A Novel Organocatalytic Asymmetric Transfer Hydrogenation of α,β-Unsaturated Aldehydes

by **Bao-Hua Zhang**, **Lan-Xiang Shi***, and **Rui-Xia Guo**

College of Chemical Engineering, Shijiazhuang University, Shijiazhuang 050035, P. R. China (phone: +86-311-66617320; e-mail: kedashilanxiang@126.com)

α,β-Unsaturated aldehydes reacted with diimide (diazene) in the presence of optically active ammonium salt **1** as a catalyst to give the corresponding saturated aldehydes in excellent yields and up to 98:2 er. Attractive features of the asymmetric transfer hydrogenation are its high yields, and chemo-, and enantioselectivities.

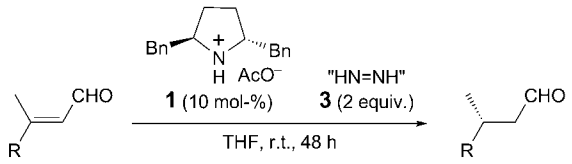
Introduction. – Asymmetric catalytic hydrogenations are used in large-scale industrial production of pharmaceuticals and fine chemicals. Metal-catalyzed hydrogenations are the most frequently used catalytic asymmetric processes. But their disadvantage is the need of complete removal of metal impurities from the reaction product in order to meet the quality requirements of pharmaceutical intermediates [1]. Organocatalysis is free of metals and, therefore, of increased interest [2]. Here, we report on a chiral ammonium salt, **1**, which effectively catalyze the asymmetric transfer hydrogenation of α,β-unsaturated aldehydes **2** with diimide (diazene; **3**).

Results and Discussion. – We found that treating aromatic, trisubstituted α,β-unsaturated aldehyde **2** with diimide (**3**; produced *in situ* from potassium diazene-1,2-dicarboxylate ($KO_2CN{=}NCO_2K$) and glacial AcOH) and a catalytic amount of chiral ammonium salt **1** in THF at room temperature, the corresponding saturated aldehydes **4** were obtained in high yields and excellent enantioselectivities (*Table*).

We also investigated the influence of the configuration at the C=C bond. Remarkably, when we subjected both the isolated pure (*E*)- and (*Z*)-isomers of 3-NO_2 derivative **2c** to our reaction conditions, the same (*R*)-enantiomer of product **4c** was obtained with the same enantiomeric ratio (er) of 98:2. Similarly, (*E*)-**2c**/(*Z*)-**2c** mixtures always gave the same result, and, independent of their exact ratio, all furnished (*R*)-**4c** with er of 98:2. Thus, our process is enantioconvergent, a highly desirable yet rare feature of a catalytic asymmetric reaction, where a mixture of stereoisomers furnishes only one product enantiomer. Carbonyl reduction or aldolization products were not detected.

Mechanistically, we assume that the reaction takes place by formation of iminium ion **5**, which presumably isomerizes quickly *via* dienamine **6** (*Scheme*). The following rate-determining hydride transfer from diimide **3** to enal (*E*)-**5** *via* transition state **A** proceeds faster than to (*Z*)-**5** ($k_E > k_Z$) and, as a result, saturated aldehyde (*R*)-**4** is formed predominantly.

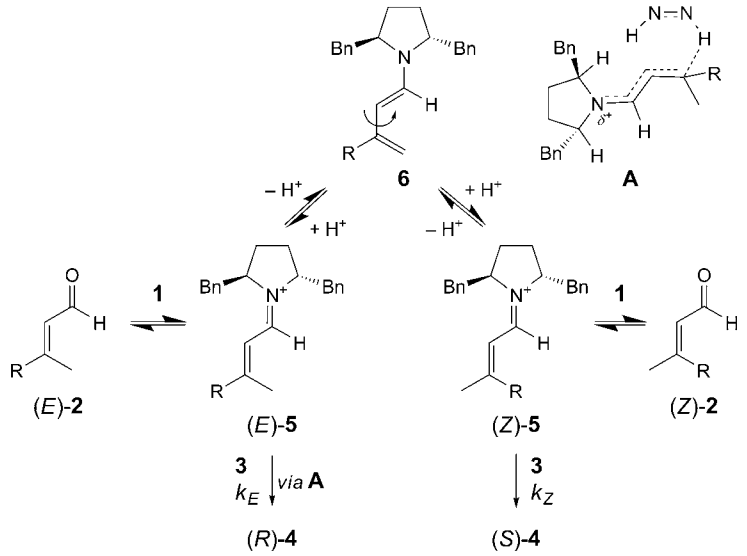
Table. *Organocatalytic Asymmetric Transfer Hydrogenation of α,β-Unsaturated Aldehydes*



2a – 2f **4a – 4f**

Entry	R	Product	Yield [%]	er
1	Ph	**4a**	79	96 : 4
2	4-Cl–C_6H_4	**4b**	91	97 : 3
3	3-O_2N–C_6H_4	**4c**	85 (from (*E*)-**2c**)	98 : 2
			80 (from (*Z*)-**2c**)	98 : 2
			82 (from (*E*)-**2c**/(*Z*)-**2c** 1 : 1)	98 : 2
4	4-NC–C_6H_4	**4d**	89	97 : 3
5	4-F_3C–C_6H_4	**4e**	83	98 : 2
6	Naphthalen-2-yl	**4f**	85	96 : 4

Scheme. *Proposed Mechanism of the Organocatalytic Asymmetric Transfer Hydrogenation*



Conclusions. – The reaction of α,β-unsaturated aldehydes and diimide (=diazene) in the presence of catalytic amounts of (2*R*,5*R*)-**1** is a highly efficient asymmetric transfer hydrogenation. Attractive features of the process are high yields, chemo- and enantioselectivities, and simplicity. Applications in the synthesis of natural products, pharmaceuticals, and fine chemicals can be envisaged.

Experimental Part

General. The starting materials, aldehydes **2a**–**2f**, and potassium diazene-1,2-dicarboxylate ($KO_2CN{=}NCO_2K$) were synthesized as described in [3] and [4], resp. (2*R*,5*R*)-2,5-Dibenzylpyrrolidine was synthesized as described in [5]. Gas chromatography (GC): *Agilent 7890A* gas chromatograph. Optical rotations: *WZZ-2B* digital polarimeter. ^{1}H- and ^{13}C-NMR spectra: *Bruker Avance 400* spectrometer. Elemental analyses: *Vario EL III* instrument.

General Procedure for the Preparation of Chiral Ammonium Salt **1**. To a soln. of (2*R*,5*R*)-dibenzylpyrrolidine (251 mg, 1.0 mmol) in Et_2O (5 ml) was added glacial AcOH (132 mg, 2.2 mmol) with stirring. The salt **1** precipitated immediately. It was filtered and washed with Et_2O.

Data of **1**. ^{1}H-NMR (300 MHz, $CDCl_3$): 1.50–2.10 (*m*, CH_2CH_2), 2.99 (*dd*, *J* = 7, 13, PhCH_2), 3.54 (*dd*, *J* = 7, 13, PhCH_2), 3.80–4.10 (*m*, 2 CH), 7.20 (*s*, 10 arom. H). MS: 252 ($[M+H]^+$), 251 (M^+), 160 ($[M-CH_2Ph]^+$). Anal. calc for $C_{18}H_{21}N \cdot AcOH$: C 77.20, H 8.11, N 4.52; found: C 77.12, H 8.03, N 4.50.

General Procedure for the Asymmetric Transfer Hydrogenation. To a stirred solution of a α,β-unsaturated aldehyde **2** (0.5 mmol) in THF (10 ml) at r.t. were added catalyst **1** (15.5 mg, 0.05 mmol, 10 mol-%), potassium diazene-1,2-dicarboxylate (114 mg, 0.6 mmol) and pyridine (94.8 mg, 1.2 mmol), and, after 5 min, AcOH (72 mg, 1.2 mmol) was slowly added dropwise. After 48 h, the mixture was poured into dist. H_2O (20 ml) and extracted with CH_2Cl_2 (2 × 15 ml). The combined org. layers were dried ($MgSO_4$), filtered, and concentrated. The product was isolated by flash chromatography (SiO_2; AcOEt/hexane) to give the saturated aldehyde **4**. The absolute configuration of (*R*)-**4** was determined by measurement of their optical rotation and comparison with the literature value [3][6]. Enantiomeric ratio (er) was determined by chiral-stationary-phase GC analysis.

This study was supported by the *China's Hebei Province Science and Technology Support Project* (No.13964002D) and the *Shijiazhuang University Project* (No. XJPT007).

REFERENCES

[1] C. E. Garrett, K. Prasad, *Adv. Synth. Catal.* **2004**, *346*, 889.
[2] P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840; P. I. Dalko, L. Moisan, *Angew. Chem., Int. Ed.* **2001**, *40*, 3726.
[3] R. Martín, I. Islas, A. Moyano, M. A. Pericàs, A. Riera, *Tetrahedron* **2001**, *57*, 6367; M. I. Al-Hassan, *Gazz. Chim. Ital.* **1985**, *115*, 441; M. Akhtar, L. Jallo, A. Johnson, *J. Chem. Soc., Chem. Commun.* **1982**, 44; A. I. Meyers, A. Nabeya, H. W. Adickes, J. M. Fitzpatrick, G. R. Malone, I. R. Politzer, *J. Am. Chem. Soc.* **1969**, *91*, 764.
[4] D. J. Pasto, R. T. Taylor, Organic Reactions, L. A. Paquethe, John Wiley & Sons, New York, 1991, Vol. 40, p. 91.
[5] M. Nakajima, K. Tomioka, K. Koga, *Tetrahedron* **1993**, *49*, 9735.
[6] T. Lee, J. B. Jones, *J. Am. Chem. Soc.* **1997**, *119*, 10260.

Received January 15, 2013