

Department of Chemistry, Purdue University, West Lafayette, Indiana 47906, United States

pfuchs@purdue.edu

Received April 17, 2012

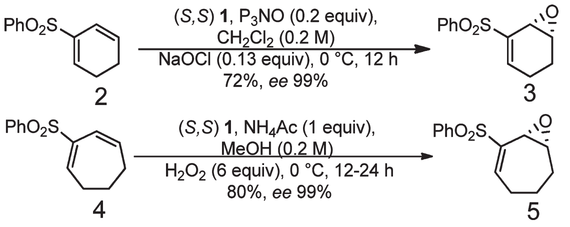
ABSTRACT



A Jacobsen epoxidation protocol using H_2O_2 as oxidant was designed for the large-scale preparation of various epoxy vinyl sulfones. A number of cocatalysts were screened, and pH control led to increased reaction rate, higher turnover number, and improved reliability.

The formation of the C–O bond via epoxidation is one of the most widely used reactions in the toolbox of the synthetic organic chemist. Jacobsen and Katsuki further expanded the synthetic utility of this transformation in the early 1990s with the design of salen Mn(III) catalysts offering access to a wide range of enantiomerically pure epoxides.[1] The nature of the oxidant (H_2O_2, NaOCl, *m*-CPBA, urea hydrogen peroxide, PhIO)[2] as well as the presence of additives and axial ligands (carboxylates, *N*-oxides)[3] and the structure of the catalyst itself has been studied, thus leading to numerous variants of the Jacobsen protocol. In the last 15 years, Fuchs' group further extended the applicability of Jacobsen's protocol to epoxidation of dienyl sulfones in the course of the synthesis of naturally occurring products such as apoptolidin, aplyronine A, and (+)-discodermolide. In the late 1990s, Hentemman demonstrated the synthetic utility of Jacobsen's asymmetric epoxidation (JAE) to obtain good yield and high ee of enantiopure epoxy vinylsulfones **3** and **5** (Scheme 1).[4] Despite its high efficiency on small scale, this method was not transferable to large scale.

Scheme 1. Hentemann and Myers/Torres epoxidations of Dienyl Sulfones **1** and **2**



---

(1) (a) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063–7064. (b) Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345–7348.

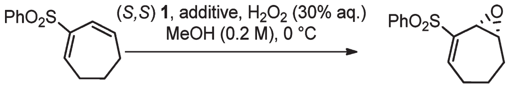
(2) (a) Jacobsen, E. N.; Deng, L.; Furukawa, Y.; Martínez, L. E. *Tetrahedron* **1994**, *50*, 4323–4334. (b) Chang, S.; Galvin, J. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1994**, *116*, 6937–6938.

(3) Brandes, D. B.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 4378.

(4) Hentemann, M.; Fuchs, P. L. *Org. Lett.* **1999**, *1*, 355.

10.1021/ol300996m

Table 1. Optimization of the Large-Scale Epoxidation of Dienyl Phenyl Sulfone **4**



4 **5**

entry	scale (g)/cat. load (mol %)	additive (equiv)	oxidant (equiv)	time (h)	conversion (yield (%), ee (%))
1	0.2/1	n-Bu_4NF (1)	6	17	traces
2	0.2/1	NH_4F (1)	6	17	25
3	0.2/1	DMAP (1) or $NH_2C(S)NH_2$ (1)	6	17	traces
4	0.2/1	Me_3NO (1)	6	2	50–60
5	0.2/1	Ph_3PO (1)	6	17	traces
6	0.2/1	HMPA (1)	6	2	50–60
7	0.2/1	Na_3PO_4 (1)	6	17	10
8	0.2/1	Na_3PO_4 (0.4)/NH_4BF_4 (1.2)	4	4.5	>97 (72,[a] 99[b])[c]
9	0.2/1	Na_2HPO_4 (0.4)/NH_4BF_4 (1.2)	4	17	NR
10	1/0.9	Na_3PO_4 (0.4)/NH_4BF_4 (1.2)	4	4.5	>95[c]
11	30/0.8	Na_3PO_4 (0.4)/NH_4BF_4 (1.2)	4	4.5	>95 (99)[c]
12	120/0.6	Na_3PO_4 (0.4)/NH_4BF_4 (1.2)	4	4.5	>95 (99)[c]
13	350/0.6	Na_3PO_4 (0.4)/NH_4BF_4 (1.2)	4	3[d]	>95 (66[e]; 99)[c]

[a] The product was purified by flash chromatography. [b] The ee of the reaction was determined via chrial HPLC using a chiralpack AD column. [c] The addition of H_2O_2 was performed dropwise and portionwise (1 equiv/30–40 min). [d] The reaction was run in MeOH (0.5 M), the concentration increase afforded faster reaction. [e] the product was isolated by crystallization from MeOH (1 M) according to Torres' procedure.

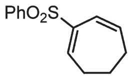
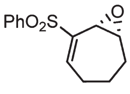
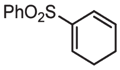
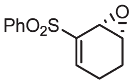
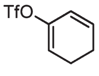
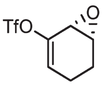
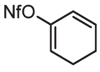
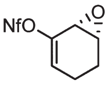
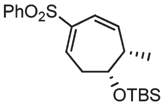
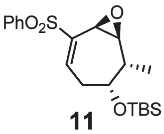
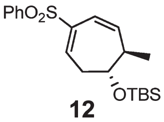
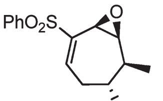
The reaction was usually carried out in methylene choride with 5–15% of (salen)Mn(III) catalyst, 10–40 mol % of 4-(3-phenylpropyl)pyridine *N*-oxide (P_3NO) as cocatalyst, and buffered bleach as oxidant. The estimated first generation cost of of preparation of 1 mol of epoxide **3** was > $6000 without factoring waste processing. Recently, Torres used Pietikainen's conditions[5] and reported an improved environmentally friendly large-scale preparation of epoxy dienyl sulfone **5**.[6] The reaction was run for 12–24 h in methanol with 1 mol % of catalyst, 1 equiv of ammonium acetate, and 6 equiv of hydrogen peroxide. Along with the substantially decreased cost associated with using 1% catalyst, the switch to MeOH made this new protocol more environmentally friendly. Using this method, epoxy vinylsulfone **5** was obtained in 72% yield and 99% ee. Further optimization of this transformation through screening of new additives led to a significant rate increase at further decreased catalyst load. Using TBAF or NH_4F as sources of fluoride for chloride–fluoride exchange met with little success. The size of the countercation was only slightly advantageous in the case of NH_4F. Switching to 4-(dimethylamino)pyridine (DMAP) or thiourea did not accelerate the reaction under similar conditions which employed Me_3NO (Table 1, entry 4). Phosphorus-centered species were screened next. However, $Ph_3P(O)$ had little effect presumably for steric reasons (Table 1, entry 5). Interestingly, HMPA dramatically increased the rate of the reaction (Table 1, entry 6) but did not meet environmental requirements. Significantly, the use of Na_3PO_4 accelerated the reaction when NH_4BF_4 was also included to increase the solubility of the additive. It is believed that the acceleration of the reaction was due to the basicity of the additive which formed HOO^- in situ and accelerated the formation of the Mn=O complex. Filtration of the salts also improved purification of the product on a large scale. Base-catalyzed epoxide opening being one of the major pathways of decomposition of the product, it was believed that using Na_2HPO_4 would afford higher yield. However, no reaction and complete decomposition of the catalyst were observed (Table 1, entry 9). Attempts at decreasing the amount of Na_3PO_4 beyond 40 mol % were unsuccessful, as lower reaction rate and decreased conversions resulted. Finally, at higher scales (Table 1, entries 10–12), the catalyst load was gradually decreased to 0.6 mol % without a detrimental effect on the ee and the reaction rate. However, portionwise (epoxidation on scale larger than 10 g) and dropwise (epoxidation on 100 g scale) additions were critical for the success of the reaction (Table 1, entries 8–12). Finally, for concerns of scalability (concentration scale larger than 100 g), addition of oxidant to 0.5 M was found to have no visible effect on the outcome of the reaction despite a noticeable increase in the exotherm of the reaction. Direct crystallization of the product from the methanolic reaction media according to Torres' protocol provided two crops of the desired epoxide in 60–70% overall yield and 99% ee. The scope of this new protocol was extended to various dienyl sulfones such as the analogous 6-membered dienyl sulfone **2**. Satisfactorily, this protocol was extended to this substrate, although partial aromatization of the product to diphenyl sulfone could not be avoided under these conditions. Extension to dienyl triflate and its more stable

---

(5) Pietikainen, P. *Tetrahedron* **1998**, *54*, 4319.

(6) Park, T.; Torres, E.; Fuchs, P. L. *Synthesis* **2004**, 1895.

Table 2. Extension of the Na_3PO_4/NH_4BF_4 Protocol to Various Dienyl Sulfones and Dienyl Triflates

Entry[a]	Substrate	Product	Catalyst load (mol%)	Additive (equiv)	Oxidant (equiv)	Time (h)	Yield (ee)
1	 **4**	 **5**	1 mol %	NH_4OAc (1)	H_2O_2 (6 equiv)	12-24	60-78% (99)
2			0.6 mol %	Na_3PO_4 (0.4)/NH_4BF_4 (1.2)	H_2O_2 (4 equiv)	3-4	66% (99)
3	 **2**	 **3**	1 mol %		NaOCl	0.5	72(99)[b]
4			2.5 mol %	Na_3PO_4 (0.4)/NH_4BF_4 (1.2	H_2O_2 (4 equiv)	2-3	70
5	 **6**	 **7**	20 mol %	P_3NO (0.4)	NaOCl	2	65(91)
6			2.5 mol %	Na_3PO_4 (0.4)/NH_4BF_4 (1.2)	H_2O_2 (4 equiv)	2-3	86(>91)
7	 **8**	 **9**					
8			2.5 mol %	Na_3PO_4 (0.4)/NH_4BF_4 (1.2)	H_2O_2 (4 equiv)	3-4	83
9	 **10**	 **11**	5-7 mol %	P_3NO (0.3)	NaOCl	12-17	60-70%
10			2 mol %	Na_3PO_4 (0.5)/NH_4BF_4 (1.5)	H_2O_2 (5 equiv)	1.5	63%
11	 **12**	 **13**	2 mol %	Na_3PO_4 (0.5)/NH_4BF_4 (1.5)	H_2O_2 (5 equiv)	1.5	75%
12			5 mol %	NH_4OAc	H_2O_2 (5 eq)	7 d	35%

[a] For entries 1–8, (*S*,*S*)-**1** was used, and for entries 9–12, (*R*,*R*)-**1** was used. [b] Low yield is due to aromatization and formation of diphenyl sulfone.

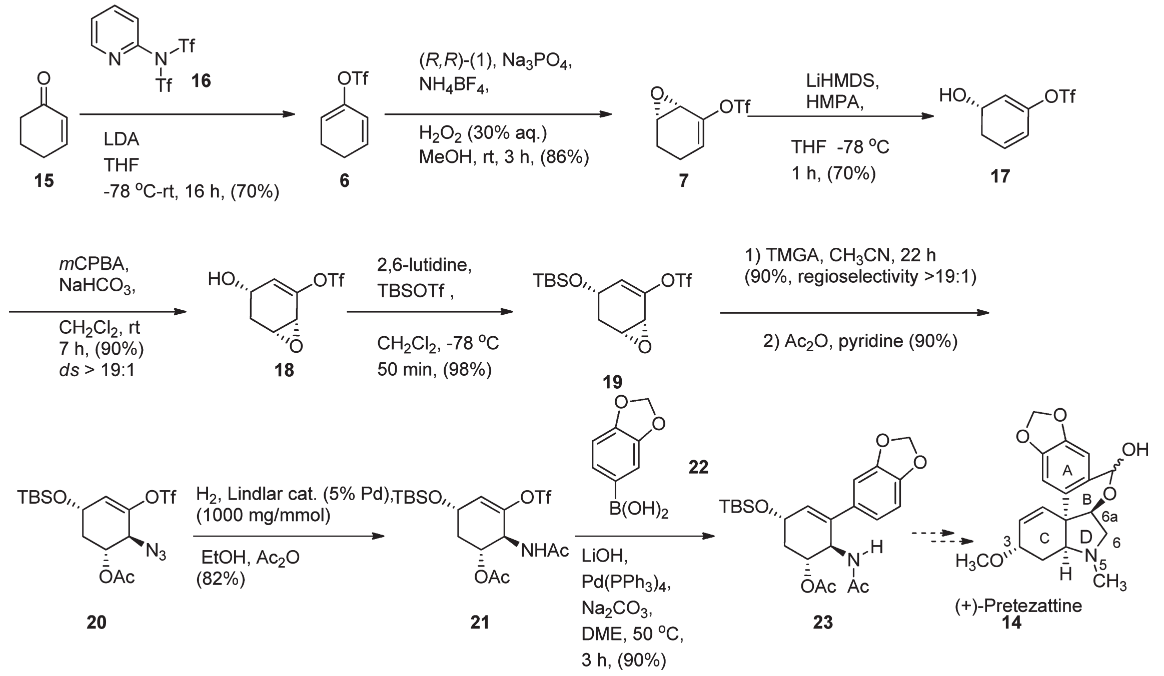
nonaflate analogue was also successful and gave a good yield and satisfactory ee. Finally, extension of this protocol to more sterically hindered substrates was also attempted. Although epoxidation leading to **11** under substrate-directed conditions provided satisfactory results, it was studied under Jacobsen conditions to test this new protocol. Fortunately, epoxidation of **10** on the side opposite to the neighboring –Me and –OTBS subsituents proved successful. In practice, the desired epoxide was obtained in 62–63% yield after 1.5 h at 0 °C with 1–2 mol % of catalyst. Increased reaction rate as well as lower catalyst load could be achieved under these new conditions. Contrary to epoxide **11**, epoxidation to epoxide **13** constitutes a more challenging transformation since epoxidation occurs on the same side of the ring as the neighboring –Me substituent. Switching to our new modified protocol increased the yield to 75% and shortened the time of reaction Although fast in the early stages of the reaction, epoxidation of dienyl sulfone **12** could not be driven to completion and 75% yield based upon recovered starting material resulted. This protocol was successfully used in the synthesis of an advanced intermediate leading to (+)-pretazettine. Amaryllidaceae alkaloids have stimulated the attention to the organic synthetic community due to their complex structure and wide range of biological activities.

Over 100 alkaloids of this family have been isolated including (+)-pretazettine (**14**).[7] There have been only two enantioselective total syntheses of (+)-pretazettine to date: one starts from chiral α-methyl-D-mannopyranoside,[7g] and the other suffers from harsh reaction conditions and moderate yield.[7h,i] It was envisioned that the new epoxidation might enable a concise approach to the core skeleton of (+)- pretazettine **14** (Scheme 2). Using the above protocol (Table 2, entry 6), epoxide **7** was obtained with good stereocontrol, high yield (86%), and low catalyst loading. On a 10 g scale, this reaction furnished epoxide **7** in 70% isolated yield. It is noteworthy that **7** is unstable in its pure form and aromatizes within 30 min. Having the epoxide in hand, the nitrogen stereocenter was installed after epoxide

---

[7] Previous syntheses: (a) Tsuda, Y.; et al. *Tetrahedron Lett.* **1972**, 3153. (b) Danishefsky, S.; Morris, J.; Mullen, G.; Gammil, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591. (c) Martin, S. F.; Davidson, S. K. *J. Am. Chem. Soc.* **1984**, *106*, 6431. (d) Martin, S. F.; Davidson, S. K.; Puckette, T. A. *J. Org. Chem.* **1987**, *52*, 1962. (e) Abelman, M. M.; Overman, L. E.; Tran, V. D. *J. Am. Chem. Soc.* **1990**, *112*, 6959. (f) White, J. D.; Chong, W. K.-M.; Thirring, K. *J. Org. Chem.* **1983**, *48*, 2300. (g) Baldwin, S. W.; Debenham, J. S. *Org. Lett.* **2000**, *2*, 99. (h) Nishimata, T.; Mori, M. *J. Org. Chem.* **1998**, *63*, 7586. (i) Nishimata, T.; Sato, Y.; Mori, M. *J. Org. Chem.* **2004**, *69*, 1837. (j) Rigby, J. H.; Cavezzo, A.; Hegg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664.

Scheme 2. Synthesis of (+)-Pretazettine Core



opening with LiHMDS, −OH-directed epoxidation of the resulting dienol, TBS protection, and stereo- and regiocontrolled opening of the epoxide using tetramethylguanidinium azide (TMGA), which afforded azide **20** in good yield (> 19:1 stereoselectivity at the N center). Reduction of the azide followed by protection of the amine afforded amine **21** in 82% yield. Finally, Suzuki coupling was smoothly run with boronic acid **22** and provided advanced intermediate **23** in excellent yield (90% as single diastereomer). It is noteworthy to mention that Suzuki coupling prior to azide reduction and nitrogen protection diminished the overal yield of the reaction by 20% and generated unidentifiable side products.

In conclusion, a new Jacobsen protocol has been designed and optimized for the large scale (up to 300−400 g) asymmetric preparation of epoxy vinyl sulfones, key starting materials, and intermediates for the synthesis of apoptolidin, aplyronine A, (+)-discodermolide, and (+)-pretazettine. A Na_3PO_4/NH_4BF_4 combination is used for the routine epoxidation of sterically less demanding substrates on a 1−350 g scale. The advantages of these protocols combine increased reaction rate, higher turn over number, and significantly increased reproducibility.

Acknowledgment. We thank Arlene Rothwell and Dr. Karl Wood from Purdue University for MS data and Purdue University for support of this research.

Supporting Information Available. Procedures, spectroscopic data, and spectra.This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.