Organocatalysis

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

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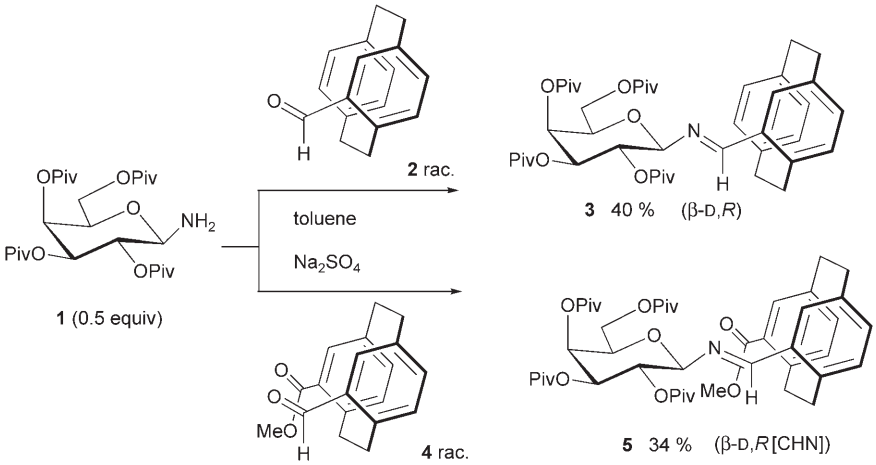
Dedicated to Professor Dieter Seebach on the occasion of his 70th birthday

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]

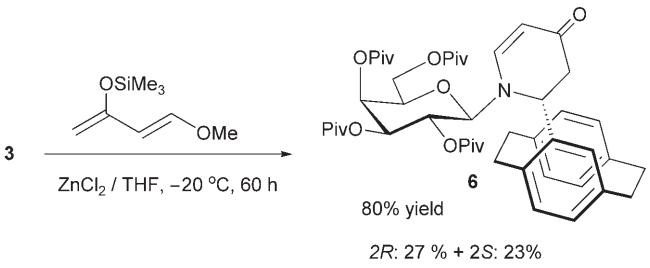


Scheme 1. Synthesis of *N*-galactosyl[2.2]paracyclophane carbaldimines.

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 feacture 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 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

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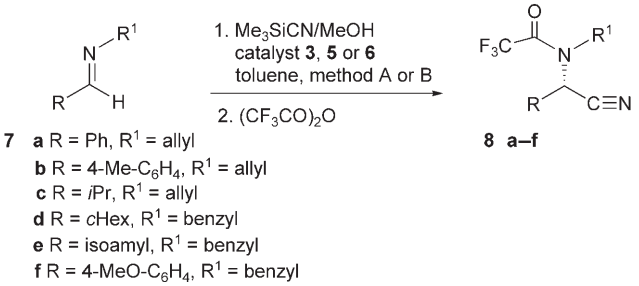
trimethylsilyl cyanide in methanol/toluene at temperatures between −50 °C and −20 °C (Scheme 3, Table 1).

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



7 **a** R = Ph, R^1 = allyl
b R = 4-Me-C_6H_4, R^1 = allyl
c R = *i*Pr, R^1 = allyl
d R = *c*Hex, R^1 = benzyl
e R = isoamyl, R^1 = benzyl
f R = 4-MeO-C_6H_4, R^1 = benzyl

8 **a–f**

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**	[%]	*ee*[b] [%]
1 (A)	**7a**	**5** (2)	20	−50→−20	**8a**	55	71
2 (A)	**7a**	**6** (10)	19	−50→−20	**8a**	15	34
3 (A)	**7b**	**3** (10)	20	−50→−20	**8b**	68	67
4 (A)	**7c**	**5** (5)	30	−50→−20	**8c**	20[c]	96
5 (A)	**7d**	**5** (5)	30	−50→−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 Me_3SiCN/MeOH at (2 equiv) −50 °C was added. Method B: Catalyst and Me_3SiCN/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 $(CF_3CO)_2O$.

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 Me_3SiCN 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, Me_3SiCN/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 properties.[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

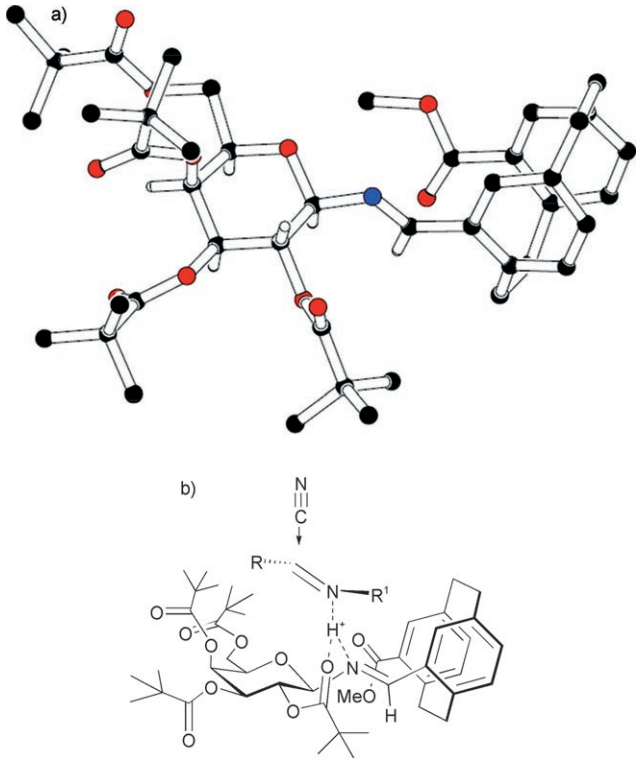


Figure 1. a) X-ray crystal structure of **5** (O red, N blue, C black, H white). b) Proposal for the enantioselectively effective reaction site of catalyst **5**.

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 R^1 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 Brønstedt acid group. They effect an efficient enantioselective formation of

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

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[15] The ^{1}H NMR signals of the aldimine groups are found at $\delta =$ 7.82–7.45 ppm for the aliphatic aldimines **7c**–**e**, and at $\delta = 8.32$–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, $[\alpha] = -139.2$ ($c = 1$, CH_3CN); FD-MS (positive): m/z 794 $[M+H^+]$. Elemental analysis ($C_{45}H_{61}O_{11}N$, 791.97): found (calcd): C 66.53 (66.58), H 7.68 (7.69), N 1.67 (1.76). ^{1}H NMR (400 MHz, $CDCl_3$, COSY): $\delta = 8.38$ (s, 1H, -N=C*H*-), 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 (Piv*C*=O), 166.7 (Phan-17), 160.5 (-*C*=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 (Piv*C*Me$_3$), 35.0, 34.9 (Phan-2, Phan-10), 34.4, 30.8 (Phan-9, Phan-1), 27.14, 27.11, 27.02 ppm (Piv*C*H$_3$). 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, $\beta = 95.649(6)°$, $V = 4770(1)$ Å^3, $Z = 4$; temperature: −80 °C; density: $d = 1.103$ g cm^{-3}; irradiation: $Cu_{K\alpha}$ graphite monochromator, $\lambda = 1.54178$ Å; $2\theta_{max} = 140°$; number of reflections: measured 19513, independent 9894 ($R_{int} = 0.0902$); 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; $[\alpha] = 53.1$ ($c = 1$, CH_2Cl_2) [Ref. [4b]: $[\alpha] = 57.7$ ($c = 1$, CH_2Cl_2)]; **8b**: HPLC (Chiralpak AS, *n*-hexane/2-propanol 95:5): t_r (major) 7.7 min, (minor) 5.65 min; $[\alpha] = 45.1$ ($c = 1$, CH_2Cl_2) [Ref. [4b]: $[\alpha] = 42.4$ ($c = 1$, CH_2Cl_2)]; **8c**: HPLC (Chiralpak AS, *n*-hexane/2-propanol 98:2): t_r (major) 9.5 min, (minor) 12.5 min; $[\alpha] = 5.5$ ($c = 1$, CH_2Cl_2); **8d**: HPLC (Chiralpak AS, *n*-hexane/2-propanol 70:30): t_r (major) 3.6 min, (minor) 5.3 min; $[\alpha] = -10.5$ ($c = 1$, CH_2Cl_2) [Ref. [4b]: $[\alpha] = -10.4$ ($c = 1$, 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); $[\alpha] = -19.7$ ($c = 1$, $CHCl_3$); **8f**: HPLC (Chiralpak AS, *n*-hexane/2-propanol 60:40): t_r (major) 3.2 min, (minor) 5.4 min; $[\alpha] = -2.12$ ($c = 0.67$, $CHCl_3$).

