Pergamon

SCIENCE @ DIRECT®

Tetrahedron Letters 44 (2003) 3115–3117

TETRAHEDRON
LETTERS

Asymmetric synthesis by vapor phase pyrolysis

Takashi Sugimura,* Takahiro Tei and Tadashi Okuyama

Graduate School of Science, Himeji Institute of Technology, 3-2-1 Kohto, Kamigori, Ako-gun, Hyogo 678-1297, Japan

Received 10 January 2003; revised 21 February 2003; accepted 21 February 2003

Abstract—The first vapor phase asymmetric synthesis was successfully carried out by FVP of a 2,4-pentanediol (PD)-tethered substrate carrying cyclohexene and diazo ester moieties at high temperature up to 400°C. The intramolecular [2+2] cycloaddition of the ketene was strictly stereocontrolled by the entropy term. © 2003 Elsevier Science Ltd. All rights reserved.

To achieve better selectivity of reaction, lower temperature is required, while the reaction slows down. This is generally the case for chemical reactions, and compatibility of high selectivity and high conversion is frequently a difficult task in asymmetric synthesis. An exceptional case is the reactions using a chiral 2,4-pentanediol (PD) tether that has always brought us sufficient stereoselectivity (>99%) irrespective of the reaction types and conditions.[1,2] Stereoselectivity of tethered [2+2] cycloadditions of ketene, generated by photolysis of diazo ester **1**, is independent of the reaction temperature from −78 to 130°C, and the stereocontrol is ascribed to mostly the entropy term in activation.[3–5] Using the benefit of this behavior of the PD-tethered reaction, an asymmetric synthesis by vapor phase pyrolysis, where an extremely high reaction temperature of at least 250°C is required to generate the ketene from **1**, was studied.

Flash vacuum pyrolysis (FVP) is a flow reaction activated by short contact of a substrate with a surface heated to high temperature.[6] The substrates **1a**–**d** were vaporized under vacuum (30 Pa/50–80°C), passed through a heated quartz tube (i.d. 1 cm×35 cm), and trapped at the outlet of the tube (ca. −50°C). At tube temperatures below 220°C, no reaction took place, while a mixture of **1** and cycloadduct **2** was obtained at higher temperatures. In the range of 260–300°C, **1** was almost completely decomposed to give **2** in high yield.[7] Above 300°C, isomeric product **3**[8] was additionally obtained, and it became the major product at 400°C. Since FVP of the isolated **2** produced **3**, **3** must be a secondary product. Table 1 shows diastereomeric excess ($\%\mathrm{de} = 100([R]-[S])/([R]+[S])$) of **2**, and the isolated yields in a larger scale (20–40 mg).[9] Previous results of the photolysis of **1** in solution are also included.

The FVP of **1a** and **1b** gives (1*R*)-**2**, but the amounts of their diastereomers (1*S*)-**2** are less than the detection limit (0.5%) of the analysis at all the temperatures. Thus, the reaction selectivity with **1a** is >99% in a temperature range of 250–400°C (250–350°C for **1b**).

Table 1. Diastereomeric excess and isolated yield of **2a**–**d**

Substrate	Diastereomeric excess[a] (%de)					Isolated yield[a] (%)	
	−78 to 130[b]	260	300	350	400	20[b]	270[c]
1a	>99	>99	>99	>99	>99	33	70
1b	>99	>99	>99	>99	>80[d]	14	57
1c	84–88	82	79	72	17	15	54
1d	10–11	13	13	12	3	8	57

[a] Results at temperatures given (°C).
[b] Obtained in solution by photolytic generation of the ketene.[3]
[c] The yields depend on the vaporization process and are not optimized.
[d] The detection limit of the diastereomer becomes larger due to decomposed products.

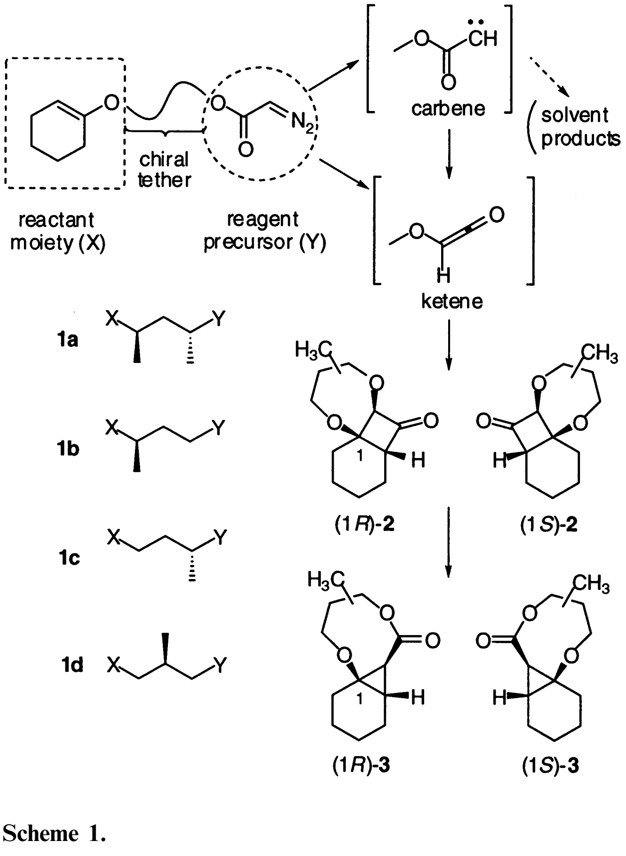
---

* Corresponding author. Tel.: +81-791-58-0168; fax: +81-791-58-0115; e-mail: sugimura@sci.himeji-tech.ac.jp

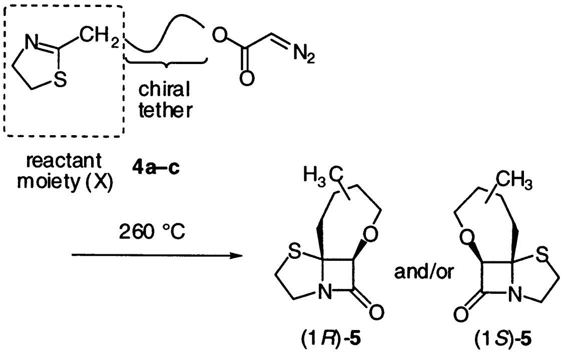
doi:10.1016/S0040-4039(03)00549-5

Together with the solution results,[3] PD tether (**a**) was found to strictly stereocontrol the cycloaddition of the ketene to the cyclohexene moiety in the temperature range of nearly 500 degrees. Pyrolysis of **1c** and **1d** gave pairs of diastereomers of **2**. The de values of **2c** and **2d** obtained at 260°C are similar to those obtained by the solution photolysis below 130°C. The values gradually decreased at higher temperatures, and drastically decreased at 400°C. The de change of **2** is attributable to the results of a secondary reaction of **2** because FVP of the isolated **2** resulted in a decrease in its de to a different extent depending on the temperature. For example, FVP of **2c** (65% de) resulted in 7% loss in the de of recovered **2c** even at 300°C. It should be noted that the FVP (270°C) gives higher yields of **2a**–**d** than the photolysis in solution. This must be due to the minimization of side reactions. In solution, not only the carbene but also a part of the ketene react with the solvent or other internal species, while the carbene in vapor phase gives the ketene through the Wolff rearrangement[10] and all the ketene produced is destined only for internal reaction with the alkene (Scheme 1).

The chiral-tethered vapor phase asymmetric synthesis was applied to the synthesis of an optically active β-lactam by replacing the alkene moiety in **1** by an imine (Scheme 2).[11] When **4a**–**c** were pyrolyzed in vacuo at 260°C, lactam **5** was obtained as the sole product (15–40% yields). The de of **5a**–**c** were 86, 80 and 60% of the 1*R*-isomers, respectively.



Scheme 1.



Scheme 2.

In this report, an outstanding potential of the PD-tethered reaction in its stereocontrollability owing to entropy control is revealed by carrying out the reaction in the vapor phase at unusually high temperatures. Similar stereoselectivities observed in the vapor phase and in solution indicate that the entropy term caused as difference at the transition states is not due to solvation, which frequently plays a major role in entropy change during the reaction. It is also shown that the vapor-phase reaction has a benefit when the reaction intermediates are very reactive towards solvent or internal species. Thermal vapor-phase flow reaction is not common in synthesis of fine chemicals, but now it is available for asymmetric synthesis.

Acknowledgements

This work was supported by KAKENHI (13440192) from JSPS.

References

1. Sugimura, T. In *Recent Research Developments in Organic Chemistry*; Pandalai, S. G., Ed.; Transworld Research Network: Trivandrum, 1998; pp. 47–53.
2. For recent examples, see: (a) Sugimura, T.; Nagano, S.; Tai, A. *Chem. Lett.* **1998**, 45–46; (b) Yamaguchi, K.; Sugimura, T.; Nishida, F.; Tai, A. *Tetrahedron Lett.* **1998**, *39*, 4521–4524; (c) Fujita, M.; Matsushima, H.; Sugimura, T.; Tai, A.; Okuyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 2946–2956.
3. Sugimura, T.; Tei, T.; Mori, A.; Okuyama, T.; Tai, A. *J. Am. Chem. Soc.* **2000**, *122*, 2128–2129.
4. Importance of the entropy term in asymmetric synthesis has also been pointed out for other reactions. See: (a) Buschmann, H.; Scharf, H. D.; Hoffmann, N.; Esser, P. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 477–515; (b) Otera, J.; Sakamoto, K.; Tsukamoto, T.; Orita, A. *Tetrahedron Lett.* **1998**, *39*, 3201–3204; (c) Inoue, Y.; Ikeda, H.; Kaneda, M.; Sumimura, T.; Everitt, S. R. L.; Wada, T. *J. Am. Chem. Soc.* **2000**, *122*, 406–40; Inoue, Y.; Sugahara, N.; Wada, T. *Pure Appl. Chem.* **2001**, *73*, 475–40; (d) Nishida, T.; Miyafuji, A.; Ito, Y. N.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 7053–7058; (e) Sugimura, T.; Hagiya, K.; Sato, Y.; Tei, T.; Tai, A.; Okuyama, T. *Org. Lett.* **2001**, *3*, 37–40; Tei, T.; Sato, Y.; Hagiya, K.;

Tai, A.; Okuyama, T.; Sugimura, T. *J. Org. Chem.* **2002**, *67*, 6593–6598.

5. For general references, see: (a) Eliel, E. L. *Stereoselectivity of Carbon Compounds*; MacGraw-Hill: New York, 1962; pp. 151–152, 237–239; (b) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*; Wiley: New York, 1995; pp. 1–6; (c) Nogradi, M. *Stereoselective Synthesis*; VCH: Weinheim, 1995; pp. 41–43; (d) Gawley, R. E. *Principles of Asymmetric Synthesis*; Pergamon: Oxford, 1996; pp. 7–10.
6. (a) Brown, R. F. C. *Pyrolytic Methods in Organic Chemistry*; Academic Press: New York, 1980; pp. 21–43; (b) Wiersum, U. E. *Aldrichimica Acta* **1984**, *17*, 31–40.
7. (a) Sinder, B. B. *Chem. Rev.* **1988**, *88*, 793–811; (b) Hyatt, J. A.; Raynolds, P. W. *Org. React.*; Wiley: New York, 1994; Vol. 45, pp. 159–646; (c) Tidwell, T. T. *Ketenes*; Wiley: New York, 1995; pp. 459–529.
8. Mori, A.; Sugimura, T.; Tai, A. *Tetrahedron: Asymmetry* **1997**, *8*, 661–664.
9. The cycloaddition was confirmed to occur in the vapor phase. When methanol was placed at the cold trap prior to the pyrolysis of **1**, only **2** (and **3**) was obtained, but no methanol adduct was obtained. The reaction of the ketene intermediate with methanol was proved to be faster than the intramolecular cycloaddition by the photolysis of **1** in a solvent containing methanol.
10. (a) Meier, H.; Zeller, K.-P. *Angew. Chem.* **1975**, *87*, 52–63; (b) Gill, G. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, pp. 887–912. For recent studies, see: (c) Toscano, J. P.; Platz, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 4712–4713; (d) Chiang, Y.; Kresge, A. J.; Popik, V. V. *J. Am. Chem. Soc.* **1999**, *121*, 5930–5032; (e) Wang, Y.; Toscano, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4512–4513.
11. Ojima, I. In *Advances in Asymmetric Synthesis*; Hassner, A., Ed.; JAI: Greenwich, 1995; pp. 95–146.