

Enantioselective Strecker Reaction Catalyzed by an Organocatalyst Lacking a Hydrogen-Bond-Donor Function**

Mihaela Negru, Dieter Schollmeyer, and Horst Kunz*

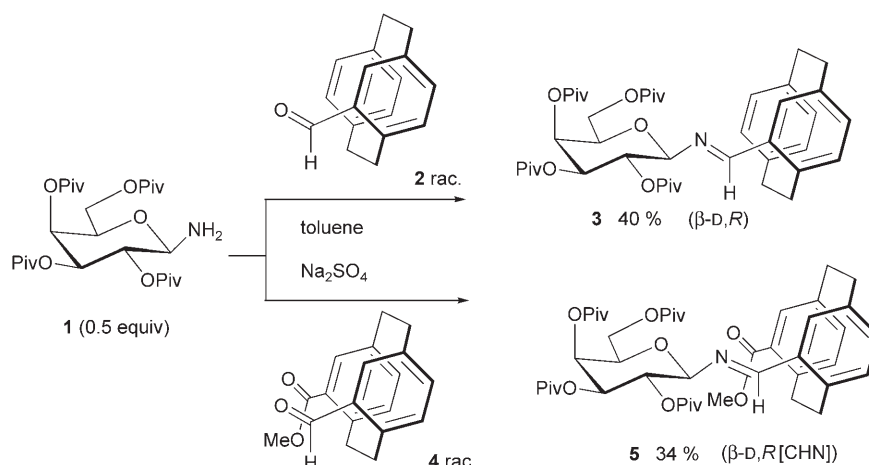
Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

The Strecker reaction^[1] is of great interest for the synthesis of natural products and drugs. The products, α -amino nitriles, can readily be converted to α -amino acids, 1,2-diamines, and 2-amino alcohols, all of which are valuable building blocks for the synthesis of biologically active compounds. Therefore, stereoselective Strecker reactions^[2,3] resulting in amino nitriles with high enantiopurity receive particular attention. With this aim, chiral catalysts have been developed in the form of transition-metal complexes^[4] or organocatalysts which, as a rule, are efficient hydrogen-bond donors^[5] or Brønsted acids.^[6] Axially chiral aryl-di-*N*-oxides have also been applied, albeit in equimolar amounts.^[7]

We here describe a new type of organocatalyst for the enantioselective Strecker reaction which consist of glycosyl amines^[8] and planar-chiral [2.2]paracyclophane derivatives. Compounds with [2.2]paracyclophane structure^[9] have already been applied in enantioselective synthesis, for example, titanium complexes of salen-type derivatives of [2.2]paracyclophane^[10] in the enantioselective formation of cyanohydrins of aromatic aldehydes^[11] and in the enantioselective addition of diethylzinc to aromatic aldehydes.^[12]

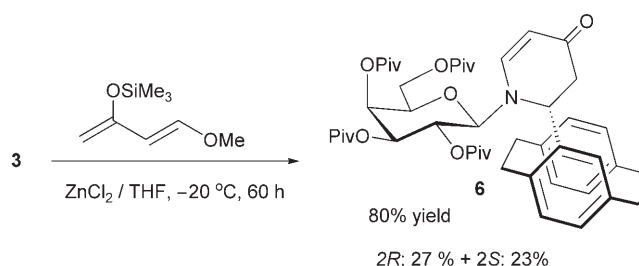
The attempt to kinetically separate racemic [2.2]paracyclophane-4-carbaldehyde (**2**)^[13] by imine formation with 2,3,4,6-tetra-*O*-pivaloyl- β -D-galactopyranosyl amine (**1**)^[8a,b] was not successful. However, the diastereomeric imines could be separated, and the imine **3** was isolated in pure form as the β -D,*R* stereoisomer (Scheme 1). In analogy, racemic methyl 15-formyl-[2.2]paracyclophane-4-carboxylate (**4**)^[13] gave pure aldimine **5** after separation by HPLC.

A key feature of the aldimines **3** and **5** is that the C=N bond is sterically shielded on the *Re* face as well as on the *Si* face (back side). Consequently, every nucleophilic attack at the imine proceeds slowly. The domino Mannich–Michael



Scheme 1. Synthesis of *N*-galactosyl[2.2]paracyclophane carbaldimines.

reaction with the Danishefsky diene, which proceeded smoothly with more simple *N*-galactosyl aldimines,^[14] was quite sluggish with **3**. The diastereoselectivity was low (55:45) and with a slight preference for the *R* diastereomer of **6** (Scheme 2).



Scheme 2. Domino Mannich–Michael reaction of imine **3** with the Danishefsky diene.

The surprising and even slightly preferred attack of the nucleophile at the *Re* face indicates that the nitrogen of the imine is more shielded on the *Re* face, the imine carbon, however, more on the *Si* face. As a consequence, the nucleophile enters the π^* orbital with a slight preference from the front side.

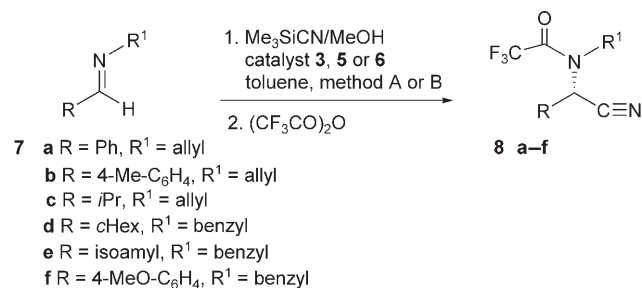
Unexpectedly, the *N*-galactosyl[2.2]paracyclophane carbaldimines proved to be efficient enantioselective catalysts of the Strecker reaction between *N*-alkyl aldimines **7** and

[*] Dr. M. Negru, Dr. D. Schollmeyer, Prof. Dr. H. Kunz
Institut für Organische Chemie
Universität Mainz
Duisbergweg 10–14, 55128 Mainz (Germany)
Fax: (+49) 6131-392-4786
E-mail: hokunz@mail.uni-mainz.de

[**] This work was supported by the Fonds der Chemischen Industrie.

trimethylsilyl cyanide in methanol/toluene at temperatures between -50°C and -20°C (Scheme 3, Table 1).

N-Galactosyl aldimine **5** bearing a methoxycarbonyl group in the neighboring cyclophane phenyl ring proved to



Scheme 3. Enantioselectively catalyzed Strecker reaction with catalysts **3**, **5**, and **6**.

Table 1: Enantioselective Strecker reaction according to Scheme 3.

Entry (Method) ^[a]	Imine 7	Cat. (mol %)	Reaction ^[15] t [h] T [°C]	Yield 8 [%]	<i>ee</i> ^[b] [%]
1 (A)	7a	5 (2)	20 $-50 \rightarrow -20$	8a 55	71
2 (A)	7a	6 (10)	19 $-50 \rightarrow -20$	8a 15	34
3 (A)	7b	3 (10)	20 $-50 \rightarrow -20$	8b 68	67
4 (A)	7c	5 (5)	30 $-50 \rightarrow -20$	8c 20 ^[c]	96
5 (A)	7d	5 (5)	30 $-50 \rightarrow -20$	8d 88	65
6 (B)	7c	5 (10)	24 -50	8c 89	96
7 (B)	7d	5 (10)	24 -50	8d 87	88
8 (B)	7e	5 (10)	24 -50	8e 84	99
9 (B)	7f	5 (10)	24 -50	8f 87	82

[a] Method A: A solution of imine in toluene was cooled to -78°C and Me₃SiCN/MeOH at (2 equiv) -50°C was added. Method B: Catalyst and Me₃SiCN/MeOH (1.2 equiv) were dissolved in toluene, and imine **7** was added at -50°C . [b] HPLC on chiral column Chiralpak AS. [c] Incomplete reaction with (CF₃CO)₂O.

be the more efficient enantioselective organocatalyst (entries 6–9, Table 1). In particular, the best results were obtained when the catalyst **5** and HCN (from Me₃SiCN and methanol) were dissolved in toluene, and the imine **7**^[15] was added at -50°C (method B). In contrast, when the catalyst and imine **7** were dissolved in toluene and cooled to -78°C , Me₃SiCN/methanol (2 equiv) added at -50°C , and the reacting mixture allowed to warm to -20°C (method A), yield and enantioselectivity were lower. Catalyst **3** (entry 3, Table 1) is slightly less efficient than **5**.^[16] Piperidone **6** is an only weakly stereodifferentiating catalyst. In reactions catalyzed by **5**, imines of aliphatic aldehydes react with high enantioselectivity to give the (*S*)-amino nitriles (**8c**, **8e**), in particular, if procedure B is applied. In contrast to other reported enantioselectively catalyzed Strecker reactions, the reactions with aromatic aldimines (**8f**) proceed with slightly lower enantioselectivity.

The catalytic effect of the *N*-galactosyl-[2.2]paracyclophane carbaldimines **3** and **5** is surprising because they neither contain a Lewis acidic metal ion^[4] nor display hydrogen-bond-donor^[5] or Brønsted acid proper-

ties.^[6] Their peculiar features are the asymmetric (quasi-*C*₂-symmetric) shielding of the double bond and a Lewis basic center cooperatively formed by the imine nitrogen and the carbonyl oxygen of the 2-pivaloyl group (Figure 1a). The

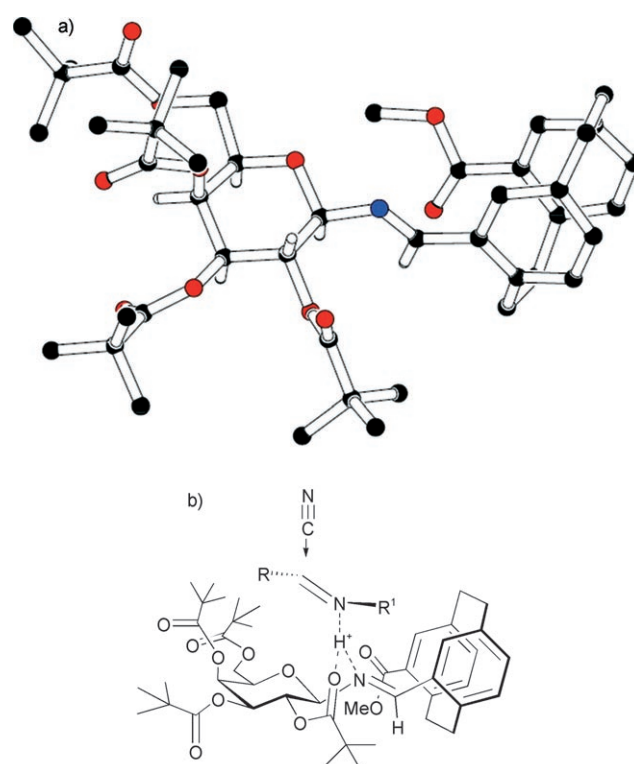


Figure 1. a) X-ray crystal structure of **5** (O red, N blue, C black, H white). b) Proposal for the enantioselectively effective reaction site of catalyst **5**.

conformation shown (Figure 1) is favored for glycosyl imines owing to the *exo*-anomeric effect. In the case of **5** the basic center could be supported by the carbonyl oxygen of the pseudo-geminal ester group (Figure 1b). This basic center could trap the proton from the weak acid HCN. The formation of this protonated catalyst **5** should be favored when method B is applied. The imine should then be dragged electrophilically into the reaction site in such a way that the large groups R and R¹ are positioned pointing toward the back and left and toward the front and right, respectively (as shown in Figure 1b or horizontally flipped in the plane of the σ framework). This interpretation of the enantioselective catalysis of the Strecker reaction by **5** via an S-shaped reaction site explains the selective formation of the (*S*)-amino nitriles. To some extent it resembles the hypothesis of Corey^[6a] who postulated a U-shaped binding pocket for the Brønsted acid catalyst he developed from a chinchona alkaloid structure. It is a particular feature of the planar-chiral *N*-galactosyl-[2.2]paracyclophane carbaldimines **3** and **5** as enantioselective catalysts that they contain neither an electrophilic metal ion nor a hydrogen-bond-donor structure nor a Brønsted acid group. They effect an efficient enantioselective formation of

the corresponding α -amino nitriles also in reactions of aliphatic aldimines.

Received: July 16, 2007

Revised: August 23, 2007

Published online: October 29, 2007

Keywords: glycosyl imines · organocatalysis · paracyclophanes · planar chirality · Strecker reaction

- [1] A. Strecker, *Am. Chem. Pharm.* **1850**, 75, 27.
- [2] Reviews on diastereoselective Strecker reactions: a) R. M. Williams, J. A. Hendrix, *Chem. Rev.* **1992**, 92, 889; b) R. O. Duthaler, *Tetrahedron* **1994**, 50, 1539; c) for a recent example, see: J.-C. Rossi, M. Marull, L. Boiteau, J. Taillades, *Eur. J. Org. Chem.* **2007**, 662.
- [3] Reviews on enantioselective Strecker reactions a) L. Yet, *Angew. Chem.* **2001**, 113, 900; *Angew. Chem. Int. Ed.* **2001**, 40, 875; b) H. Gröger, *Chem. Rev.* **2003**, 103, 2795; c) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, 32, 289; d) C. Spino, *Angew. Chem.* **2004**, 116, 1796; *Angew. Chem. Int. Ed.* **2004**, 43, 1764; e) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, 118, 1550; *Angew. Chem. Int. Ed.* **2006**, 45, 1520.
- [4] a) H. Ishitani, S. Koniya, S. Kobayashi, *Angew. Chem.* **1998**, 110, 3369; *Angew. Chem. Int. Ed.* **1998**, 37, 3186; b) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, 120, 5315; c) N. S. Josephsohn, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, 123, 11594; d) M. Chavarot, J. J. Byrne, P. Y. Chavaut, Y. Vallee, *Tetrahedron: Asymmetry* **2001**, 12, 1147; b) Therrieu, M. Kawano, K. Yamaguchi, H. Danjo, Y. Sei, A. Sato, S. Furusho, M. Shibasaki, *J. Am. Chem. Soc.* **2006**, 128, 6768, and references therein.
- [5] a) M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, 120, 4901; b) E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**, 1, 157; c) A. G. Wenzel, M. P. Lalonde, E. N. Jacobsen, *Synlett* **2003**, 1919; d) Z. Jiao, X. Feng, B. Liu, F. Chen, G. Zhang, Y. Jiang, *Eur. J. Org. Chem.* **2003**, 3818; e) A. Berkessel, S. Mukherjee, J. Lex, *Synlett* **2006**, 41; f) T. Ooi, Y. Uematsu, J. Fujimoto, K. Fujimoto, K. Maruoka, *Tetrahedron Lett.* **2007**, 48, 1337; g) C. Becker, C. Hoben, H. Kunz, *Adv. Synth. Catal.* **2007**, 349, 417; h) S. C. Pan, J. Zhou, B. List, *Angew. Chem.* **2007**, 119, 618; *Angew. Chem. Int. Ed.* **2007**, 46, 612.
- [6] a) J. Huang, E. J. Corey, *Org. Lett.* **2004**, 6, 5027; M. Rueping, E. Sugiono, C. Azap, *Angew. Chem.* **2006**, 118, 2679; *Angew. Chem. Int. Ed.* **2006**, 45, 2617; M. Rueping, E. Sugiono, S. A. Moreth, *Adv. Synth. Catal.* **2007**, 349, 759.
- [7] B. Liu, X. Feng, F. Chen, G. Zhan, X. Cui, Y. Jiang, *Synlett* **2001**, 1551.
- [8] a) H. Kunz, W. Sager, *Angew. Chem.* **1987**, 99, 595; *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 557; b) H. Kunz, W. Sager, D. Schanzenbach, M. Decker, *Liebigs Ann. Chem.* **1991**, 649; c) H. Kunz, W. Pfrengle, *Tetrahedron* **1988**, 44, 5487; d) Übersicht: S. Knauer, B. Kranke, L. Krause, H. Kunz, *Curr. Org. Chem.* **2004**, 8, 1739.
- [9] T. I. Danilova, V. I. Rozenberg, E. V. Vorontsov, Z. A. Starikova, H. Hopf, *Tetrahedron: Asymmetry* **2003**, 14, 1375.
- [10] a) S. El-Tamany, F. W. Raulfs, H. Hopf, *Angew. Chem.* **1983**, 95, 631; *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 633; b) S. El-Tamany, Dissertation, Univ. Braunschweig, **1983**.
- [11] Y. Belokon, M. Moskalenko, N. Ikonikov, L. Yashikina, D. Antonov, E. Vorontsov, V. Rozenberg, *Tetrahedron: Asymmetry* **1997**, 8, 3245.
- [12] T. Danilova, V. Rozenberg, Z. A. Starikova, S. Bräse, *Tetrahedron: Asymmetry* **2004**, 15, 223.
- [13] H. Hopf, H. Zitt, *Eur. J. Org. Chem.* **2002**, 2298.
- [14] a) H. Kunz, W. Pfrengle, *Angew. Chem.* **1989**, 101, 1041; *Angew. Chem. Int. Ed. Engl.* **1989**, 28, 1067; b) M. Weymann, W. Pfrengle, D. Schollmeyer, H. Kunz, *Synthesis* **1997**, 1151.
- [15] The ^1H NMR signals of the aldimine groups are found at $\delta = 7.82\text{--}7.45$ ppm for the aliphatic aldimines **7c–e**, and at $\delta = 8.32\text{--}8.22$ ppm for the aromatic aldimines **7a,b,f**.
- [16] Like **3**, a compound analogous to **5** but having a bromo substituent instead of the ester group in the second cyclophane phenyl ring also leads to lower enantioselectivity.
- [17] M.p. 125–127°C, $[\alpha]_D^{25} = -139.2$ ($c = 1$, CH_2CN); FD-MS (positive): m/z 794 $[\text{M}+\text{H}^+]$. Elemental analysis ($\text{C}_{45}\text{H}_{61}\text{O}_{11}\text{N}$, 791.97): found (calcd): C 66.53 (66.58), H 7.68 (7.69), N 1.67 (1.76). ^1H NMR (400 MHz, CDCl_3 , COSY): $\delta = 8.38$ (s, 1H, $-\text{N}=\text{CH}-$), 7.14 (d, $^4J_{5\text{-H},7\text{-H,or } 16\text{-H},12\text{-H}} = 1.86$ Hz, 1H, Phan-5 or Phan-16), 6.71 (dd, $^4J_{7\text{-H},5\text{-H}} = 1.83$ Hz, $^3J_{7\text{-H},8\text{-H}} = 5.88$ Hz, 1H, Phan-7), 6.60 (d, $^3J_{12\text{-H},13\text{-H}} = 7.71$ Hz, 1H, Phan-12), 6.54 (dd, $^3J_{8\text{-H},7\text{-H}} = 6.24$ Hz, $^4J_{12\text{-H},16\text{-H}} = 1.83$ Hz, 2H, Phan-8, Phan-16), 6.47 (d, $^3J_{13\text{-H},12\text{-H}} = 7.71$ Hz, 1H, Phan-13), 5.51 (d, $^3J = 1.47$ Hz, 1H, Gal-4), 5.21 (m, 2H, Gal-2, Gal-3), 4.75 (dd, $^4J = 1.83$ Hz, $^3J_{1/2} = 7.35$ Hz, 1H, Gal-1), 4.26–4.13 (m, 3H, Gal-5, Gal-6a,b), 3.76 (s, 3H, OCH_3), 3.72–3.69 (m, 1H, Phan-2s), 3.11–2.91 (m, 7H, Phan-2a, Phan-1a,s, Phan-9a,s, Phan-10a,s), 1.25, 1.18, 1.07, 0.89 ppm (4 s, 36H, PivCH_3). ^{13}C NMR (100.6 MHz CDCl_3 , HMQC): $\delta = 177.9$, 177.7, 177.3, 175.9 ($\text{PivC}=\text{O}$), 166.7 (Phan-17), 160.5 ($-\text{C}=\text{N}-$), 142.4 (qC^{Ar}), 141.7 (qC^{Ar}), 139.9 (qC^{Ar}), 136.3 (qC^{Ar}), 138.1, 136.0 (Phan-7, Phan-12), 134.9, 134.7, 134.4, 133.7 (Phan-8, Phan-13, Phan-5, Phan-16), 130.4 (qC^{Ar}), 129.5 (qC^{Ar}), 85.4 (Gal-1), 72.6, 71.2, 69.8, 67.1 (Gal-2, Gal-3, Gal-4, Gal-5), 61.2 (Gal-6), 51.5 (Phan-18), 39.0, 38.7, 38.6, 38.5 (PivCMe_3), 35.0, 34.9 (Phan-2, Phan-10), 34.4, 30.8 (Phan-9, Phan-1), 27.14, 27.11, 27.02 ppm (PivCH_3). Crystal structure analysis: $M_r = 791.95$ g mol^{-1} ; absorption: $\mu = 0.64$ mm^{-1} ; Crystal size: $0.128 \times 0.192 \times 0.8$ mm^3 , colorless needles; space group: $P2_1$ (monoclinic); lattice constants: $a = 15.472(2)$, $b = 10.061(1)$, $c = 30.791(4)$ Å, $\beta = 95.649(6)^\circ$, $V = 4770(1)$ Å 3 , $Z = 4$; temperature: -80°C ; density: $d = 1.103$ g cm^{-3} ; irradiation: $\text{CuK}\alpha$ graphite monochromator, $\lambda = 1.54178$ Å; $2\theta_{\text{max}} = 140^\circ$; number of reflections: measured 19513, independent 9894 ($R_{\text{int}} = 0.0902$); discrepancy factor: $wR2 = 0.1262$ ($R1 = 0.0480$ for observed reflections, 0.0606 for all reflections); diff. Fourier synthesis: 0.21, -0.23 e Å $^{-3}$; CCDC 619295 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [18] **8a**: HPLC (Chiralpak AS, *n*-hexane/2-propanol 95:5): t_r (major comp.) 7.8 min, (minor) 5.5 min; $[\alpha]_D^{25} = 53.1$ ($c = 1$, CH_2Cl_2) [Ref. [4b]: $[\alpha]_D^{25} = 57.7$ ($c = 1$, CH_2Cl_2)]; **8b**: HPLC (Chiralpak AS, *n*-hexane/2-propanol 95:5): t_r (major) 7.7 min, (minor) 5.65 min; $[\alpha]_D^{25} = 45.1$ ($c = 1$, CH_2Cl_2) [Ref. [4b]: $[\alpha]_D^{25} = 42.4$ ($c = 1$, CH_2Cl_2)]; **8c**: HPLC (Chiralpak AS, *n*-hexane/2-propanol 98:2): t_r (major) 9.5 min, (minor) 12.5 min; $[\alpha]_D^{25} = 5.5$ ($c = 1$, CH_2Cl_2); **8d**: HPLC (Chiralpak AS, *n*-hexane/2-propanol 70:30): t_r (major) 3.6 min, (minor) 5.3 min; $[\alpha]_D^{25} = -10.5$ ($c = 1$, CH_2Cl_2) [Ref. [4b]: $[\alpha]_D^{25} = -10.4$ ($c = 1$, CH_2Cl_2)]; **8e**: HPLC (Chiralpak AS, *n*-hexane/2-propanol 70:30): t_r (major) 6.5 min, (minor) 7.7 min (from racemic mixture); $[\alpha]_D^{25} = -19.7$ ($c = 1$, CHCl_3); **8f**: HPLC (Chiralpak AS, *n*-hexane/2-propanol 60:40): t_r (major) 3.2 min, (minor) 5.4 min; $[\alpha]_D^{25} = -2.12$ ($c = 0.67$, CHCl_3).