Organocatalysis of C=N/C=N and C=C/C=N Exchange in Dynamic Covalent Chemistry

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Dedicated to Professor *Dieter Seebach*

The reversibly formed C=N bond plays a very important role in dynamic covalent chemistry and the C=N/C=N exchange of components between different imine constituents to create dynamic covalent libraries has been extensively used. To facilitate diversity generation, we have investigated an organocatalyzed approach, using L-proline as catalyst, to accelerate the formation of dynamic libraries of $[n \times n]$ imine components. The organocatalysis methodology has also been extended, under somewhat modified conditions, to reversible C=C/C=N exchange processes between *Knoevenagel* derivatives of barbituric acid and imines, allowing for the generation of increased diversity.

1. Introduction. – Dynamic Covalent Chemistry (DCC) [1][2], the covalent wing of Constitutional Dynamic Chemistry (CDC) [3][4], rests on the implementation of reversible chemical reactions to generate dynamic covalent libraries (DCLs) based on interconverting molecular constituents. A major feature of DCLs is the production of high molecular-structure diversity for application in both biological [1–5] and material sciences [1–4][6]. Reversible reactions such as amine/carbonyl condensations, disulfide exchange, boronic ester formation, *Diels–Alder* condensations, *etc.* have been implemented in numerous studies in DCC [1–8]. The C=N bond is of particular interest regarding its range of structural variations, such as imines, hydrazones, and oximes, its reversibility, its easy synthetic availability, and its broad range of implementation [1–4][8].

The reversibility of condensation/hydrolysis processes in (amine + carbonyl)/imine interconversion is highly suitable for DCC applications, and a major goal is to achieve fast component exchange. In recent years, organocatalysis has developed as an efficient methodology for the acceleration of various chemical reactions [9]. Among the different types of catalytic processes, the enamine/iminium pathway is well-established. Especially, L-proline, a naturally occurring chiral secondary amine, and its derivatives have been extensively used and studied as catalysts to increase reaction rates as well as in asymmetric synthesis [10]. The implementation of organocatalysis in DCC offers much potential for extending the range of exchange processes and improving their reactional features.

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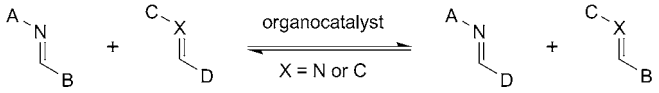
We herein describe DCC processes involving reversible exchange of components between imine constituents (imine/imine, C=N/C=N exchange) as well as between benzylidene and imine constituents (C=C/C=N exchange), and investigate the ability of selected secondary amines such as L-proline to catalyze these reactions (*Scheme 1*). The dynamic exchange between *Knoevenagel*-type C=C bonds and imines is of special interest for increasing diversity generation. Thus, the possibility to achieve efficient reversible C=C/C=N exchange by means of organocatalysis was examined. Cross-*Knoevenagel* C=C/C=C exchange represents a further step along this line [11][12].

Scheme 1. *Representation of the [2 × 2] C=N/C=N and C=N/C=C Exchange Reactions Implemented for the Investigation of Organocatalysis*



2. Results and Discussion. – 2.1. *Organocatalysis of Imine/Imine, C=N/C=N, Exchange Processes.* The C=N/C=N exchange of residues within pairs of imines, chosen among the imines **1a** – **1s** (*Figs. 1 – 3*, and *Table 1*, below), was examined under different reaction conditions. The process is represented in *Scheme 1* and in the caption of *Table 1*. It generates [2 × 2] DCLs of four constituents. The acid-catalyzed version of the imine-exchange reaction has been described in the literature [13][14]. For the present study of organocatalysis, (D_6)DMSO was chosen as solvent, in view of its ability to dissolve most organic substances. One % D_2O was added to ensure reproducible conditions and to avoid that the exchange be not just caused by the presence of traces of H_2O in the solvent.

Furthermore, to maintain a constant apparent pH, 10% BIS-TRIS (=2,2-bis(hydroxymethyl)-2,2′,2″-nitrilotriethanol) was added as buffer to the reaction mixture. It is highly soluble in (D_6)DMSO and does not contain free NH groups, thus avoiding undesired side reactions. All imines were prepared by a standard procedure [15]. *Fig. 2* shows a control experiment, indicating that the imine/imine exchange was not much influenced by the added D_2O and BIS-TRIS buffer. The concentrations of the imines, [Im], were determined as a function of time by integration of the imine H-atom ^{1}H-NMR signals. The graphs of ln [Im] as a function of time ([Im] is the concentration of either of the imines used for a given exchange process), for both blank and catalyzed reactions, fitted first-order processes. The corresponding rate constants k_c and k_b were calculated as indicated in the *Exper. Part* and are compiled in *Table 1* [16]. The equilibrium constants were calculated from the rate constants (see caption of *Table 1*).

To investigate the potential of organocatalysis in imine/imine exchange, transimination processes were studied in absence and in presence of L-proline and of its derivatives. The results are presented in *Figs. 3* and *4*, and in *Table 1*. The mechanism of the process is depicted in *Scheme 2*, following that proposed in the literature [9].

The reactions in presence of *N*-Boc-protected L-proline, L-proline *tert*-butyl ester, L-proline, and benzoic acid were compared with the blank reaction. Only in the case of L-proline did a marked increase in C=N/C=N exchange rate occur, and the equilibrium state of the mixture was reached within a comparatively short time.

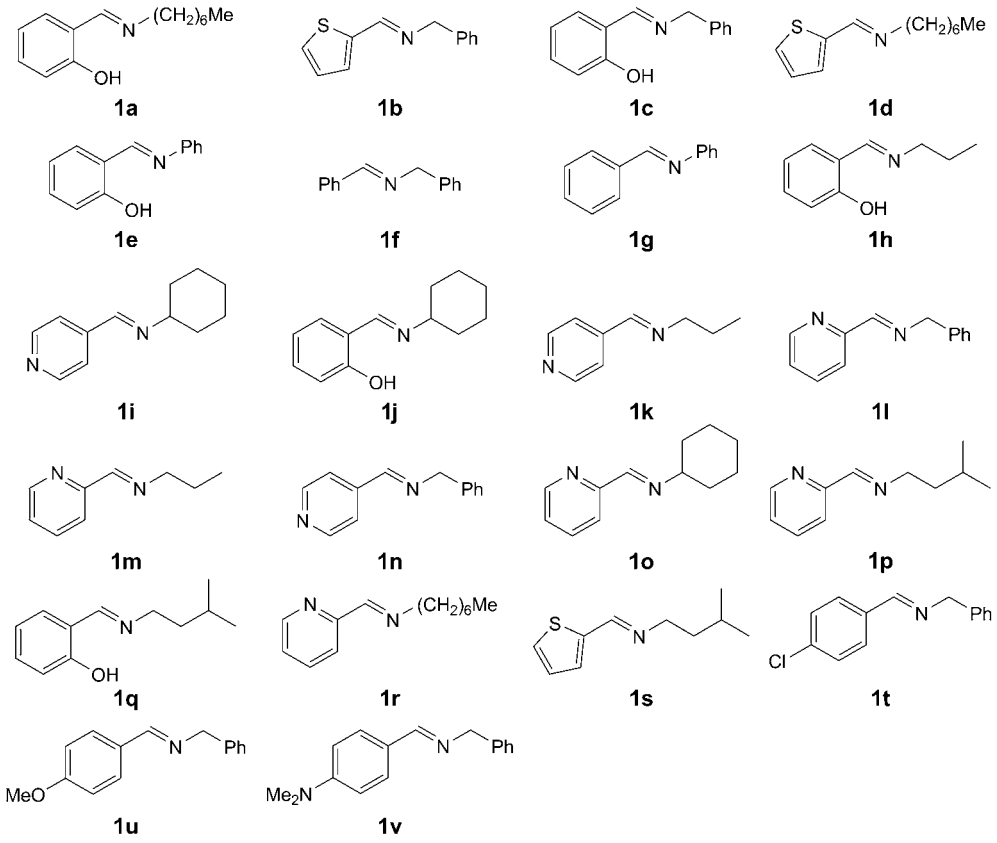


Fig. 1. *Structures of the imines used in the present study*

A crucial factor for fast imine/imine exchange was the structure of the studied imines, besides the solvent and catalytic additive. In a first set of experiments, imines with only aromatic substituents were used. In these reactions, exchange could not be achieved either without or with catalytic species. The intermediate aromatic amines generated in the catalytic process (according to [9]), depicted in *Scheme 2*, were not nucleophilic enough to condense with an intermediate aromatic aldehyde–proline adduct under the conditions of the experiments. As a consequence, mostly hydrolysis was observed. Next, the attempt to conduct the exchange reaction with imines derived from aliphatic amines and aliphatic aldehydes failed as well because of the fast hydrolysis of both imines selected for component exchange.

Finally, aliphatic/nucleophilic amines were condensed with electrophilic hetero-aromatic aldehydes (pyridin-2-, pyridin-4-, and 2-sulfanylbenzenecarboxaldehydes) as well as with salicylaldehyde to give the imines **1a** – **1d** and **1h** – **1s**. Using these substrates led to the desired C=N/C=N exchange that could be followed by ^{1}H-NMR (*Fig. 4*). No hydrolysis products were observed after completion of the reaction.

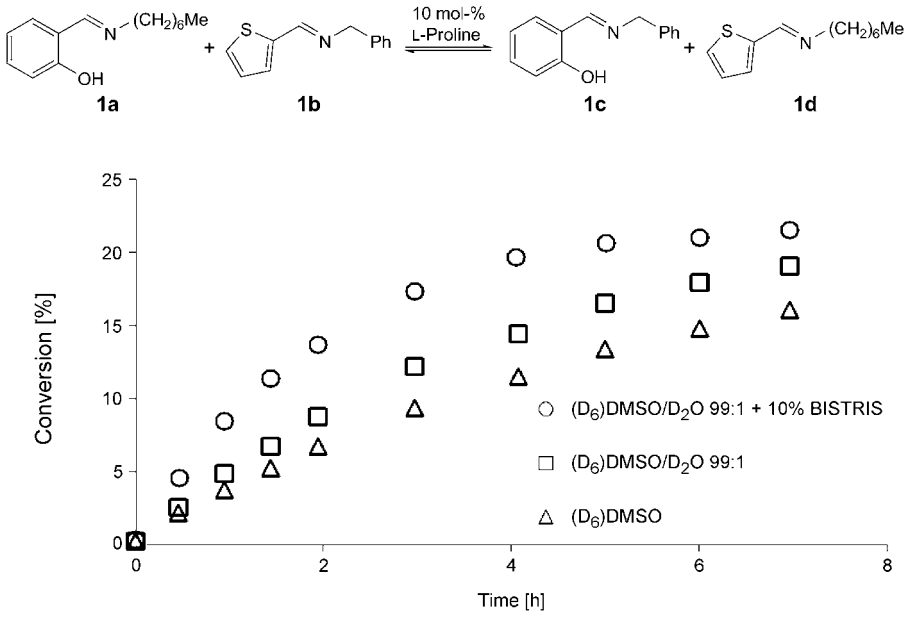


Fig. 2. *Influence of the addition of 1% D_2O and 10% BIS-TRIS in the presence of 10 mol-% L-proline in (D_6)DMSO solution*

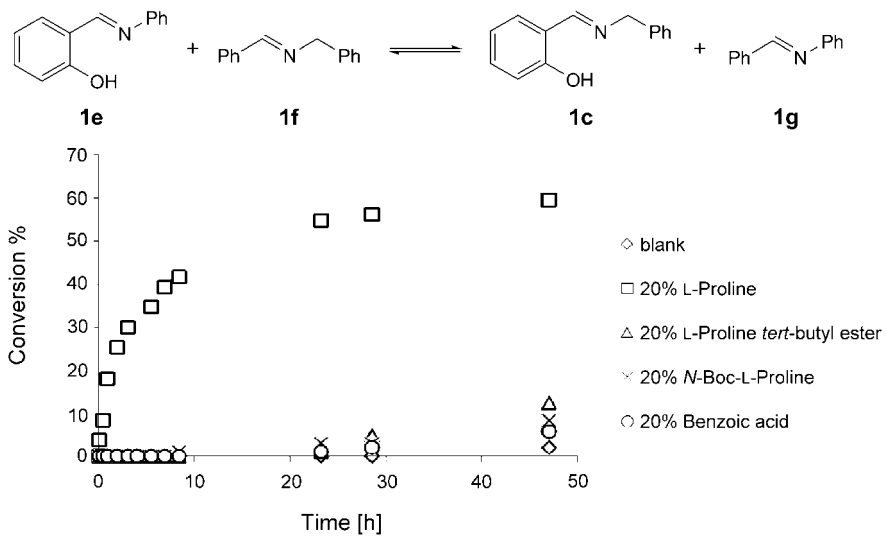


Fig. 3. *Screening for organocatalytic activity of L-proline, of its derivatives, and of benzoic acid on the imine exchange process shown above*

To evaluate the scope of the organocatalysis of imine/imine exchange, a number of [2×2] imine libraries were explored (*Table 1*). For each pair of imines, both the

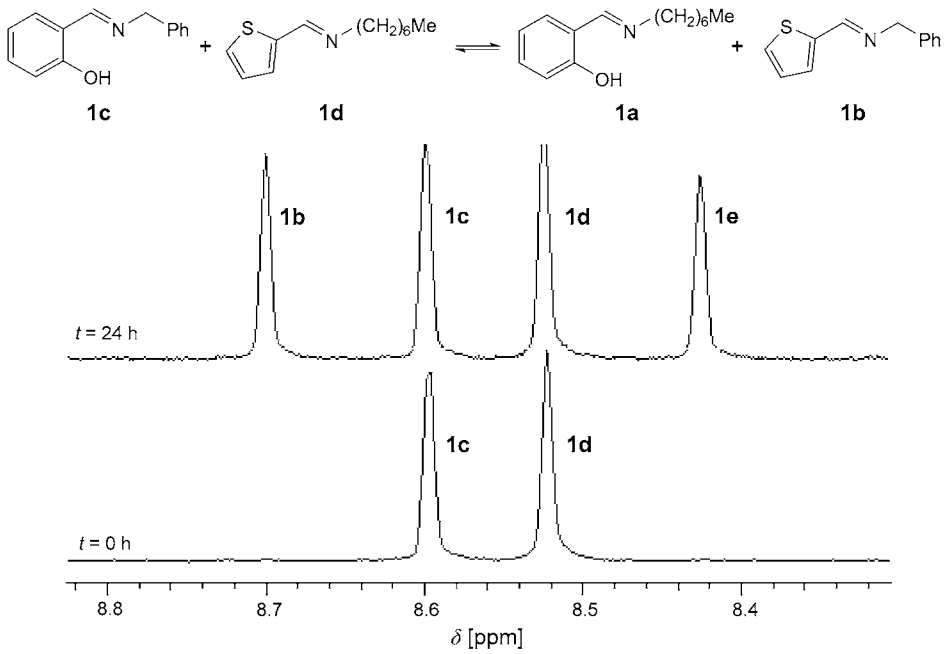


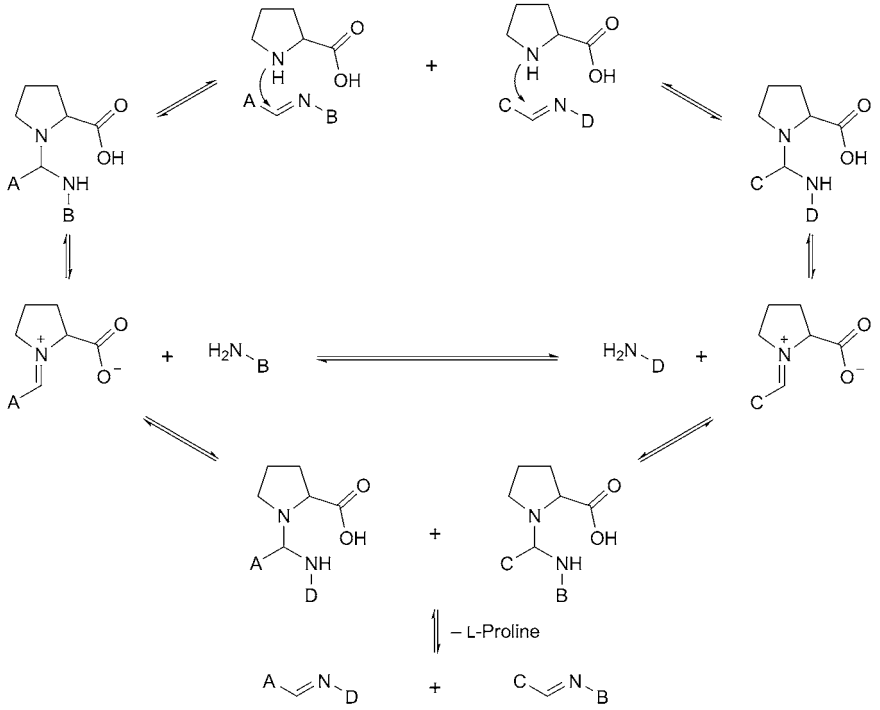
Fig. 4. *^{1}H-NMR Study of C=N/C=N exchange of* **1c** *and* **1d** *by observation of the signals of the imine H-atoms, –CH=N–, before* (*bottom*) *and after* (*top*) *exchange*

forward and reverse reactions were followed without (blank) or with added L-proline. Kinetic studies led to the calculated rates and equilibrium constants listed (see *Exper. Part*). The equilibrium constants of both the blank and the catalyzed reactions were in the same range, as expected.

An acceleration of the C=N/C=N exchange up to *ca.* 10.7-fold was achieved (*Table 1*, *Entry 4*). The accelerations of the forward and reverse reactions were similar. The equilibrium constants K_b and K_c obtained for the blank and catalyzed reactions in both the forward and backward directions were similar within experimental accuracy, indicating that the reactions were under thermodynamic control.

To explore the broader applicability of the present organocatalysis procedure to biology and material science, two $[3 \times 3]$ dynamic libraries of imines were generated (*Scheme 3*). Library 1 consisted of the previously studied imines **1h**, **1i**, and **1l** (see *Table 1*, *Entries 1–3*). Thus, the three $[2 \times 2]$ libraries can be directly compared to the equivalent $[3 \times 3]$ library based on the same three aldehydes and three amines. Here, an acceleration of 7.9-fold was observed, which corresponds to the exchange of *Entry 3*. Thus, the larger library reaches approximately the same rate constant as the fastest of the three smaller libraries. The second DCL consisted of **1c**, **1d**, and **1p**, and refers to the $[2 \times 2]$ libraries shown in *Entries 4–6* of *Table 1*. The rate constant lies between those of *Entry 5*, and *Entries 4* and *6*. The equilibrium constants were not calculated for the $[3 \times 3]$ libraries, as none of the possible reverse reactions was carried out.

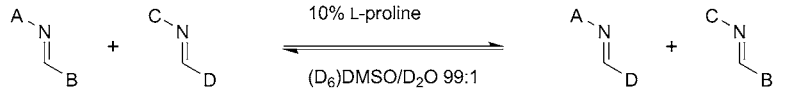
Scheme 2. *Proposed Mechanism for the Organocatalysis of C=N/C=N Exchange* [9]. Hydrolysis has not been represented in this mechanistic scheme.



2.2. *Organocatalysis of Benzylidene/Imine, C=C/C=N, Exchange Processes.* After the successful implementation of organocatalysis in the generation of DCLs of imines, we were interested in exploring its extension to other related reactions. In particular, the C=C/C=N exchange, involving two different types of double bonds, appeared of much value for generating dynamic libraries of constituents of increased diversity. Together with the reversibility of imine formation, the possibility that the condensations giving benzylidene-barbiturate derivatives may also be reversible [17] seemed to be a promising premise for achieving such an exchange process.

To this end, the benzylidene-barbiturates **2a**–**2d**, and imines **1b** and **1t**–**1v** were prepared from aromatic aldehydes bearing different substituents, and the cross-exchange between these substrates was studied. The reactions were carried out with stoichiometric amounts of benzylidene derivatives and imine compounds (19.35 mM each) first in a mixture of (D_6)DMSO/D_2O 99:1 at 60° with 10% L-proline as organocatalyst. As for the C=N/C=N exchange studies above, the reactions were conducted with addition of 1% D_2O, but without BIS-TRIS buffer due to fast hydrolysis of the benzylidenes under these conditions. Both the forward and reverse reactions were followed by ^{1}H-NMR spectroscopy. Compared to C=N/C=N exchange, a higher temperature was required. The proportions of the different compounds were determined by integration of the imine (CH=N) as well as of the benzylidene (CH=C)

Table 1. *Organocatalysis by* L-*Proline of a Set of Imine/Imine Exchange Reactions for [2 × 2] Imine Libraries in (D_6)DMSO/D_2O 99 : 1 and 10% BIS-TRIS Buffer at Room Temperature*



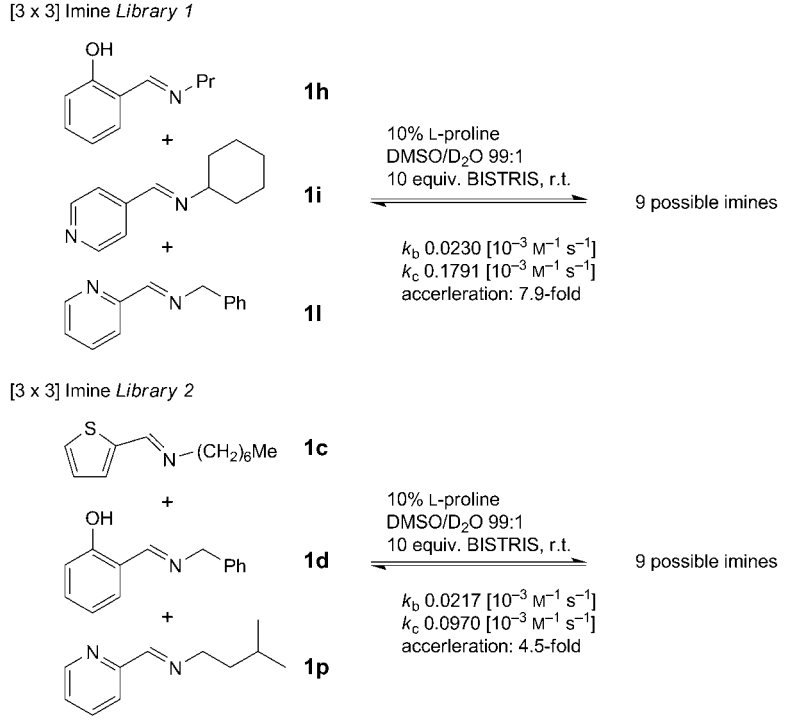
Entry	ER[a])	A[b])	B[b])	C[b])	D[b])		k_b[c])	k_c[d])	K_b[e])	K_c[f])	Acc[g])
1	**1h** + **1i**	Pr	2-HO–C_6H_4	cHex	Pyridin-4-yl	f[h])	0.0327	0.0849			2.6
	⇅								0.49	0.48	
	1j + **1k**					r[i])	0.0665	0.1770			2.7
2	**1h** + **1l**	Pr	2-HO–C_6H_4	Bn	Pyridin-2-yl	f	0.0128	0.0450			3.5
	⇅								2.13	1.74	
	1c + **1m**					r	0.0060	0.0258			4.3
3	**1i** + **1l**	cHex	Pyridin-4-yl	Bn	Pyridin-2-yl	f	0.0090	0.0621			6.9
	⇅								3.22	3.27	
	1n + **1o**					r	0.0028	0.0190			6.8
4	**1c** + **1d**	Heptyl	Thiophen-2-yl	Bn	2-HO–C_6H_4	f	0.0060	0.0636			10.6
	⇅								0.48	0.48	
	1a + **1b**					r	0.0124	0.1330			**10.7**
5	**1p** + **1c**	Isopentyl	Pyridin-2-yl	Bn	2-HO–C_6H_4	f	0.0808	0.1950			2.4
	⇅								1.58	1.30	
	1l + **1q**					r	0.0511	0.1500			2.9
6	**1p** + **1d**	Isopentyl	Pyridin-2-yl	Heptyl	Thiophen-2-yl	f	0.0295	0.2940			10.0
	⇅								0.75	0.89	
	1r + **1s**					r	0.0398	0.3303			8.3
7	**1h** + **1n**	Pr	2-HO–C_6H_4	Bn	Pyridin-4-yl	f	0.0209	0.1084			5.2
	⇅								1.72	1.99	
	1e + **1k**					r	0.0121	0.0545			4.5
8	**1h** + **1o**	Pr	2-HO–C_6H_4	cHex	Pyridin-2-yl	f	0.0441	0.1070			2.4
	⇅								0.93	0.99	
	1j + **1m**					r	0.0472	0.1077			2.3

[a]) ER, Exchange reaction. [b]) A – D: Substituents of the studied imines. [c]) k_b, Rate constant of the blank reaction [10^{-3} M^{-1} s^{-1}]. [d]) k_c, Rate constant of the catalyzed reaction [10^{-3} M^{-1} s^{-1}]. [e]) K_b, Equilibrium constant of the blank reaction = k_b(forward)/k_b(reverse). [f]) K_c, Equilibrium constant of the catalyzed reaction = k_c(forward)/k_c(reverse). [g]) Acc, Acceleration = k_c/k_b. [h]) f, Forward reaction. [i]) r, Reverse reaction.

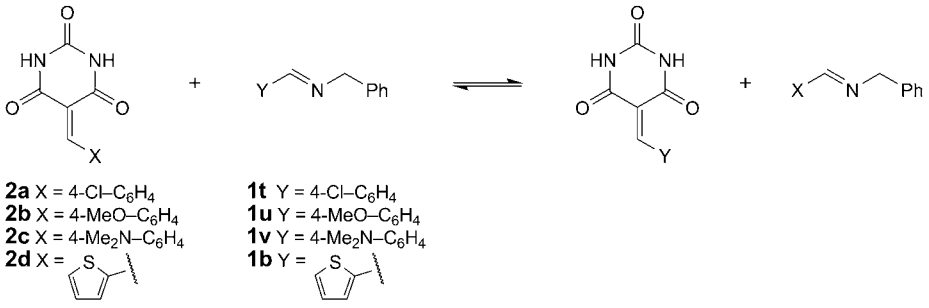
H-atom ^{1}H-NMR signals. In view of the marked hydrolysis occurring in the reactions (see below), the rate constants of the exchange reactions were not determined. The results are illustrated in *Scheme 4* and compiled in *Table 2*. In all cases, the compositions of the mixtures are given for a reaction time at which no further change in compound-% was observed.

The ability of benzylidene-barbiturates and imines to undergo exchange was probed by considering the effect of the substituents on the vinylidene head groups of

Scheme 3. *Imine Exchange in Two [3 × 3] Imine Libraries – Applicability of Organocatalysis to Larger Libraries for Increasing Diversity*



Scheme 4. *Representation of the Cross-Exchange C=C/C=N Reaction between the Benzylidene-barbiturate Derivatives* **2a**–**2d** *and Different Imines*



both starting materials. Thus, the reaction between the benzylidene-barbiturate **2c**, bearing an electron-donating group (EDG), and the imine **1t**, bearing an electron-withdrawing group (EWG), gave only the imine **1v**, but the expected new benzylidene-barbiturate **2a** did not form, due to hydrolysis (*Table 2*, *Entry 1*). The ^{1}H-NMR spectrum of the equilibrated mixture (*Fig. 5*) showed a new signal at 5.9 ppm, which is

Table 2. *Proportions* [%] *of Different Compounds in the Cross-Exchange Reactions C=C/C=N between Benzylidene-barbiturates and Imines in (D_6)DMSO/D_2O 99:1 at 60°* (*Scheme 4*). **g** = 4-Chlorobenzaldehyde, **h** = 4-methoxybenzaldehyde, **i** = 4-(dimethylamino)benzaldehyde, **j** = thiophene-2-carboxaldehyde, **l** = 4-chlorobenzaldehyde hydrate, **m** = 4-methoxybenzaldehyde hydrate, **n** = 4-(dimethylamino)-benzaldehyde hydrate, and **o** = thiophene-2-carboxaldehyde hydrate.

Entry[a])	Reaction time [h]	Compound distribution [%]							
		Starting compounds **2c** + **1t**							
		2c	**1t**	**2a**	**1v**	**g**	**i**	**l**	**n**
1b	0	48	52	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	5	35	36	< 1[c])	10	1	13	5	–[b])
	30	17	21	< 1[c])	11	20	20	11	–[b])
1c	0	48	52	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	5	6	22	< 1[c])	7	19	29	17	–[b])
		Starting compounds **2a** + **1v**							
		2a	**1v**	**2c**	**1t**	**g**	**i**	**l**	**n**
2b	0	28	48	–[b])	–[b])	15	< 1[c])	9	–[b])
	6	< 1[c])	14	21	21	16	14	14	–[b])
	20	< 1[c])	9	16	22	22	18	13	–[b])
2c	0	30	46	–[b])	2	1	14	7	–[b])
	6	< 1[c])	5	8	21	18	30	18	–[b])
		Starting compounds **2c** + **1b**							
		2c	**1b**	**2d**	**1v**	**i**	**j**	**n**	**o**
3b	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	4	43	43	7	7	1	< 1[c])	–[b])	1
	24	20	20	24	25	4	3	–[b])	5
3c	0	45	55	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	4	11	18	16	20	19	5	0	11
		Starting compounds **2d** + **1v**							
		2d	**1v**	**2c**	**1b**	**i**	**j**	**n**	**o**
4b	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	2	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	27	21	21	15	18	12	7	–[b])	6
4c	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	3	13	14	7	17	25	12	–[b])	12
		Starting compounds **2b** + **1v**							
		2b	**1v**	**2c**	**1u**	**h**	**i**	**m**	**n**
5b	0	49	51	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	1	42	47	2	1	4	< 1[c])	4	–[b])
	6	4	17	24	22	16	7	10	–[b])
5c	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	1	2	12	14	21	15	21	15	–[b])
		Starting compounds **2c** + **1u**							
		2c	**1u**	**2b**	**1v**	**h**	**i**	**m**	**n**
6b	0	52	48	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	2	49	48	< 1[c])	2	1	< 1[c])	< 1[c])	–[b])
	22	26	23	1	16	16	8	10	–[b])
6c	0	48	52	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	2	23	23	1	14	16	12	11	–[b])

[a]) b, Blank reactions; c, catalyzed reactions with 10 mol-% L-proline as catalyst. [b]) Compound not observed. [c]) Only traces of product detected.

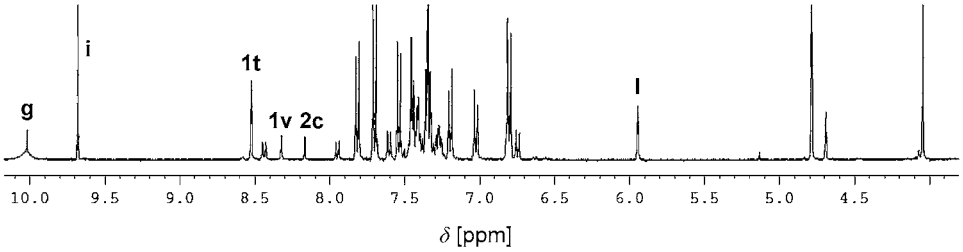


Fig. 5. ^{1}H-NMR *Spectrum of the products of the exchange reaction between* **2c** *and* **1t** *at equilibrium.* The characteristic –CH= peaks are indicated for **2c**, **1t**, **1v**, 4-chlorobenzaldehyde (**g**), 4-(dimethylamino)-benzaldehyde (**i**), and 4-chlorobenzaldehyde hydrate (**l**) in (D_6)DMSO/D_2O 99 : 1.

assigned to the –C*H*$(OH)_2$ H-atom of 4-chlorobenzaldehyde hydrate. The formation of **2a** is apparently hindered by the tendency of 4-chlorobenzaldehyde to give a hydrate at equilibrium. It was assumed that decreasing the hydration tendency of the aldehyde of the imine by replacing the EWG by an EDG would favor its condensation with barbiturate to give the *Knoevenagel* product in this medium.

Conversely, the backward reaction was performed by mixing compounds **2a** and **1v** in a 1 : 1 ratio in the same solvent (*Table 2*, *Entry 2*). Both starting compounds hydrolyzed over a few hours (as followed by observation of the aldehydes formed) after mixing. Simultaneously, the exchanged new compounds, the benzylidene-barbiturate **2c** and the imine **1t**, were progressively formed, but at the end of the reaction the hydrolyzed compounds were predominant. The 4-chlorobenzaldehyde recombined partially with the benzylamine to form **1v**, while the 4-(dimethylamino)benzaldehyde gave only a small amount of the condensation product with barbiturate **2c**. The addition of L-proline increased the speed of the reaction, leading to completion within 6 h compared to 20 h in the absence of L-proline.

Next, the structure of the starting material was chosen, taking into account the outcome of experiments of *Entries 3* and *4* in *Table 2*. Thus, the interconversion of **2c** and **1b**, both bearing EDGs, was examined. As anticipated, these substrates were more suitable for the cross-exchange than molecules with EWGs, and both products **2d** and **1v** were formed (*Table 2*, *Entry 3*). Again, the hydrolysis products 4-(dimethylamino)benzaldehyde and thiophene-2-carboxaldehyde were observed. Conducting the opposite experiment, starting with **2d** and **1v** (*Table 2*, *Entry 4*), components **2c** and **1b** were obtained in comparable amounts as in the forward case above, indicating that the reaction was reversible and under thermodynamic control.

Finally, the exchange reaction of **2b** and **1v**, both bearing EDGs, gave **2c** and **1u** (*Table 2*, *Entry 5*). In the reverse process, starting with **2c** and **1u**, compound **1v** was obtained in significant amounts. However, only very little **2b** was formed, but large amounts of the corresponding aldehyde and its hydrate, due to hydrolysis.

To avoid, or at least to reduce the amount of hydrolysis, exchange reactions were performed in presence of lower amounts of H_2O. The reaction between **2b** and **1v** was run with 0.5% ((D_6)DMSO/D_2O 99.5 : 0.5) as well as with only 0.2% ((D_6)DMSO/D_2O 99.8 : 0.2) added H_2O. The products **2c** and **1u** were obtained under these conditions (averaging 20% each), along with large amounts of hydrolysis products.

As a further exploration to decrease the hydrolysis products, we conducted the benzylidene/imine exchange in pure (D_6)DMSO (given as containing less than 0.02% of H_2O) at 60°. The reaction of benzylidene **2b** with imine **1v** (*Table 3*; *Entry 1*), both bearing EDGs, gave **2c** and **1u**. The equilibrium was reached after 2 h in the presence of L-proline as compared to 22 h in its absence. Under these conditions, the hydrolysis products amounted now to less than 10%. The reverse process, starting with **2c** and **1u**, furnished **2b** and **1v** in similar amounts as the forward reaction. Finally, the exchange reaction between **2d** and **1v** (*Table 3*, *Entry 3*), and its reverse reaction **2c** and **1b** (*Table 3*, *Entry 4*) yielded the exchanged compounds in comparable amounts, indicat-

Table 3. *Proportions* [%] *of Different Compounds in the Cross Exchange Reactions C=C/C=N between Benzylidene-barbiturates and Imines in (D_6)DMSO at 60°.* **h** = 4-Methoxybenzaldehyde, **i** = 4-(dimethylamino)benzaldehyde, **j** = thiophene-2-carboxaldehyde, **m** = 4-methoxybenzaldehyde hydrate, **n** = 4-(dimethylamino)benzaldehyde hydrate and, **o** = thiophene-2-carboxaldehyde hydrate.

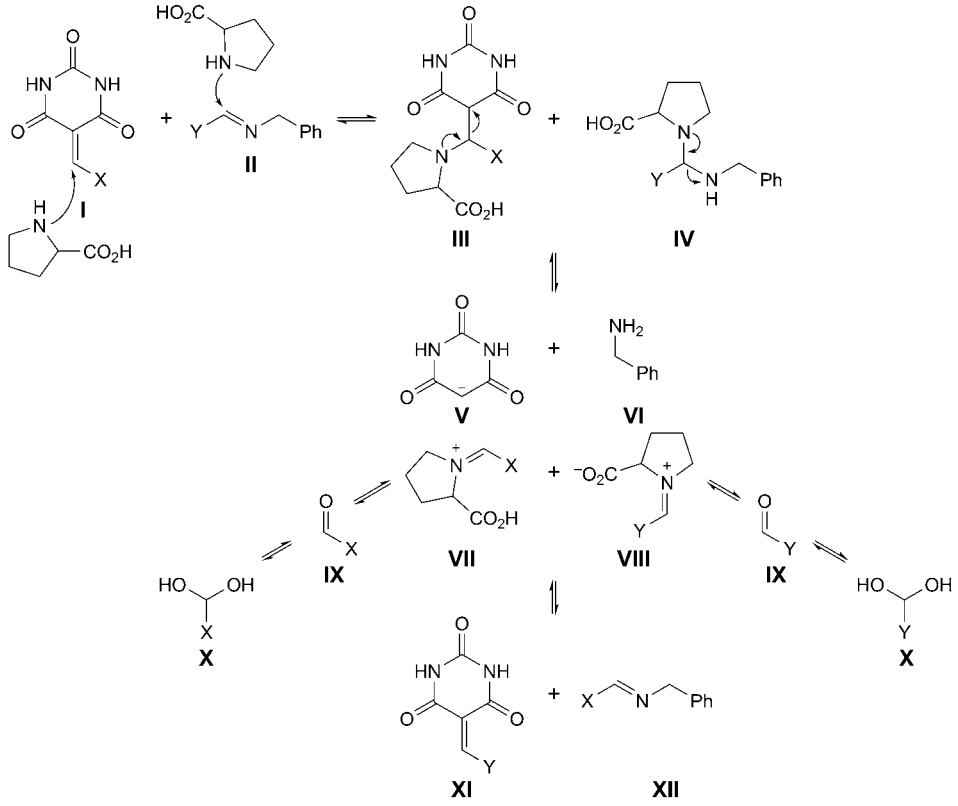
Entry[a])	Reaction time [h]	Compound distribution [%]							
		Starting compounds **2b** + **1v**							
		2b	**1v**	**2c**	**1u**	**h**	**i**	**m**	**n**
*1*b	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	2	50	50	< 1[c])	< 1[c])	< 1[c])	< 1[c])	< 1[c])	–[b])
	22	7	12	34	33	7	3	4	–[b])
*1*c	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	2	5	9	32	33	8	7	6	–[b])
		Starting compounds **2c** + **1u**							
		2c	**1u**	**2b**	**1v**	**h**	**i**	**m**	**n**
*2*b	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	2	49	49	1	1	< 1[c])	< 1[c])	< 1[c])	–[b])
	24	39	39	7	10	3	< 1[c])	2	–[b])
*2*c	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	2	34	32	4	12	7	5	6	–[b])
		Starting compounds **2d** + **1v**							
		2d	**1v**	**2c**	**1b**	**i**	**j**	**n**	**o**
*3*b	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	3	50	50	< 1[c])	< 1[c])	< 1[c])	< 1[c])	–[b])	< 1[c])
	66	28	27	20	20	3	< 1[c])	–[b])	2
*3*c	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	3	21	28	16	20	10	< 1[c])	–[b])	5
		Starting compounds **2c** + **1b**							
		2c	**1b**	**2d**	**1v**	**i**	**j**	**n**	**o**
*4*b	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	4	42	44	7	7	< 1[c])	< 1[c])	–[b])	< 1[c])
	25	22	24	26	26	< 1[c])	1	–[b])	1
*4*c	0	50	50	–[b])	–[b])	–[b])	–[b])	–[b])	–[b])
	4	16	24	23	29	4	< 1[c])	–[b])	4

[a]) *b*, Blank reactions, and *c*, catalyzed reactions with 10 mol-% L-proline as catalyst. [b]) Compound not observed. [c]) Only traces of product detected.

ing again that the reaction was reversible and at equilibrium. Under these conditions, L-proline performed marked organocatalysis, as it accelerated the reaction from six-fold (*Table 3*, *Entry 4*) up to 22-fold (*Table 3*, *Entry 3*), when one compares the blank reaction at the same reaction time as that of the completed catalyzed reaction.

From the results mentioned above, and taking into account the occurrence of hydrolysis, the mechanism of the C=C/C=N exchange in the presence of L-proline may be outlined by *Scheme 5*, following sequential hydrolysis/condensation steps (see also [18]). It may be considered to involve addition of L-proline on the benzylidene and imine conjugate leading to an iminium intermediate by addition–elimination, followed by condensation of the released anionic barbiturate and benzylamine with the aldehydes resulting from the cleavage. Besides, the formation of the hydrates [18] of the aldehydes bearing EWGs resists the formation of the exchanged products.

Scheme 5. *Possible Mechanism of the Cross-Exchange between a* Knoevenagel-*Type Substrate* (C=C) *and an Imine* (C=N) *Following Sequential Hydrolysis/Condensation Steps* [19]



3. Conclusions. – The results described above lead to the following conclusions. Significant organocatalysis can be achieved in DCC processes. The secondary amine L-proline is an efficient organocatalyst to enable and accelerate C=N/C=N imine-

exchange reactions at a catalyst-loading of 10 mol-%, achieving accelerations up to *ca.* 10.7-fold at ambient temperature. Imines derived from aliphatic/nucleophilic amines and highly electrophilic aldehydes were found to be the most suitable starting components, giving only the exchange and no hydrolysis products after completion of the reaction. In contrast, the C=C/C=N interconversion of *Knoevenagel* substrates and imines could not be performed under similar conditions, as extensive hydrolysis was occurring. Conducting the reactions in pure (D_6)DMSO greatly reduced hydrolysis (less than 10%), and C=C/C=N exchange took place, displaying marked acceleration by L-proline. Compounds bearing electron-donating substituents gave the least hydrolysis in the cross-exchange. The results described herein stress the potential of organocatalysis for DCC, facilitating the formation of dynamic libraries and allowing for increased diversity generation.

Experimental Part

General. Reagents (heptylamine (99%), thiophene-2-carboxaldehyde (98%), benzaldehyde (98%), propylamine (98%), pyridine-4-carboxaldehyde (97%), pyridine-4-carboxaldehyde (99%), cyclohexylamine (99%), 4-(dimethylamino)benzaldehyde (99%), barbituric acid (99%), 1,3-dimethylbarbituric acid (99%), benzylamine (99%), isopentylamine (99%), 2-bis(2-hydroxyethyl)amino-2-(hydroxymethyl)propane-1,3-diol (BIS-TRIS; 99%) were purchased from *Aldrich Chemical*. Salicylaldehyde (99%) and 4-methoxybenzaldehyde (98%) purchased from *Alfa Aesar*. L-Proline (99%) and 4-chlorobenzaldehyde (98%), purchased from *Avocado* and *Lancaster*, resp., were used as received from commercial suppliers. Deuterated solvents were purchased from *Euriso-TOP* and used without further purification. Anh. CH_2Cl_2 was obtained by passage through columns of activated molecular sieves. Yields refer to homogenous, anal. pure (^{1}H-NMR) material, and have not been optimized. Deionized water was obtained from a *Millipore Synergy 185* water purifier. All pH and pD measurements were recorded with a *Mettler-Toledo Multi-Seven pH meter* using a *Hamilton Spintrodemini* probe. The pD values were uncorrected. Column chromatography (CC): *Geduran* silica gel *60* (230–400 mesh, 40–63 μm, *Merck*). M.p.: *Büchi B-540* apparatus. NMR Spectra: *Bruker Avance 400* spectrometer; referenced to the solvent; δ in ppm, J in Hz. High-resolution (HR) MS: *Bruker Micro TOF* mass spectrometer; in m/z (rel. %). Elemental analysis: *Flash 2000* from *Thermo Fisher Scientific*.

General Procedure for the Synthesis of Imines. Equimolar amounts of amine and aldehyde were dissolved in dry CH_2Cl_2, and $MgSO_4$ was added. The mixture was stirred at r.t. for 24 h – 5 d, and the solid was filtered off. After drying or distillation under vacuum, the product were isolated as colored oils or needles.

General Procedure for the Synthesis of Knoevenagel *Condensation Products.* To 30 ml of anh. EtOH were added barbituric acid (3.0 mmol), the corresponding substituted benzaldehyde (3.0 mmol), and L-proline in a cat. amount (10%). The soln. was then refluxed for 3–4 h. The *Knoevenagel* condensation products that precipitated out of the cooled soln. were filtered and washed with Et_2O.

General Procedure for C=N/C=N Exchange. All reactions with two imines were carried out at r.t. with a final concentration of 19.35 mM and a total volume of 620 μl with 10 equiv. of BIS-TRIS to maintain a constant pH. For mixtures of three imines, the final concentration was *ca.* 14.63 mM and the total volume of 615 μl. All stock solns. of reactants and catalyst were 60 mM and had a total volume of 1 ml. The BIS-TRIS stock soln. was 600 mM.

All measurements were repeated three times. The reproducibility of the values obtained was ±2%.

General Procedure for C=N/C=N Exchange of Two Imines. A NMR tube was first charged with 200 μl of BIS-TRIS stock soln. (600 mM in (D_6)DMSO/D_2O 99:1). For the catalyzed reaction, 20 μl of a L-proline stock soln. (60 mM in (D_6)DMSO/D_2O 99:1) was added. For the uncatalyzed reaction, 20 μl of (D_6)DMSO/D_2O 99:1 were mixed with 200 μl of BIS-TRIS stock soln. (600 mM in (D_6)DMSO/D_2O

99 : 1) in another NMR tube. To these prepared solns., 200 µl of each imine soln. (60 mM in (D_6)DMSO/D_2O 99 : 1) were added, and the NMR spectra were recorded immediately after mixing.

General Procedure for C=C/C=N Exchange. Stock solns. (0.50 ml) of *Knoevenagel* and imine products (60 mM) in (D_6)DMSO/D_2O 99 : 1 were freshly prepared. For the uncatalyzed reaction, 200 µl of each soln. was added to a NMR tube then followed by 220 µl of (D_6)DMSO/D_2O 99 : 1 to adjust to a final volume as 620 µl. For the catalyzed reaction, 20 µl of a L-proline stock soln. (60 mM in (D_6)DMSO/D_2O 99 : 1) were added to a NMR tube, followed by the addition of 200 µl of each soln. and 200 µl of (D_6)DMSO/D_2O 99 : 1. The procedure for C=C/C=N exchange under condition (D_6)DMSO was similar to that with (D_6)DMSO/D_2O 99 : 1.

Kinetics of C=N/C=N Exchange. The rate constants were determined by integration of the imine H-atom ^{1}H-NMR signals as a function of time and analyzing the curves obtained. The imine-exchange reactions were found to follow the kinetic equation for equilibrium reactions [16]. The rate constants for the forward and reverse reaction were calculated as follows:

$$[A] + [B] k_f k_r [C] + [D] \tag{1}$$

$$-d([A] - [A_{eq}])/dt = k([A] - [A_{eq}]) \tag{2}$$

The equilibrium constants were calculated using the rate constants for the forward and reverse reaction.

$$K_{eq} = k_f/k_r \tag{3}$$

*2-[(*E*)-(Heptylimino)methyl]phenol* (**1a**) [20]. Yield: 2.08 g, 99%. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.89 (*t*, *J* = 6.72, 3 H); 1.46 – 1.20 (*m*, 8 H); 1.75 – 1.65 (*m*, 2 H); 3.58 (*t*, *J* = 6.82, 2 H); 6.86 (*t*, *J* = 7.44, 1 H); 6.96 (*d*, *J* = 8.25, 1 H); 7.24 (*d*, *J* = 6.32, 1 H); 7.32 – 7.26 (*m*, 1 H); 8.33 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 14.0; 22.6; 27.1; 29.0; 30.9; 31.7; 59.5; 117.0; 118.3; 118.8; 131.0; 132.0; 161.4; 164.4. ESI-MS: 220.2 (100). HR-ESI-MS: 220.170 ($[M+H]^+$, $C_{14}H_{22}NO^+$; calc. 220.170).

N-*[(1*E*)-Thiophen-2-ylmethylidene]benzenemethanamine* (**1b**) [15]. Yield: 1.93 g, 90%. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.80 (*s*, 2 H); 7.15 – 6.96 (*m*, 1 H); 7.39 – 7.23 (*m*, 6 H); 7.41 (*d*, *J* = 5.0, 1 H); 8.46 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 64.4; 127.0; 127.3; 128.0; 128.5; 129.0; 130.6; 139.0; 142.4; 155.2. ESI-MS: 202.1 (100). HR-ESI-MS: 202.070 ($[M+H]^+$, $C_{12}H_{12}NS^+$; calc. 202.068).

*2-[(*E*)-(Benzylimino)methyl]phenol* (**1c**) [21]. Yield: 0.143 g, 68%. Yellow needles. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.82 (*s*, 2 H); 6.89 (*t*, *J* = 7.5, 1 H); 6.97 (*d*, *J* = 8.3, 1 H); 7.40 – 7.25 (*m*, 7 H); 8.45 (*s*, 1 H); 13.41 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 63.2; 117.1; 118.6; 118.8; 127.4; 127.8; 127.9; 128.7; 131.4; 132.4; 138.2; 161.2; 165.6. ESI-MS: 212.1 (100). HR-ESI-MS: 212.107 ($[M+H]^+$, $C_{14}H_{14}NO^+$; calc. 212.107).

N-*[(*E*)-Thiophen-2-ylmethylidene)]heptan-1-amine* (**1d**) [22]. Yield: 1.68 g, 75%. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (*t*, *J* = 6.5, 3 H); 1.21 – 1.39 (*m*, 9 H); 1.64 – 1.72 (*m*, 2 H); 3.56 (*t*, *J* = 7.1, 2 H); 7.06 (*t*, *J* = 4.2, 1 H); 7.28 (*d*, *J* = 3.5, 2 H); 7.38 (*d*, *J* = 4.8, 2 H); 8.35 (*s*, 1 H). ESI-MS: 210.131 (100). HR-ESI-MS: 210.131 ($[M+H]^+$, $C_{12}H_{20}NS^+$; calc. 210.131).

N-*[(1*E*)-Phenylmethylidene]benzenemethanamine* (**1f**) [23]. Yield: 0.463 g, 79 %. Yellow oil. ^{1}H-NMR (400 MHz, (D_6)DMSO): 4.78 (*s*, 2 H); 7.25 – 7.30 (*m*, 1 H); 7.33 – 7.38 (*m*, 4 H); 7.45 – 7.49 (*m*, 3 H); 7.78 – 7.81 (*m*, 2 H); 8.52 (*s*, 1 H).

*2-[(*E*)-(Propylimino)methyl]phenol* (**1h**) [24]. Yield: 3.39 g, 75 %. Yellow oil. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.92 (*t*, *J* = 7.34, 3 H); 1.64 (*sext.*, *J* = 7.0, 2 H); 3.54 (*t*, *J* = 6.7, 2 H); 6.94 – 6.78 (*m*, 2 H); 7.31 (*t*, *J* = 7.8, 1 H); 7.42 (*d*, *J* = 7.5, 1 H); 8.53 (*s*, 1 H). ESI-MS: 164.1 (100). HR-ESI-MS: 164.107 ($[M+H]^+$, $C_{10}H_{14}NO^+$; calc. 164.107).

N-*[(1*E*)-Pyridin-4-ylmethylidene]cyclohexanamine* (**1i**) [25]. Yield: 1.99 g, quant. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.20 – 1.42 (*m*, 3 H); 1.57 (*ddd*, *J* = 15.0, 12. 7, 3.2, 2 H); 1.76 – 1.63 (*m*, 3 H); 1.90 – 1.77 (*m*, 2 H); 3.47 – 2.92 (*m*, 1 H); 7.57 (*d*, *J* = 5.9, 2 H); 8.27 (*s*, 1 H); 8.65 (*d*, *J* = 5.9, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 24.5; 25.5; 34.1; 70.0; 121.9; 143.3; 150.3; 156.5. ESI-MS: 189.1 (100). HR-ESI-MS: 189.138 ($[M+H]^+$, $C_{12}H_{17}N_2^+$; calc. 189.139).

*2-[(*E*)-(Cyclohexylimino)methyl]phenol* (**1j**) [26]. Yield: 1.80 g, 93%. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.46–1.23 (*m*, 3 H); 1.61–1.49 (*m*, 2 H); 1.65 (*d*, *J* = 11.4, 1 H); 1.88–1.77 (*m*, 4 H); 3.24 (*t*, *J* = 9.8, 1 H); 6.86 (*t*, *J* = 7.4, 1 H); 6.95 (*d*, *J* = 8.3, 1 H); 7.24 (*d*, *J* = 7.6, 1 H); 7.32–7.26 (*m*, 1 H); 8.36 (*s*, 1 H); 13.83 (*s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 24.3; 25.5; 34.3; 67.4; 117.0; 118.3; 118.9; 131.0; 131.9; 161.5. ESI-MS: 204.1 (100). HR-ESI-MS: 204.137 ($[M+H]^+$, $C_{13}H_{18}NO^+$; calc. 204.138).

*(*E*)-*N*-(Pyridin-4-ylmethylene)propan-1-amine* (**1k**) [27]. Yield: 1.49 g, 95%. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.95 (*t*, *J* = 7.4, 3 H); 1.74 (*sext.*, *J* = 7.2, 2 H); 3.62 (*t*, *J* = 6.8, 2 H); 7.58 (*d*, *J* = 5.3, 2 H); 8.25 (*s*, 1 H); 8.67 (*d*, *J* = 5.2, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 60.6; 63.6; 73.6; 88.3; 93.6; 95.4; 97.6. ESI-MS: 149.1 (100). HR-ESI-MS: 149.107 ($[M+H]^+$, $C_9H_{13}N_2^+$; calc. 149.107).

N-*[(1*E*)-Pyridin-2-ylmethylidene]benzenemethanamine* (**1l**) [28]. Yield: 0.947 g, 92%. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.88 (*s*, 2 H); 7.30 (*ddd*, *J* = 4.9, 7.5, 15.8, 2 H); 7.35 (*d*, *J* = 4.2, 4 H); 7.74 (*t*, *J* = 7.7, 1 H); 8.07 (*d*, *J* = 7.9); 8.49 (*s*, 1 H); 8.65 (*d*, *J* = 4.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 64.9; 121.3; 124.8; 127.1; 128.1; 128.5; 136.5; 138.6; 149.4; 154.5; 162.8. ESI-MS: 197.1 (100). HR-ESI-MS: 197.108 ($[M+H]^+$, $C_{13}H_{13}N_2^+$; calc. 197.107).

N-*[(1*E*)-Pyridin-2-ylmethylidene]propan-1-amine* (**1m**) [29]. Yield: 0.357 g, 80%. Orange oil. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.95 (*t*, *J* = 7.4, 3 H); 1.74 (*sext.*, *J* = 7.2, 2 H); 3.63 (*t*, *J* = 6.9, 2 H); 7.28 (*ddd*, *J* = 1.1, 4.9, 7.4, 1 H); 7.72 (*dt*, *J* = 1.6, 7.7, 1 H); 7.97 (*d*, *J* = 7.9, 1 H); 8.36 (*s*, 1 H); 8.63 (*d*, *J* = 4.80, 1 H). ESI-MS: 149.1 (100). HR-ESI-MS: 149.107 ($[M+H]^+$, $C_9H_{13}N_2^+$; calc. 149.107).

N-*[(1*E*)-Pyridin-4-ylmethylidene]benzenemethanamine* (**1n**) [30]. Yield: 1.87 g, 90%. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.87 (*s*, 2 H); 7.39–7.24 (*m*, 5 H); 7.63 (*d*, *J* = 4.8, 2 H); 8.36 (*s*, 1 H); 8.69 (*d*, *J* = 4.9, 2 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 65.0; 122.0; 127.2; 128.0; 138.4; 142.8; 150.4; 159.8. ESI-MS: 197.1 (100). HR-ESI-MS: 197.107 ($[M+H]^+$, $C_{13}H_{13}N_2^+$; calc. 197.107).

N-*[(1*E*)-Pyridin-2-ylmethylidene]cyclohexanamine* (**1o**) [25]. Yield: 1.80 g, 91%. Orange oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 1.31–1.17 (*m*, 1 H); 1.37 (*dd*, *J* = 25.0, 12.3, 2 H); 1.64–1.52 (*m*, 2 H); 1.68 (*d*, *J* = 12.5, 1 H); 1.79 (*dd*, *J* = 28.1, 12.2, 4 H); 3.38–3.19 (*m*, 1 H); 7.29 (*d*, *J* = 6.0, 1 H); 7.71 (*t*, *J* = 7.6, 1 H); 7.98 (*d*, *J* = 7.8, 1 H); 8.39 (*s*, 1 H); 8.63 (*d*, *J* = 4.3, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 24.7; 25.6; 34.1; 68.6; 121.3; 124.5; 136.5; 149.3; 154.9; 159.5. ESI-MS: 189.1 (100). HR-ESI-MS: 189.141 ($[M+H]^+$, $C_{12}H_{17}N_2^+$; calc. 189.139).

3-Methyl-N-*[(1*E*)-pyridin-2-ylmethylidene]butan-1-amine* (**1p**). Yield: 0.492 g, 93%. Orange oil. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.97 (*d*, *J* = 6.5, 6 H); 1.63 (*q*, *J* = 7.2, 2 H); 1.71 (*octet*, *J* = 6.7, 1 H); 3.71 (*t*, *J* = 7.3, 2 H); 7.32 (*m*, 1 H); 7.75 (*dt*, *J* = 1.5, 7.7, 1 H); 8.00 (*d*, *J* = 7.9, 1 H); 8.40 (*s*, 1 H); 8.66 (*d*, *J* = 4.6, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.4; 25.4; 39.3; 58.5; 120.3; 125.0; 136.8; 149.3; 154.2; 161.5. Anal. calc. for $C_{11}H_{16}N_2$ (176.258): C 74.96, H 9.15, N 15.89; found: C 74.87, H 9.16, N 15.69. ESI-MS: 177.1 (100). HR-ESI-MS: 177.138 ($[M+H]^+$, $C_{11}H_{17}N_2^+$; calc. 177.139).

*2-[(*E*)-[(3-Methylbutyl)imino]methyl]phenol* (**1q**) [31]. Yield: 0.489 g, 85%. Orange oil. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.99 (*d*, *J* = 6.6, 6 H); 1.62 (*q*, *J* = 7.1, 2 H); 1.76 (*m*, 1 H); 3.64 (*t*, *J* = 7.1, 2 H); 6.90 (*t*, *J* = 7.5, 1 H); 6.99 (*d*, *J* = 8.3, 1 H); 7.27 (*d*, *J* = 7.6, 1 H); 7.33 (*t*, *J* = 7.5, 1 H); 8.37 (*s*, 1 H); 13.73 (br. *s*, 1 H). ESI-MS: 192.1 (100). HR-ESI-MS: 192.139 ($[M+H]^+$, $C_{12}H_{18}NO^+$; calc. 192.138).

N-*[(1*E*)-Pyridin-2-ylmethylidene]heptan-1-amine* (**1r**) [32]. Yield: 0.368 g, 86%. Brown oil. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.84 (*t*, *J* = 6.8, 3 H); 1.36–1.13 (*m*, 8 H); 1.68–1.52 (*m*, 2 H); 3.61 (*t*, *J* = 6.4, 2 H); 7.55–7.31 (*m*, 1 H); 7.85 (*dt*, *J* = 7.7, 1.6, 1 H); 7.94 (*d*, *J* = 7.8, 1 H); 8.32 (*s*, 1 H); 8.62 (*d*, *J* = 4.8, 1 H). ESI-MS: 205.2 (100). HR-ESI-MS: 205.170 ($[M+H]^+$, $C_{13}H_{21}N_2^+$; calc. 205.170).

3-Methyl-N-*[(1*E*)-thiophen-2-ylmethylidene]butan-1-amine* (**1s**) [22]. Yield: 0.314 g, 81%. Yellow oil. ^{1}H-NMR (400 MHz, (D_6)DMSO): 0.90 (*dd*, *J* = 6.5, 3.3, 6 H); 1.46 (*dd*, *J* = 14.0, 7.0, 2 H); 1.60 (*dt*, *J* = 13.3, 6.7, 1 H); 3.51 (*t*, *J* = 7.0, 2 H); 7.27–6.99 (*m*, 1 H); 7.43 (*d*, *J* = 2.9, 1 H); 7.63 (*d*, *J* = 4.8, 1 H); 8.46 (*s*, 1 H). ESI-MS: 182.1 (100). HR-ESI-MS: 182.101 ($[M+H]^+$, $C_{10}H_{16}NS^+$; calc. 182.100).

N-*[(1*E*)-(4-Chlorophenyl)methylidene]benzenemethanamine* (**1t**) [33]. Yield: 0.592 mg, 86%. Yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.80 (*s*, 2 H); 7.38–7.25 (*m*, 7 H); 7.70 (*d*, *J* = 8.4, 2 H); 8.34 (*s*, CH=N).

N-*[(1*E*)-(4-Methoxyphenyl)methylidene]benzenemethanamine* (**1u**) [34]. Yield: 2.308 g, 93%. Pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.88 (*s*, 3 H); 4.83 (*s*, 2 H); 6.96 (*d*, *J* = 9.1, 2 H); 7.31–7.26 (*m*, 1 H); 7.39–7.34 (*m*, 4 H); 7.76 (*d*, *J* = 8.4, 2 H); 8.36 (*s*, CH=N).

N-*{(1*E*)-[4-(Dimethylamino)phenyl]methylidene}benzenemethanamine* (**1v**) [35]. Yield: 0.698 g, 98%. Pale yellow solid. ^{1}H-NMR (400 MHz, $CDCl_3$): 2.99 (*s*, Me_2N, 6 H); 4.74 (*s*, 2 H); 6.68 (*d*, *J* = 8.8, 2 H); 7.21 (*m*, 1 H); 7.31 (*d*, *J* = 4.4, 4 H); 7.64 (*d*, *J* = 8.7, 2 H); 8.25 (*s*, CH = N).

*5-(4-Chlorobenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**2a**) [36]. Yield: 0.505 g, 67%. Yellow solids. M.p. 282° ([37]: 280°). ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.54 (*d*, *J* = 8.8, 2 H); 8.08 (*d*, *J* = 8.6, 2 H); 8.25 (*s*, 1 H); 11.27 (*s*, 1 H); 11.41 (*s*, 1 H).

*5-(4-Methoxybenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**2b**) [36]. Yield: 0.622 g, 90%. Yellow solids. M.p. 278° ([37]: 276°). ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.88 (*s*, 3 H); 7.07 (*d*, *J* = 9.1, 2 H); 8.25 (*s*, 1 H); 8.37 (*d*, *J* = 8.9, 2 H); 11.17 (*s*, 1 H); 11.29 (*s*, 1 H).

*5-[4-(Dimethylamino)benzylidene]pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**2c**) [37]. Yield: 0.620 g, 80%. Orange solids. M.p. 259–260° ([38]: 262–263°). ^{1}H-NMR (400 MHz, (D_6)DMSO): 3.12 (*s*, 6 H); 6.80 (*d*, *J* = 9.3, 2 H); 8.15 (*s*, 1 H); 8.43 (*d*, *J* = 9.3, 2 H); 10.92 (*s*, 1 H); 11.05 (*s*, 1 H).

*5-(Thiophen-2-ylmethylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione* (**2d**) [36]. Yield: 0.580 g, 87%. Brown yellow solids. M.p. 275° ([37]: 273°). ^{1}H-NMR (400 MHz, (D_6)DMSO): 7.36 (*dd*, *J* = 5.0, 1 H); 8.18 (*d*, *J* = 3.9, 1 H); 8.28 (*d*, *J* = 4.6, 1 H); 8.57 (*s*, 1 H); 11.26 (*s*, 1 H); 11.30 (*s*, 1 H).

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