Concave Reagents, 26[◇]

Concave Pyridines for Selective Acylations of Polyols

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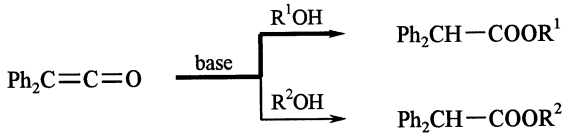
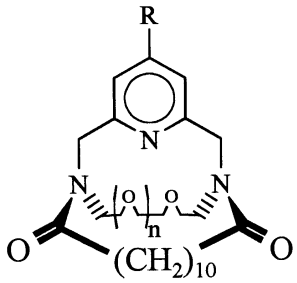
Selectivity enhancements in the base-catalyzed acylation of polyols (1,2- or 1,3-alkanediol, partially protected glucoside) have been found with (bi)macrocyclic pyridines **2** and **9** as catalysts. The different selectivities obtained for concave pyridines of varying ring sizes (**1** vs. **2**) are probably caused by their different geometries as a number of X-ray analyses (**1a**, **1b**, **2a**, **2b**, **2e**, **9**) indicate. The methyl glucoside **7** can selectively be acylated in 2-position.

Two major goals of synthetic chemistry are the development of new reactions and the optimization of the yields. In organic chemistry most unsatisfying yields are caused by side reactions, rather than by uncomplete turnover due to the formation of equilibria. The challenge is therefore to avoid side reactions and thus many *selective* reagents have been developed. But it is still difficult to distinguish very similar functional groups in intramolecular competitions, e. g. to acylate one OH group in carbohydrates selectively, especially when secondary OH groups shall be distinguished from one another.

Promising selectivities in the preferred acylation of primary alcohols in the presence of secondary ones have been found when the OH groups have been functionalized by reaction with a ketene in the presence of a pyridine catalyst.[1][2] In principle, two mechanisms are conceivable for a pyridine catalyzed addition of alcohols to ketenes: a nucleophilic attack of the pyridine on the ketene forming a betaine,[3] and the formation of a hydrogen bond between the alcohol and the pyridine nitrogen atom which activates the alcohol.[4] In the case of concave pyridines, the latter mechanism, the increase of the nucleophilicity of the oxygen atom of the alcohol is responsible[2] for the catalysis because the 2,6-disubstitution of the pyridine does not allow the nucleophilic attack of the betaine pathway. A hydrogen bond to an alcohol, however, can be formed. In this case, the substitution pattern of the pyridine determines its reactivity and selectivity.



By using catalysts like **2** in reaction mixtures containing primary and secondary hydroxyl groups, the primary al-



R	n = 1	n = 2
H	**1a**	**2a**
OMe	**1b**	**2b**
OEt	**1c**	**2c**
NEt_2	–	**2d**
OCH_2CH_2OH	–	**2e**
$OCH_2CH_2OCH_2Ph$	–	**2f**

[◇] Part 25: M. Gelbert, U. Lüning, *Supramol. Chem.*, in press.

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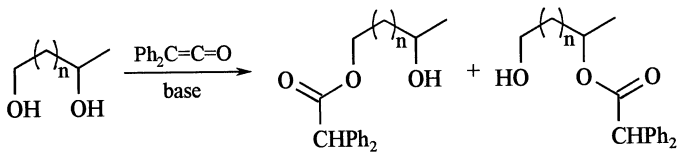
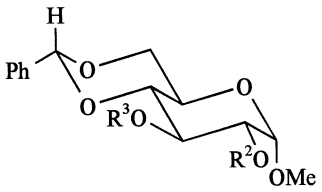


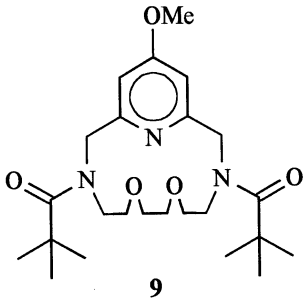
n = 0 **3** **4a** **4b**
n = 1 **5** **6a** **6b**



7 **8a** **8b** **8c**

$R^2 = H$, $R^3 = H$ —$Ph_2C=C=O$, base→ $R^2 = CO-CHPh_2$, $R^3 = H$ | $R^2 = H$, $R^3 = CO-CHPh_2$ | $R^2 = CO-CHPh_2$, $R^3 = CO-CHPh_2$

cohols have been acylated in selectivities exceeding 12:1.[1] These selectivities have been found for intermolecular (EtOH/*i*PrOH) and intramolecular competition (1,2-propanediol, **3**).[1] In the present work we have extended the acylation reaction to 1,3-butanediol (**5**) and to the glucose derivative **7**. In **7**, the two OH groups to be differentiated are extremely similar, they are both secondary and equatorial!



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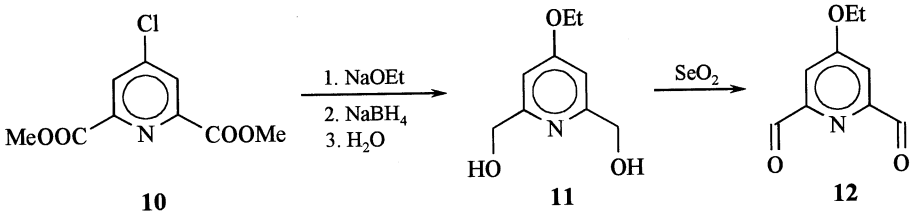
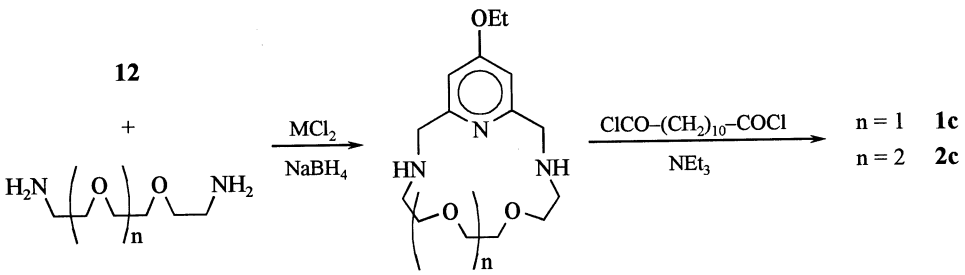
Selectivity Measurements

As described in the literature or analogously (see Scheme 1 and Experimental), the catalysts **1** and **2**[5][6] and diphenylketene[7] have been synthesized. To synthesize **1c** and **2c**, first an ethoxy group was introduced in 4-position of the chloropyridine derivative **10**. Total reduction to the bisalcohol **11** and selective oxidation with SeO_2 afforded the dialdehyde **12** which was cyclized with a diamine **13** or **14**

Scheme 1



10 **11** **12**



n = 1 **13** n = 1 M = Mg n = 1 **15**
n = 2 **14** n = 2 M = Ca n = 2 **16**

Table 1. Selectivities of the base-catalyzed acylation of different hydroxyl groups with diphenylketene in four sets of experiments: Intermolecular competition: EtOH/*i*PrOH, intramolecular competition: **3**, **5** and **7**[a]

Alcohol(s)	R	**2**	**9**	**1**
EtOH/*i*PrOH[b][8]	**a** H	7.9		3.5
	b OMe	10.0	12.8	4.1
	c OEt	10.5		4.0
	d NEt_2	12[1]		
	dendrimer A[c][9]	11.6		
	dendrimer B[d]	11.4		
	soluble polymer[e][11]	9.5		
	insoluble polymer[f]	7.4		
3 → **4a/4b**[g]	**a** H	10.3		4.0
	b OMe	13	24	4.5
	c OEt	13.2		5.0
	d NEt_2	15.2		
	soluble polymer[e]	16.2		
	insoluble polymer[f]	10.6		
	insoluble polymer[h]	10.8		
5 → **6a/6b**	**b** OMe	23	21	4.2
7 → **8a/8b**[i]	**a** H	∞[j]		
	b OMe	∞[j]	4.8	3
	c OEt	∞[j]		
	soluble polymer[e]	>50		
	insoluble polymer[f]	>30		

[a]All experiments were repeated several times. When in doubt, the smaller selectivities are always listed. – [b]The reaction conditions were chosen as in ref.[1]. A mixture of EtOH, *i*PrOH and *t*BuOH was used, the *tert*-butyl ester was not detected. – [c]Dendrimer with four **2e** units bound as ethers, molecular weight: 2557, ref.[9][10]. – [d]Dendrimer with six **2e** units bound as ethers, molecular weight: 3863, ref.[9][10]. – [e]Soluble polymer from poly(vinylbenzyl chloride) and **2e**, containing 60 weight% of **2f**. Remaining chlorine atoms had been substituted by NaOMe.[11] – [f]Insoluble polymer from a Merrifield resin (3.9 mmol Cl/g) and **2e**, containing 20 weight% of **2f**. Remaining chlorine atoms had been substituted by NaOMe.[11] Batch reaction. – [g]Reaction conditions were chosen as in ref.[1]. – [h]An HPLC column was packed with the insoluble polymer[f], and the reaction mixture was slowly pressed through the column.[11] – [i]**8c** could never be detected. – [j]Only **8a** could be detected.

in the presence of a template metal ion Mg^{2+} or Ca^{2+}. Obeying the high dilution principle a second cyclization with decanedicarbonyl dichloride gave the products **1c** and **2c**.

9 was synthesized by reaction of pivaloyl chloride with the macrocyclic diamine[5] precursor. Reaction of diphenylketene with the diols **3**, **5** and **7** afforded mixtures of the products **4a/4b**, **6a/6b** and **8a**–**8c**. The selectivities were determined by GC (**4a/4b** and **6a/6b** as trimethylsilyl ethers) or by ^{1}H-NMR (**8a**–**8c**). The selectivities found for various catalysts **1**, **2** and **9** are compared in Table 1.

For each acylation reaction of Table 1, drastically larger selectivities were found with the larger concave pyridines **2** in comparison to the smaller bimacrocycles **1**. In most cases, substitution of the pyridine unit in 4-position had only small influences on the selectivities, as did a fixation of the concave pyridines **2** to polymers or dendrimers. The reduced selectivities of **2a** in comparison to **2b**–**d** reflect its smaller basicity which causes a lower reactivity and allows the less selective uncatalyzed reaction to occur partially.

In addition to **1** and **2**, the monomacrocyclic catalyst **9** was investigated, which contains a dioxaoctane chain between the amide nitrogen atoms as the smaller bimacrocycle **1**. But in **9** there is no second macrocycle. This results in increased selectivities as shown in Table 1.

To elucidate the geometry of the catalysts X-ray analyses were carried out on single crystals of **1a**, **1b**, **2a**, **2b**, **2e** and **9** (Figures 1–3), and the conformer distribution was investigated in $CDCl_3$ solution. All catalysts **1** and **2** contain two amide groups with hindered rotation along the CO–NH axis.[5] Therefore, *ZZ*, *ZE* and *EE* conformers exist (Table 2). In the monomacrocyclic pyridine **9**, the barrier to rotation is smaller. In the NMR spectra, amide conformers were only found below room temperature.

Table 2. Conformer distribution of concave pyridines due to *E*- and *Z*-amide conformations

	ZZ	*ZE*	*EE*
1a[5]	63	25	12
1b[5]	54	28	18
1c	34	46	20
2a[5]	75	≈23	<5
2b[5]	68	27	5
2c	68	27	5
2d[6]	71	23	6
2e[10]	66	28	6
2f[10]	66	28	6
dendrimer A[10]	61	33	6
dendrimer B[10]	62	33	5

The NMR data and the X-ray structures show that the small bimacrocycles **1** differ from the large ones **2**: While both macrocyclic classes **1** and **2** crystallize as *ZZ* conformers, the conformer distribution in solution shows a higher tendency for **1** to build *E*-amide groups. In Figure 1 the X-ray structures for **1** and **2** are compared. As observed in the selectivities, a 4-substitution of the pyridine also had only a small influence on the overall structures. These are primarily determined by the length of the polyether chains. The polyether and the polymethylene chains of **2a**, **2b** and **2e** form a relatively flat macrocycle over which the pyridine ring is oriented almost perpendicular (Figure 1b). In this conformation a coordination of a substrate molecule is easily possible by the formation of a hydrogen bond. In the acylation experiments this hydrogen bond will activate the alcohol molecule. In the X-ray structure of **2e**, such a hydrogen bond was formed between the acidic hydrogen atom of a chloroform molecule and the pyridine nitrogen atom (Figure 2).

In contrast to **2a**, **2b** and **2e**, the smaller bimacrocycles **1** adopt a different geometry. The macrocycle formed by the polyether and the polymethylene chains is not flat resulting in a stronger shielding of the pyridine nitrogen atom (Figure 1a). The hydrogen bond discussed above cannot be formed easily resulting in a lower reactivity of these catalysts.[2] In fact the reactivity of **1a** is close to the catalytic power of an amide.[2] Therefore the amide groups contribute to the catalysis and cause the smaller selectivities.

The monomacrocycle **9** possesses the short dioxaoctane chain of the small bimacrocycles **1** but shows selectivities

Figure 1a. Superimposed X-ray structures of **1a** (solid bonds) and **1b** (open bonds). Atoms of the pyridine rings were fitted.

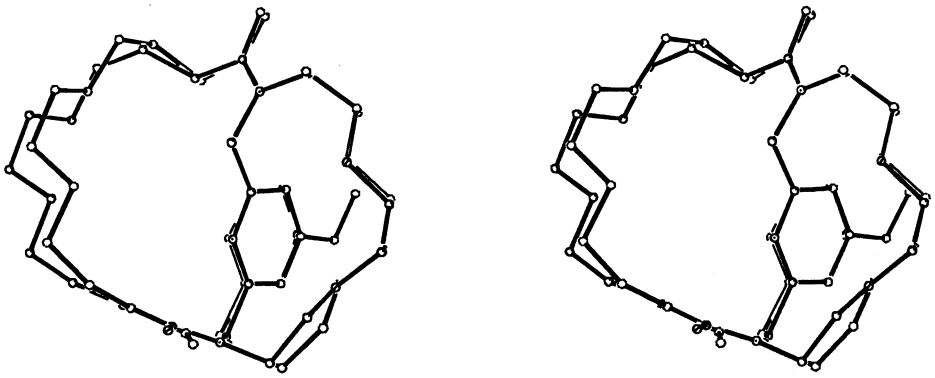


Figure 1b. Superimposed X-ray structures of **2a** (dotted lines), **2b** (full lines) and **2e** (dashed lines). The atoms of the pyridine rings were fitted.

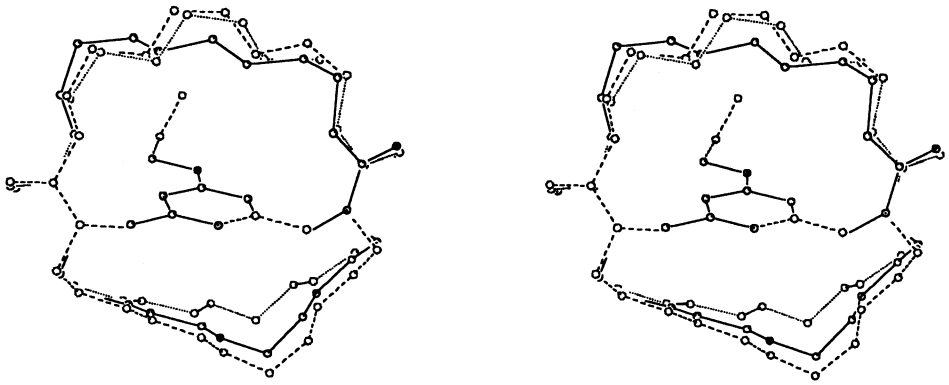
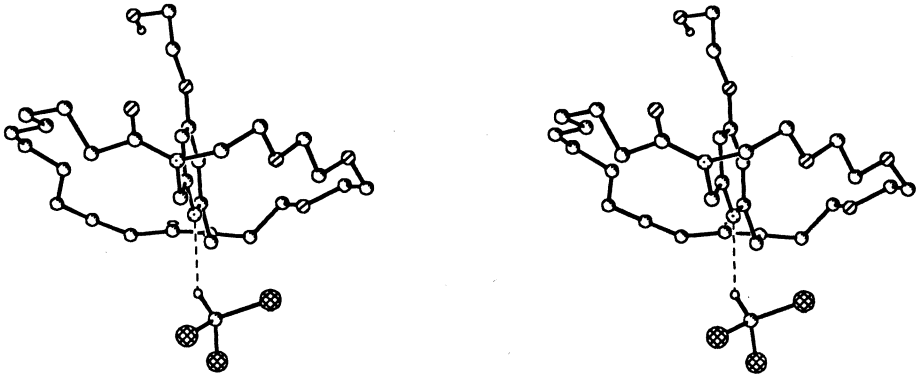


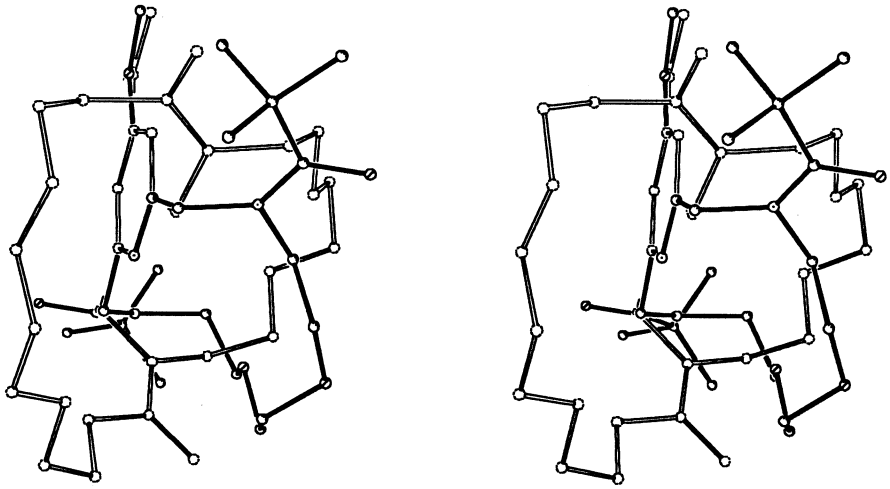
Figure 2. In the crystal, **2e** forms a hydrogen bond between its pyridine nitrogen atom and the acidic hydrogen atom of a chloroform molecule (dashed line). The hydroxyl group forms an intermolecular hydrogen bond to one of the carbonyl oxygen atoms.



close to those of the large bimacrocycles **2**. In the NMR spectra only one conformer is observed, and in the crystal, **9** exists as a *ZE* conformer (Figure 3). Thus the conformation of **9** is different from **1** and **2** but in contrast to **1** where the pyridine nitrogen atom hardly can form the hydrogen bond required for the catalysis, one bridge is missing in **9**. In addition, the monomacrocycle is bent allowing the pyridine nitrogen atom to form the hydrogen bond to the alcohol(s).

For the reactive catalysts, the first step of the reaction is probably the formation of complexes between the different OH groups in the substrates and the catalyst, e. g. one complex where the 2-OH group of the carbohydrate **7** is bound to the catalyst and one complex where the 3-OH group is bound. To form the acylated products these complexes must react with the ketene. The rate of formation of a specific product (e. g. **8a** or **8b**) is then determined by the rate with which the complex can be attacked by the ketene. For a selective catalyst (**2** or **9**) these rates differ strongly for different OH groups which means that the accessibility of the oxygen atom of each alcohol in each complex is different depending on the chain(s) of the pyridine catalysts. According to the selectivities listed in Table 1 the shielding of the oxygen atom in 3-position of the carbohydrate **7** by the hydrogen bonded catalyst must therefore be much larger than the shielding of the oxygen atom in 2-position.

Figure 3. Superimposed X-ray structures of the bimacrocycle **1b** (open bonds), and the monomacrocycle **9** (solid bonds) both containing a dioxaoctane chain. Atoms of the pyridine rings were fitted. In contrast to the bimacrocycles **1**, the nitrogen atom of **9** is less shielded allowing catalysis by hydrogen bond formation to a hydroxyl group.



These assumptions are supported by experiments in which the size of the ketene was varied (e. g. diphenylketene, bis(2,4,6-trimethylphenyl)ketene).[13] When the sterical demand of the ketene was increased the overall rate dropped drastically and the selectivity vanished.

This leads to the conclusion that for an optimal selectivity the catalyst must be optimized in such a way that only one of the two possible reaction pathways is slowed down by the concave shielding. If the shielding is not sufficient the selectivity will only be small, but if the shielding is extreme both reactions pathways are hindered and if products are formed at all the selectivity will be determined by other factors, for instance by a non-catalyzed background reaction.

The results of Table 1 demonstrate that concave reagents are a powerful tool for selective acylation of very similar hydroxyl groups. Future work will concentrate on the development of tailored concave bases for the selective acylation of other carbohydrates.

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Experimental Section

General Remarks: See ref.[1] Radial chromatography was carried out with chromatotron from Harrison Research Co. (silica gel layers with a thickness of 2 mm were used).

4-Ethoxy-2,6-bis(hydroxymethyl)pyridine (**11**): 1.13 g (50.0 mmol) of sodium was dissolved in 200 ml of dry ethanol and 10.0 g (43.6 mmol) of dimethyl 4-chloro-2,6-pyridinedicarboxylate (**10**)[12] was added in portions. The reaction mixture turned yellow and turbid. After 6 h at reflux temperature, the mixture was cooled to 0 °C and 10.0 g (260 mmol) of sodium borohydrate was added in portions. After a strong development of gas, the mixture was stirred at room temperature for 1 h and then was refluxed for additional 15 h. After cooling, 100 ml of acetone was added and the mixture was refluxed for 2 h. The solvents were evaporated *in vacuo* and the brown residue was mixed with 120 ml of saturated Na_2CO_3 solution. The slightly brown solution was heated at reflux for 2 h and was then extracted continuously for 20 h with chloroform. The solvents were evaporated *in vacuo* yielding 7.0 g (88%) of a slightly brown solid, m. p. 115−116 °C. − ^{1}H-NMR (200 MHz, [D$_6$]DMSO): δ = 1.34 (t, 6.8 Hz, 3 H), 4.11 (q, 6.8 Hz, 2 H), 4.45 (d, 5.9 Hz, 4 H), 5.39 (t, 5.9 Hz, 2 H, exchangeable with D_2O), 6.83 (s, 2 H). − IR (KBr): $\tilde{\nu}$ = 3340 cm^{-1} (br., O−H), 1604 (arom.), 1577. − MS (EI, 70 eV); *m/z* (%): 183 (50) [M$^+$], 182 (100), 164 (14), 154 (22), 139 (10), 138 (20), 137 (34), 136 (40), 125 (18). − MS (CI, isobutane); *m/z* (%): 185 (10), 184 (100) [M$^+$ + H], 139 (17) [M$^+$ + H−OCH$_2$CH$_3$]. − $C_9H_{13}NO_3$ (183.1): calcd. C 59.00, H 7.15, N 7.65, found C 58.56, H 7.05, N 7.52.

4-Ethoxypyridine-2,6-dicarbaldehyde (**12**): To a suspension of 4.20 g (38.2 mmol) of SeO_2 in 150 ml of 1,4-dioxane, 7.00 g (38.2 mmol) of **11** was added. The reaction mixture was slowly heated to 70 °C. Then the mixture turned dark red and elemental selenium precipitated. Stirring was continued at 90 °C until no further reaction was detected by TLC (reaction time 5 to 10 h). Towards the end of the reaction two times 250 mg of SeO_2 were added. Precipitated selenium was removed by filtration of the hot reaction mixture through several layers of sand and $MgSO_4$. The filter pad was washed intensively with hot 1,4-dioxane. After evaporation of the solvents *in vacuo*, the yellow residue was purified by chromatography (silica gel, 100 g, diameter 4 cm, ethyl acetate/dichloromethane, 3:1) yielding 5.4 g (78%) of a slightly yellow solid, m. p. 90−92 °C. − ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.50 (t, 7.0 Hz, 3 H), 4.22 (q, 7.0 Hz, 2 H), 7.63 (s, 2 H), 10.11 (s, 2 H). − ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 14.2 (q), 64.9 (t), 111.3 (d), 154.7 (s), 166.9 (s), 192.3 (d). − IR (KBr): $\tilde{\nu}$ = 3084 cm^{-1} (arom.), 1710 (C=O), 1595 (arom.), 1556 (arom.). − MS (EI, 70 eV); *m/z* (%): 180 (9), 179 (70) [M$^+$], 151 (100) [M$^+$−CO], 123 (35), 95 (47). − MS (CI, isobutane); *m/z* (%): 181 (10), 180 (100) [M$^+$ + H]. − HR-MS: $C_9H_9NO_3$ calcd. 179.0582 found 179.0581; $C_8{}^{13}CH_9NO_3$ calcd. 180.0616 found 180.0616. − $C_9H_9NO_3$ (179.1): calcd. C 60.33, H 5.06, N 7.82, found C 60.16, H 5.16, N 7.62.

Syntheses of Monomacrocyclic Pyridinediamines. − General Procedure: One equivalent of 4-ethoxypyridine-2,6-dicarbaldehyde (**12**) and one equivalent of the template salt MCl_2 were dissolved in 150 ml of dry methanole. Under nitrogen, one equivalent of the diamin **13** or **14**, dissolved in 30 ml of dry methanole, was added within 30 min. The mixture was stirred for 1 h at room temperature and

heated at reflux for 2.5 h. After cooling to 0 °C, sodium borohydride was added. The mixture was stirred for 15 h at room temperature, 50 ml of water was added, and stirring was continued for additional 6 h. The mixture was concentrated to 100 ml. Precipitating borates formed a strong turbidity. After filtration, the solution was extracted four times with 100 ml of dichloromethane. The combined organic layer was sucked through a $MgSO_4$ pad, the solvents were evaporated and the residue was dried *in vacuo*.

16-Ethoxy-6,9-dioxa-3,12,18-triazabicyclo[12.3.1]octadeca-1(17),14(18),15-triene (**15**): Starting materials: 0.85 g (4.7 mmol) of 4-ethoxypyridine-2,6-dicarbaldehyde (**12**), 0.70 g (4.7 mmol) of 1,8-diamino-3,6-dioxaoctane (**13**), 1.00 g (4.7 mmol) of $MgCl_2 \cdot 6 H_2O$, 1.90 g (29.1 mmol) of $NaBH_4$. Yield: 1.27 g (92%), yellow oil. − ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.41 (t, 7.1 Hz, 3 H), 2.82 (t, 4.9 Hz, 4 H), 3.65 (m_c, 4 H), 3.70 (t, 4.9 Hz, 4 H), 3.5−4.0 (br. s, ca. 2 H, exchangeable with D_2O), 3.84 (m_c, 4 H), 4.05 (q, 7.1 Hz, 2 H), 6.54 (s, 2 H). − IR (KBr): $\tilde{\nu}$ = 3300 cm^{-1} (br., NH), 1600 (arom.), 1571 (arom.). − MS (EI, 70 eV); *m/z* (%): 295 (30) [M^+], 233 (26), 220 (25), 192 (57), 178 (100), 151 (53). − MS (CI, isobutane); *m/z* (%): 296 (100) [M^+ + H], 295 (13) [M^+], 294 (12), 282 (16), 192 (13), 178 (12).

19-Ethoxy-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(20),17(21),18-triene (**16**): Starting materials: 1.50 g (8.4 mmol) of 4-ethoxypyridine-2,6-dicarbaldehyde (**12**), 1.60 g (8.4 mmol) of 1,11-diamino-3,6,9-trioxaundecane (**14**), 0.93 g (8.4 mmol) of $CaCl_2$, 2.10 g (55.5 mmol) of $NaBH_4$. Yield: 2.78 g (98%), yellow oil. − ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.41 (t, 6.8 Hz, 3 H), 2.85 (t, 5.7 Hz, 4 H), 3.66 (m_c, 12 H), 3.5−4.0 (br. s, ca. 2 H, exchangeable with D_2O), 3.80 (m_c, 4 H), 4.06 (q, 6.8 Hz, 2 H), 6.59 (s, 2 H). − IR (KBr): $\tilde{\nu}$ = 3380 cm^{-1} (br., NH), 1599 (arom.), 1571 (arom.). − MS (EI, 70 eV); *m/z* (%): 339 (25) [M^+], 281 (11), 279 (10), 233 (47), 222 (23), 220 (22), 206 (25), 192 (100), 178 (71), 166 (45). − MS (CI, isobutane); *m/z* (%): 340 (100) [M^+ + H], 326 (15).

Syntheses of Bimacrocyclic Pyridinebislactames. − General Procedure: To a well stirred solution (KPG stirrer, > 500 r/min) of six equivalents of triethylamine in 500 ml of dry dichloromethane, one equivalent of the pyridinediamine **15** or **16** in 200 ml of dichloromethane, and one equivalent of decanedicarbonyl dichloride in 250 ml of dry dichloromethane were dropped synchronically within 7 h. Stirring was continued for additional 30 min. Then the reaction mixture was allowed to stand for 15 h. The solution was concentrated to 150 ml and was washed with 50 ml 2 N NaOH. The aqueous layer was extracted three times with 100 ml of dichloromethane. The combined organic layer was dried with $MgSO_4$ and filtered. After evaporation of the solvents, the remaining oil was purified by chromatography (silica gel, 100 g, diameter 4 cm, dichloromethane/ethanol, 10:1).

26-Ethoxy-17,20-dioxa-1,14,30-triazatricyclo[12.8.7.1^{24,28}]triaconta-24(30),25,27-trien-2,13-dione (**1c**): Starting materials: 1.27 g (4.3 mmol) of 16-ethoxy-6,9-dioxa-3,12,18-triazabicyclo[12.3.1]octadeca-1(17),14(18),15-triene (**15**), 1.15 g (4.3 mmol) of decanedicarbonyl dichloride, 2.61 g (25.8 mmol) of NEt_3. Yield: 0.98 g (46%), colourless oil, slowly crystallizing, m. p. 98−102 °C. − ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.1−1.8 (m, ca. 23 H), 2.2−2.5 (m, ca. 4 H), 3.0−4.1 (m, ca. 8 H), 4.13 (q, 7.0 Hz, 2 H), 4.4−4.9 (m, ca. 4 H), 6.54 (d, 2.4 Hz, ca. 0.46 H, Py-H_{EZ}), 6.55 (s, 0.69 H, Py-H_{ZZ}), 6.80 (s, 0.39 H, Py-H_{EE}), 6.87 (d, 2.4 Hz, ca. 0.46 H, Py-H_{EZ}). − IR (KBr): $\tilde{\nu}$ = 3431 cm^{-1}, 1647 (C=O), 1600 (arom.), 1576 (arom.). − MS (EI, 70 eV); *m/z* (%): 489 (98) [M^+], 459 (52), 444 (38), 294 (20), 234 (20), 220 (22), 206 (39), 192 (35), 178 (54), 151 (100). − HR-MS: $C_{27}H_{43}N_3O_5$ calcd. 489.3203 found 489.3202. $C_{26}{}^{13}CH_{43}N_3O_5$ calcd. 490.3236 found 490.3235. − $C_{27}H_{43}N_3O_5 \cdot 0.5 H_2O$ (498.3): calcd. C 65.03, H 8.89, N 8.43, found C 65.54, H 8.73, N 8.49.

29-Ethoxy-17,20,23-trioxa-1,14,33-triazatricyclo[12.11.7.1^{27,31}]tritriaconta-27(33),28,30-trien-2,13-dione (**2c**): Starting materials: 2.78 g (8.2 mmol) of 19-ethoxy-6,9,12-trioxa-3,15,21-triazabicyclo[15.3.1]heneicosa-1(20),17(21),18-triene (**16**), 2.19 g (8.2 mmol) of decanedicarbonyl dichloride, 4.97 g (49.2 mmol) of NEt_3. Yield: 2.00 g (46%), m. p. 122−124 °C. − ^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.9−1.8 (m, ca. 23 H), 2.1−2.4 (m, ca. 4 H), 3.2−4.3 (m, ca. 14 H), 4.6−5.4 (m, ca. 4 H), 6.45 (d, 2.2 Hz, 0.27 H, Py-H_{ZE}), 6.54 (s, 1.36 H, Py-CH_{ZZ}), 6.66 (d, 2.2 Hz, 0.27 H, Py-H_{ZE}), 6.93 (s, 0.1 H, Py-H_{EE}). − IR (KBr): $\tilde{\nu}$ = 1652 cm^{-1}(C=O), 1631, 1600 (arom.), 1575 (arom.). − MS (EI, 70 eV); *m/z* (%): 533 (100) [M^+], 505 (23), 503 (37), 444 (37), 428 (25), 415 (38), 151 (71). − $C_{29}H_{47}N_3O_6$ (533.3): calcd. C 65.26, H 8.88, N 7.87, found C 64.98, H 8.81, N 7.63.

3,12-Bis(2,2-dimethyl-propionyl)-16-methoxy-6,9-dioxa-3,12,18-triazabicyclo[12.3.1]octadeca-1(17),14(18),15-triene (**9**): 1.25 g (4.5 mmol) of 16-methoxy-6,9-dioxa-3,12,18-triazabicyclo-[12.3.1]octadeca-1(17),14(18),15-triene[5] and 2.70 g (26.7 mmol) of NEt_3 were dissolved in 100 ml of dry dichloromethane. 1.21 g (9.8 mmol) of pivaloyl chloride in 25 ml of dry dichloromethane was slowly added during 1 h while stirring. After 15 h of stirring at room temperature the solution was concentrated to 50 ml and extracted with 15 ml of 2 N NaOH. The aqueous layer was extracted three times with 100 ml of dry dichloromethane. The organic layers were combined, dried with $MgSO_4$, and the solvent was evaporated. The remaining oil was purified by chromatography (silica gel, 100 g, diameter 4 cm, dichloromethane/ethanol, 10:1; Chromatotron, dichloromethane) yielding 1.21 g (61%) of **9** as a slightly yellow solid, m. p.: 153−154 °C. − ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 18 H), 3.47 (br. s, 4 H), 3.63 (br. s, 8 H), 3.80 (s, 3 H), 4.78 (br. s, 4 H), 6.72 (s, 2 H). − ^{1}H NMR (200 MHz, $CDCl_3$, 4.0 eq. of picric acid): δ = 1.35 (s, 18 H), 3.30 (s, 4 H), 3.35 (t, 5.0 Hz, 4 H), 3.88 (t, 5.0 Hz, 4 H), 4.07 (s, 3 H), 4.89 (s, 4 H), 7.10 (s, 2 H), 9.10 (br. s, ca. 8.2 H, picric acid). − IR (KBr): $\tilde{\nu}$ = 3440 cm^{-1}, 1618 (C=O), 1597 (arom.), 1570 (arom.). − MS (EI, 70 eV); *m/z* (%): 450 (5), 449 (20) [M^+], 393 (18), 392 (77) [$M^+ - C_4H_9^+$], 365 (23), 364 (100) [$M^+ - COC(CH_3)_3$], 323 (18), 248 (14), 177 (15), 137 (42). − MS (CI, isobutane); *m/z* (%): 451 (28), 450 (100) [M^+ + H], 392 (3) [$M^+ - C_4H_9^+$], 364 (3) [$M^+ - COC(CH_3)_3$]. − HR-MS; $C_{24}H_{39}N_3O_5$: calcd. 449.2890, found 449.2887; $C_{23}{}^{13}CH_{39}N_3O_5$: calcd. 450.2923, found 450.2920. − $C_{24}H_{39}N_3O_5$ (449.3): calcd. C 64.12, H 8.74, N 9.35, found C 63.43, H 8.68, N 9.16.

3-Hydroxybutyl Diphenylacetate (**6a**) *and 3-Hydroxy-1-methylpropyl Diphenylacetate* (**6b**): 1.00 g (4.3 mmol) of diphenylacetyl chloride was dissolved in 10 ml of dry dichloromethane, and 5.00 ml (55.3 mmol) of butane-1,3-diol (**5**) and 1 ml of pyridine were added. The reaction mixture was stirred for 15 h at room temperature, then 20 ml of water was added and the mixture was extracted twice with 20 ml of dichloromethane. The combined organic layer was dried with $MgSO_4$ and filtered. Evaporation of the solvent in vacuo yielded a colourless oil, which was dissolved in little dichloromethane and purified twice by chromatography (silica gel, 100 g, diameter 2 cm, ethyl acetate). Yield: 0.7 g (57%) of **6a**/**6b** in a 9:1 ratio (NMR) as colourless oil. − ^{1}H NMR (300 MHz, $CDCl_3$): signals for **6a** and **6b**: δ = 1.6−1.9 (m, ca. 2 H) 1.80 (br. s, 1 H), 7.2−7.4 (m, 10 H), signals for **6a**: δ = 1.15 (d, 6.2 Hz, 2.7 H), 3.7−3.8 (m, 0.9 H), 4.1−4.3 (m, 0.9 H), 4.3−4.5 (m, 0.9 H), 5.01 (s, 0.9 H), signals for **6b**: δ = 1.27 (d, 6.4 Hz, 0.3 H), 3.3−3.6 (m, 0.2 H), 5.01 (s, 0.1 H), 5.1−5.3 (m, 0.1 H). − IR (KBr): $\tilde{\nu}$ =

3411 cm^{-1} (br., OH), 1732 (C=O), 1600 (arom.), 1496. − MS (EI, 70 eV); *m/z* (%): 284 (2) [M^+], 195 (3), 194 (17), 167 (100) [M^+ − COOR]. − MS (CI, isobutane); *m/z* (%): 286 (9), 285 (47) [M^+ + H], 167 (5) [M^+ − COOR], 117 (100). − $C_{18}H_{20}O_3$ (284.1): calcd. C 76.03, H 7.09, found C 75.59, H 7.09.

8a−c: The diphenylacetyl derivatives of methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (**7**) were isolated from the competition experiments and separated (1.03 mmol of **7**, catalysis by pyridine). Separation and chromatography (silica gel with 5% H_2O, w/w, CH_2Cl_2/EtOH, 20:1) gave 68 mg of pure **8a** (R_f = 0.76) and 87 mg of pure **8c** (R_f = 0.81), a mixture of **8a** and **8c** (106 mg), and a mixture of **8a** and **8b** (111 mg) which was separated by a second chromatography (silica gel with 5% H_2O w/w, cyclohexane/ethyl acetate, 20:1) yielding pure **8a** (20 mg, R_f = 0.72) and pure **8b** (67 mg, R_f = 0.48).

8a: M. p. 151−152°C. − ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.29 (s, 3 H, OC*H*$_3$), 3.55 (t, 10 Hz, 1 H, 3-*H*), 3.75 (t, 10 Hz, 1 H, 6-*H*), 3.81 (dt, J_d = 4.5 Hz, J_t = 10 Hz, 1 H, 5-*H*), 4.15 (t, 10 Hz, 1 H, 4-*H*), 4.27 (dd, 4.5 Hz, 10 Hz, 1 H, 6-*H*), 4.83 (dd, 4 Hz, 10 Hz, 1 H, 2-*H*), 4.94 (d, 4 Hz, 1 H, 1-*H*), 5.14 (s, 1 H, 2-COC*H*Ph$_2$), 5.53 (s, 1 H, PhC*H*), 7.2−7.4 (m, 15 H, Ar-*H*). − IR (KBr): ṽ = 3450 cm^{-1} (br., OH), 1735 (C=O), 750, 700. − MS (EI, 70 eV): *m/z* (%): 476 (44), [M^+], 167 (100), 152 (41), 149 (24), 107 (42), 91 (32), 69 (37). − $C_{28}H_{28}O_7$ (476.5): calcd. C 70.58 H 5.92, found C 70.71 H 5.98.

8b: M. p. 185−187°C. − ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.45 (s, 3 H, OC*H*$_3$), 3.55 (t, 10 Hz, 1 H, 4-*H*), 3.66 (dd, 4 Hz, 10 Hz, 1 H, 2-*H*), 3.71 (t, 10 Hz, 1 H, 6-*H*), 3.87 (dt, J_d = 4.5 Hz, J_t = 10 Hz, 1 H, 5-*H*), 4.28 (dd, 4.5 Hz, 10 Hz, 1 H, 6-*H*), 4.78 (d, 4 Hz, 1 H, 1-*H*), 5.12 (s, 1 H, 3-COC*H*Ph$_2$), 5.40 (s, 1 H, PhC*H*), 5.44 (t, 10 Hz, 1 H, 3-*H*), 7.1−7.4 (m, 15 H, Ar-*H*). − IR (KBr): ṽ = 3450 cm^{-1} (br., OH), 1740 (C=O), 710. − MS (EI, 70 eV): *m/z* (%): 476 (33), [M^+], 167 (100), 159 (42), 141 (23), 107 (33), 99 (35), 69 (63). − $C_{28}H_{28}O_7 \cdot 0.5\ H_2O$ (476.5 + 9.0): calcd. C 69.26 H 6.02, found C 68.16 H 5.87.

8c: M. p. 155−156°C. − ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.22 (s, 3 H, OC*H*$_3$), 3.57 (t, 10 Hz, 1 H, 4-*H*), 3.72 (t, 10 Hz, 1 H, 6-*H*), 3.92 (dt, J_d = 4.5 Hz, J_t = 10 Hz, 1 H, 5-*H*), 4.37 (dd, 4.5 Hz, 10 Hz, 1 H, 6-*H*), 4.85 (s, 1 H, 2-COC*H*Ph$_2$), 4.88 (dd, 4 Hz, 10 Hz, 1 H, 2-*H*), 4.94 (d, 4 Hz, 1 H, 1-*H*), 4.95 (s, 1 H, 3-COC*H*Ph$_2$), 5.38 (s, 1 H, PhC*H*), 5.75 (t, 10 Hz, 1 H, 3-*H*), 7.0−7.4 (m, 25 H, Ar-*H*). − IR (KBr): ṽ = 1730 cm^{-1} (C=O), 1150, 755, 700. − MS (EI, 70 eV): *m/z* (%): 670 (37), [M^+], 353 (16), 194 (93), 165 (100), 109 (81), 91 (97). − $C_{46}H_{38}O_8$ (670.8): calcd. C 75.21 H 5.71, found C 75.67 H 6.20.

X-ray Analyses: Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre (No 100803). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. code +(1223)336−033, e-mail: teched@ccdc.cam.ac.uk).

1a: $C_{25}H_{41}N_3O_5$, M_r = 463.61 g/mol. Crystal data: monoclinic, space group *C*2/*c*, *Z* = 8, unit cell: *a* = 17.7544(1), *b* = 17.6531(1), *c* = 17.1207(2) Å, β = 111.749(1)°, *V* = 4984.00(7) Å^3, calcd. density *d* = 1.236 g·cm^{-3}. Data collection: Siemens CCD three-circle diffractometer, graphite-monochromated Mo-K_α radiation; colourless crystal, 0.8 x 0.4 x 0.4 mm, *T* = 143 K, ω-scans in the 2θ range 3−53°, index ranges $-22 \le h \le 22$, $-22 \le k \le 22$, $-21 \le l \le 21$; total of 43833 reflections, 5084 independent (R_{int} = 0.047), absorption coefficient = 0.086 mm^{-1}, empirical absorption correction using SADABS (Sheldrick, 1996), structure solution by direct methods, structure refinement: full-matrix least-squares on F^2, data/parameter-ratio: 5084/198, goodness-of-fit = 1.065, final *R* indices (all data): *R* = 0.063, *wR*2 = 0.177, largest difference peak and hole: 0.279 and −1.041 eÅ^{-3}.

1b: $C_{26}H_{41}N_3O_5$, M_r = 475.62 g/mol. Crystal data: orthorhombic, space group Pccn, *Z* = 8, unit cell: *a* = 21.0473(1), *b* = 23.4133(1), *c* = 10.4790(2) Å, *V* = 5163.91(6) Å^3, calcd. density *d* = 1.224 gcm^{-3}. Data collection: Siemens CCD three-circle diffractometer, graphite-monochromated Mo-K_α radiation; colourless crystal, 0.6 x 0.5 x 0.3 mm, *T* = 153 K, ω-scans in the 2θ range 3−53°, index ranges $-25 \le h \le 25$, $-29 \le k \le 29$, $-13 \le l \le 12$; total of 50744 reflections, 5301 independent (R_{int} = 0.103), absorption coefficient = 0.085 mm^{-1}, empirical absorption correction using SADABS (Sheldrick, 1996), structure solution by direct methods, structure refinement: full-matrix least-squares on F^2, data/parameter-ratio: 5301/308, goodness-of-fit = 1.152, final *R* indices (all data): *R* = 0.106, *wR*2 = 0.163, largest difference peak and hole: 0.236 and −0.266 eÅ^{-3}.

2a: $C_{27}H_{43}N_3O_5$, M_r = 489.64 g/mol. Crystal data: monoclinic, space group $P2_1/n$, *Z* = 4, unit cell: *a* = 15.5325(1), *b* = 10.3881(1), *c* = 16.3564(1) Å, β = 90.766(1)°, *V* = 2638.92(3) Å^3, calcd. density *d* = 1.232 gcm^{-3}. Data collection: Siemens CCD three-circle diffractometer, graphite-monochromated Mo-K_α radiation; colourless crystal, 1.0 x 0.9 x 0.4 mm, *T* = 173 K, ω-scans in the 2θ range 3−60°, index ranges $-21 \le h \le 20$, $-13 \le k \le 14$, $-22 \le l \le 20$; total of 39970 reflections, 7102 independent (R_{int} = 0.025), absorption coefficient = 0.085 mm^{-1}, empirical absorption correction using SADABS (Sheldrick, 1996), structure solution by direct methods, structure refinement: full-matrix least-squares on F^2, data/parameter-ratio: 7102/317, goodness-of-fit = 1.045, final *R* indices (all data): *R* = 0.045, *wR*2 = 0.107, largest difference peak and hole: 0.381 and −0.163 eÅ^{-3}.

2b: $C_{28}H_{45}N_3O_6$, M_r = 519.67 g/mol. Crystal data: triclinic, space group $P\bar{1}$, *Z* = 2, unit cell: *a* = 8.990(4), *b* = 10.070(6), *c* = 16.145(5) Å, α = 74.78(5), β = 86.74(4), γ = 77.72(4)°, *V* = 1378.1(1) Å^3, calcd. density *d* = 1.252 gcm^{-3}. Data collection: Enraf-Nonius CAD4 four-circle diffractometer, graphite-monochromated Cu-K_α radiation; colourless crystal, 0.6 x 0.5 x 0.3 mm, *T* = 123 K, ω-scans in the 2θ range 5−110°, index ranges $-9 \le h \le 2$, $-10 \le k \le 10$, $-17 \le l \le 17$; total of 4331 reflections, 3468 independent (R_{int} = 0.056), absorption coefficient = 0.710 mm^{-1}, no absorption correction, structure solution by direct methods, structure refinement: full-matrix least-squares on F^2, data/parameter-ratio: 3468/333, goodness-of-fit = 1.100, final *R* indices (all data): *R* = 0.046, *wR*2 = 0.113, largest difference peak and hole: 0.418 and −0.345 eÅ^{-3}.

2e: $C_{29}H_{47}N_3O_7 \cdot CHCl_3$, M_r = 669.06 g/mol. Crystal data: monoclinic, space group $P2_1/n$, *Z* = 4, unit cell: *a* = 10.258(1), *b* = 22.166(3), *c* = 15.002(2) Å, β = 93.26 (1)°, *V* = 3405.6(7) Å^3, calcd. density *d* = 1.305 gcm^{-3}. Data collection: Enraf-Nonius CAD4 four-circle diffractometer, graphite-monochromated Cu-K_α radiation; colourless crystal, 0.5 x 0.3 x 0.3 mm, *T* = 293 K, ω-scans in the 2θ range 7−120°, index ranges $0 \le h \le 11$, $-24 \le k \le 5$, $-16 \le l \le 16$; total of 6757 reflections, 5047 independent (R_{int} = 0.034), absorption coefficient = 2.830 mm^{-1}, no absorption correction, structure solution by direct methods, structure refinement: full-matrix least-squares on F^2, data/parameter-ratio: 5047/384, goodness-of-fit = 1.038, final *R* indices (all data): *R* = 0.103, *wR*2 = 0.261, largest difference peak and hole: 0.508 and −0.570 eÅ^{-3}.

9: $C_{24}H_{39}N_3O_5$, M_r = 449.58 g/mol. Crystal data: triclinic, space group $P\bar{1}$, Z = 2, unit cell: a = 10.2293(1), b = 10.5033(1), c = 12.7351(1) Å, α = 73.652(1), β = 88.698(1), γ = 65.506(1)°, V = 1187.86(2) Å^3, calcd. density d = 1.257 gcm^{-3}. Data collection: Siemens CCD three-circle diffractometer, graphite-monochromated Mo-K_α radiation; colourless crystal, 0.6 x 0.4 x 0.3 mm, T = 173 K, ω-scans in the 2θ range 4−52°, index ranges $-12 \le h \le 12$, $-13 \le k \le 13$, $-15 \le l \le 15$; total of 14355 reflections, 4784 independent (R_{int} = 0.027), absorption coefficient = 0.088 mm^{-1}, empirical absorption correction using SADABS (Sheldrick, 1996), structure solution by direct methods, structure refinement: full-matrix least-squares on F^2, data/parameter-ratio: 4784/290, goodness-of-fit = 1.026, final R indices (all data): R = 0.047, $wR2$ = 0.095, largest difference peak and hole: 0.290 and −0.195 eÅ^{-3}.

Selectivity Measurements

6a/6b: The experiments were carried out analogously to **4a/4b** (50 mM **5**, 50 mM catalyst, 4 mM $Ph_2C{=}C{=}O$).[1] Analysis by GC after derivatization.

8a/b: 1 mmol of **7** was dissolved in 2 ml of dry dichloromethane and 0.01 to 1.00 mmol of the catalyst was added. Then 1.25 mmol of diphenylketene was added with an Eppendorf pipette. The vial was flushed with nitrogen and closed. After 15 h at room temperature the mixtures were concentrated in vacuo and analysed by NMR spectroscopy. To remove the catalysts the NMR solvent was evaporated. 250 µl of dichloromethane was added and the solution was filtered through silica gel and washed with 20 ml of dichloromethane. After evaporation of the solvent *in vacuo,* the remaining residue was analysed by NMR spectroscopy in $CDCl_3$ and C_6D_6. With the catalysts **1**, **2** and **9**, **8c** never could be detected.

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