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An imidazolidin-1-ol, nitrone and oxadiazinane ring-chain-ring tautomeric dynamic combinatorial library

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ABSTRACT

A dynamic combinatorial library (DCL) based on benzylidene exchange reactions between imidazolidin-1-ol, nitrone and oxadiazinane (INO) ring-chain-ring tautomers at room temperature is created. The probable mechanism of the reaction is discussed based on Hammett type correlation analyses. The equilibria in the DCL are defined as interconversion of **INOAr-X** to **INOAr-Y** as a result of reactions with the corresponding aldehydes Y-ArCHO and X-ArCHO and are shown to depend on the σ constants of the substituents and are described by a simple equation $\log K_{XY} = \rho\sigma_{dif} + \log K_{XY(X=Y)}$. The prediction of K_{XY} for any **INOAr-X** and **INOAr-Y** interconversion requires only the experimental values of ρ and the known Hammett σ constants of the substituents. The effect of Zn(II) and CF_3SO_3H on the DCL equilibria is also reported.

Dynamic combinatorial chemistry[1] (DCC) has added a new dimension to the synthetic capability of combinatorial chemistry exploiting reversible covalent chemistry to generate combinatorial libraries that are under thermodynamic control. Since the library members interconvert by equilibrium processes, any stabilization of a given member of the library results in the thermodynamic redistribution of the equilibrium to yield a new thermodynamic equilibrium. Imines were first explored in a dynamic combinatorial context in 1997 by Huc and Lehn,[2] who described a virtual combinatorial library of imines the composition of which was influenced by the presence of carbonic anhydrase as a 'molecular trap'. Stabilized imines, in the form of oximes and hydrazones,[3] have since attracted significant interest in DCC as they can provide kinetically inert products without the need for subsequent reduction and the attendant change in geometry and electronics. Eliseev and co-workers have explored the use of *O*-aryl oximes to construct dynamic combinatorial libraries (DCLs).[4] The relative degree of amplification in the dynamic library will depend on the difference in binding affinity of the library components to the template.[5] The identification of dynamic covalent bonds and the development of catalysts which promote the fast exchange of covalent bonds are crucial for furthering dynamic covalent chemistry.[1b] In this respect creating DCLs based on scaffolds which could bind a compound to give several products in equilibrium would be extremely important for accessing richer DCLs than classical DCL scaffolds provide. Recently, it was reported that nitrones are able to undergo dynamic exchange in non-polar solvents such as chloroform. By coupling a nitrone-based replicator to a dynamic library based on nitrone-imine exchange, it was demonstrated that a synthetic replicator is able to exploit a network of reactions within a dynamic library to amplify its own formation at the expense of other species.[6]

Here we report on the benzylidene exchange reactions of imidazolidin-1-ol, nitrone and oxadiazinane ring-chain-ring tautomeric mixtures (INOAr-X(Y))[7] as a useful tool for the construction of DCLs. The effect of substituents on the interconversions of INOAr-X to INOAr-Y was investigated and correlations with Hammett constants and their differences were performed to elucidate the probable mechanism of the new benzylidene exchange reaction applied in the DCL formation.

Treatment of INOAr-X (X = H, R = *p*-$MeOC_6H_4$) in THF with an equimolar amount of hydroxylamine hydrochloride[8] dissolved in MeOH at 25 °C for 4 h leads quantitatively to the corresponding aldoxime and hydroxylaminoamine hydrochloride **3** (Scheme 1) as confirmed by ^1H NMR spectroscopy. A mixture of five aromatic aldehydes was added to the in situ formed **3** and the resulting mixture was left to equilibrate for 20 h.[9] The ^1H NMR analyses revealed that compound **3** was fully consumed to give the corresponding INOAr-X(Y) DCL. The concentrations of the aldehydes were monitored by gas chromatography (Table 1). There are 25 inter INOAr-X(Y) equilibria (Scheme 2) as depicted in Figure 1. Five of the latter are between INOAr-X and Y-ArCHO where X = Y and are non-productive.

The equilibrium constants K_{XY} = [INOAr-Y][X-ArCHO]/[INOAr-X][Y-ArCHO] for the equilibrium series A–E in the DCL were calculated and are presented in Table 2. A comparison of the equilibrium series A–E clearly reveals the reactivity order of the aldehydes in

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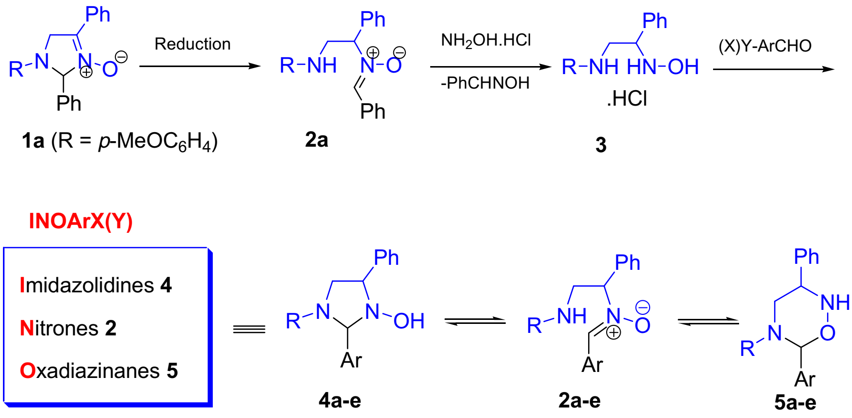


Scheme 1. Synthesis of an INO-based DCL

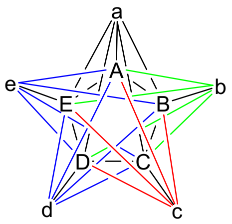
Table 1
Concentrations of the aldehydes and INOAr-X(Y) in the DCL at 25 °C in THF–MeOH after equilibration

2-5	X(Y)	[(Y)X-ArCHO][a] (M)	STDEV[b]	[INOAr-X(Y)][c] (M)
a	H	0.0186	0.0006	0.0014
b	*p*-Cl	0.0170	0.0006	0.0030
c	*p*-MeO	0.0195	0.0001	0.0005
d	*p*-NO_2	0.0096	0.0016	0.0105
e	*m*-NO_2	0.0122	0.0013	0.0078

[a] The aldehyde concentrations were measured using GC–MS and are averages of two experiments. The integral areas were corrected using butylhydroxytoluene as internal standard.
[b] STDEV = standard deviation.
[c] The INOAr-X(Y) tautomer contents were calculated as the difference of total INO (0.2 mmol) and the content of the specific aldehyde. Starting concentrations of the aldehydes and the library scaffold **3** are 0.02 M.

$$\text{INOAr-X} + \text{Y-ArCHO} \xrightleftharpoons{K_{XY}} \text{INOAr-Y} + \text{X-ArCHO}$$

Scheme 2. Benzylidene exchange equilibria.



A-E and a-e represent INOAr-X and Y-ArCHO respectively

Figure 1. Possible benzylidene exchange equilibria in the INO-based DCL.

Table 2
Equilibrium (Eqm) series in INO-based DCLs and Hammett correlations

	X	Y	K_{XY}	$\log K_{XY}$	σ_y[a]	$\sigma_x - \sigma_y$[a]
Eqm series A						
Kaa	H	H	1	0	0	0
Kab	H	*p*-Cl	2.34	0.37	0.24	−0.24
Kac	H	*p*-MeO	0.34	−0.47	−0.28	0.28
Kad	H	*p*-NO_2	14.61	1.16	0.81	−0.81
Kae	H	*m*-NO_2	8.49	0.91	0.71	−0.71
Eqm series B						
Kbb	*p*-Cl	*p*-Cl	1	0	0.24	0
Kba	*p*-Cl	H	0.43	−0.37	0	0.24
Kbc	*p*-Cl	*p*-MeO	0.15	−0.82	−0.28	0.52
Kbd	*p*-Cl	*p*-NO_2	6.23	0.80	0.81	−0.57
Kbe	*p*-Cl	*m*-NO_2	3.62	0.56	0.71	−0.47
Eqm series C						
Kcc	*p*-MeO	*p*-MeO	1	0	−0.28	0
Kca	*p*-MeO	H	2.94	0.47	0	−0.28
Kcb	*p*-MeO	*p*-Cl	6.67	0.82	0.24	−0.52
Kcd	*p*-MeO	*p*-NO_2	42.88	1.63	0.81	−1.09
Kce	*p*-MeO	*m*-NO_2	24.93	1.40	0.71	−0.99
Eqm series D						
Kdd	*p*-NO_2	*p*-NO_2	1	0	0.81	0
Kda	*p*-NO_2	H	0.068	−1.17	0	0.81
Kdb	*p*-NO_2	*p*-Cl	0.16	−0.79	0.24	0.57
Kdc	*p*-NO_2	*p*-MeO	0.023	−1.63	−0.28	1.09
Kde	*p*-NO_2	*m*-NO_2	0.58	−0.24	0.71	0.10
Eqm series E						
Kee	*m*-NO_2	*m*-NO_2	1	0	0.71	0
Kea	*m*-NO_2	H	0.12	−0.93	0	0.71
Keb	*m*-NO_2	*p*-Cl	0.28	−0.56	0.24	0.47
Kec	*m*-NO_2	*p*-MeO	0.04	−1.40	−0.28	0.99
Ked	*m*-NO_2	*p*-NO_2	1.72	0.24	0.81	−0.10

[a] The substituent constants and their difference values.[10,11]

Table 3
Linear free energy relationships (LFERs) in INO-based DCLs. Equations from the correlations with σ_Y and σ_{dif}

	σ_Y	$\sigma_x - \sigma_y = \sigma_{dif}$[a]
Eqm series A	$\log K_{ay} = 1.436\sigma_Y - 0.0257$	$\log K_{ay} = -1.436\sigma_{dif} - 0.0257$
Eqm series B	$\log K_{by} = 1.426\sigma_Y - 0.39$	$\log K_{by} = -1.426\sigma_{dif} - 0.0478$
Eqm series C	$\log K_{cy} = 1.436\sigma_Y + 0.4392$	$\log K_{cy} = -1.436\sigma_{dif} + 0.037$
Eqm series D	$\log K_{dy} = 1.436\sigma_Y - 1.19$	$\log K_{dy} = -1.436\sigma_{dif} - 0.0281$
Eqm series E	$\log K_{ey} = 1.436\sigma_Y - 0.9546$	$\log K_{ey} = -1.436\sigma_{dif} + 0.0652$
General eqs	$\log K_{XY} = \rho\sigma_Y + \log K_{XY(Y=H)}$	$\log K_{XY} = \rho\sigma_{dif}$

[a] The correlation coefficients from the correlations with σ_Y and σ_{dif} are ca. 0.995.

the DCL to be *p*-NO_2 > *m*-NO_2 > *p*-Cl > *p*-H > *p*-MeO (Table 2). The correlation equations for the equilibrium series A–E are given in Table 3. The correlations of $\log K_{XY}$ with σ_Y (the constant of the substituents on the aldehyde) produced Hammett type equations $\log K_{XY} = \rho\sigma_Y$ + intercept, where the reaction constant, $\rho = 1.44$, is the same for all series. The intercepts from these correlations deviate only by ca. 0.025 from the corresponding $\log K_{XY(Y=H)}$.

The correlations of $\log K_{XY}$ with $\sigma_{dif} = \sigma_X - \sigma_Y$ reveal that the magnitudes of the equilibrium constants are linearly dependant on the INOAr-X and INOAr-Y substituents and can be described simply by the equation $\log K_{XY} = \rho\sigma_{dif} + \log K_{XY(X=Y)}$. The reaction constants ρ are equal to those in the previous correlations but have opposite sign. The average of the intercepts from the latter correlations is 0.00012.[12] Representative graphs for the correlations in equilibrium series C are given in Figure 2. Comparing

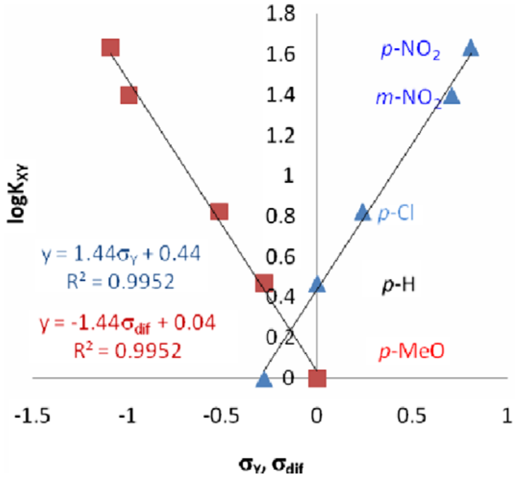


Figure 2. Plot of $\log K_{XY}$ in equilibrium series C versus σ_Y (▲) and σ_{dif} (■).

the K_{XY} predicting power of the equations from correlations with σ_Y and σ_{dif} clearly reveals the advantages of the equation $\log K_{XY} = \rho\sigma_{dif}$, where only three constants are required to calculate the corresponding K_{XY} in the library for any aldehyde and INO combination. However, the equations from the correlations with σ_Y require the experimental values of $K_{XY(Y = H)}$ which means that these data cannot be used directly to predict the K_{XY} when both substituents are different from those included in the correlations reported herein.

Thus the excellent correlations of the equilibrium series with Hammett σ constants agree with the assumption that the main equilibria in the DCL are of benzylidene exchange type between the INOArs. The values of the reaction susceptibility constants clearly implies that there should be a significant positive charge formation in the rate limiting step of this exchange reaction (Scheme 3, the formation of ammonium species **A**). The probable mechanism of the latter reaction is depicted in Scheme 3. The INO components able to undergo benzylidene exchange reactions are nitrone $\mathbf{N}_X$ and oxadiazinane $\mathbf{O}_Y$ (Scheme 3). The nucleophilic attack of $\mathbf{N}_X$ on the protonated aldehyde will lead to the formation of intermediate **A** which is probably in equilibrium with **B**. The cyclization of **B** produces the seven-membered oxadiazepine **C**, the ring-opening of which can afford iminium salt **D**. Intermediate **D** can cyclize to both cyclic components of the INO. We illustrate the benzylidene exchange through the oxadiazinane ring derivative **E**. Proton migration in **E** probably gives intermediate **F** which eliminates the protonated aldehyde X-Ar-CHO$^+$-H to give the corresponding oxadiazinane $\mathbf{O}_Y$.

To elucidate the effect of Zn(II) on the equilibria in the pre-equilibrated DCL, $ZnBr_2$ (equimolar amount with the library scaffold) was added to the mixture which was then stirred for 20 h at 25 °C (Table 4). The equilibrium constants K_{XY}, defined as given before, were calculated and the selective amplifications of the INOAr-OMe equilibria were demonstrated for equilibria series A and C (Table 5). Attempts to correlate $\log K_{XY}$ with the Hammett σ constants failed. The plots deviate from linearity with the greatest deviation from linearity observed in the case of the OMe-substituted library members.

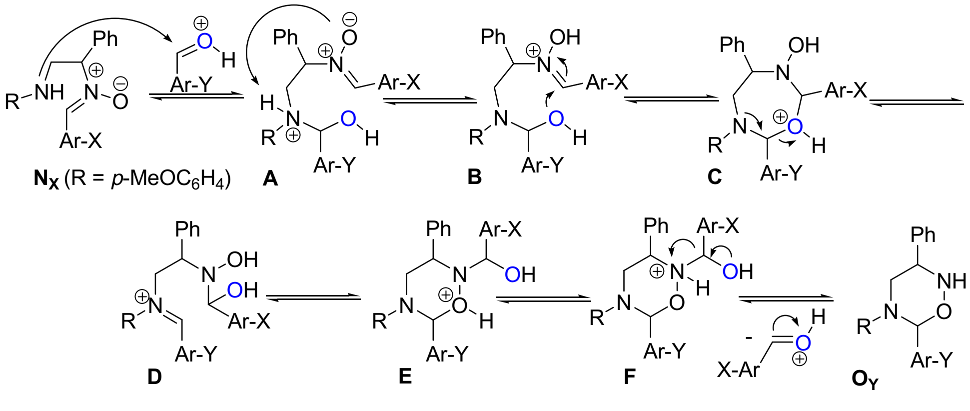
A comparison of the parent equilibria with those in the presence of Zn(II) (exemplified for series A and C; the same conclusions are true in the other series) reveal that the equilibria involving the formation of INOAr-*p*-OMe are ca. nine times more shifted than INOAr-*p*-NO_2. Even more contrasting is the comparison of benzaldehyde and *p*-methoxybenzaldehyde involving equilibria where about 20 times enhancement is seen for the latter. The reactivity order of the aldehydes in the benzylidene exchange reaction became *p*-NO_2 > *m*-NO_2 > *p*-Cl = *p*-MeO > *p*-H. In fact, the unsubstituted aldehyde-derived INO components were the more reactive species in the DCL and the enhancement of the INOAr-*p*-OMe concentration is mainly due to the right-shifted INOAr-H MeO-ArCHO equilibrium. The change of the reactivities of the latter two aldehydes is probably due to an increase of the negative inductive effect of the MeO group due to interactions with Zn(II).

Although the correlations confirm the assumed benzylidene exchange mechanism which we have proposed, experiments involving the separate treatment of INOAr-H with equimolar amounts of Y-ArCHO (Y = *p*-Cl, *p*-MeO, *p*-NO_2, *m*-NO_2) in the presence of equimolar amounts of F_3CSO_3H in THF at 25 °C undoubtedly confirmed this assumption. The equilibrium constants are given in Table 6. A comparison of the aldehyde starting concentration and after 20 h reaction with INOAr-H in the presence of CF_3SO_3H at 25 °C in THF is given in Figure 3.

Table 4
Concentrations of the aldehydes and INOAr-X(Y) in the DCL at 25 °C in THF–MeOH (24:1) with Zn(II)

2–5	X(Y)	[(Y)X-ArCHO][a] (M)	STDEV[b]	[INOAr-X(Y)][a] (M)
a	H	0.0193	0.0016	0.0007
b	*p*-Cl	0.0160	0.0010	0.0040
c	*p*-MeO	0.0161	0.0013	0.0040
d	*p*-NO_2	0.0090	0.0016	0.0110
e	*m*-NO_2	0.0113	0.0012	0.0088

[a] The concentrations of the aldehydes and INOAr-X(Y) were determined as mentioned in the legend of Table 1.
[b] STDEV = standard deviation.



Scheme 3. Probable mechanism for the benzylidene exchange reactions in the INO-based DCL.

Table 5
Equilibrium series in INO-based DCLs in the presence of the Zn(II) template

Eqm series A	X	Y	K_{XY} – template	K_{XY}[a]	K_{XY} – template/K_{XY}
Kaa	H	H	1	1	1
Kab	H	*p*-Cl	6.89	2.34	2.95
Kac	H	*p*-MeO	6.76	0.34	19.96
Kad	H	*p*-NO_2	33.70	14.61	2.31
Kae	H	*m*-NO_2	21.44	8.49	2.53
Eqm series C					K_{XY}/K_{XY} – template
Kcc	*p*-MeO	*p*-MeO	1	1	1
Kca	*p*-MeO	H	0.147	2.94	20
Kcb	*p*-MeO	*p*-Cl	0.984	6.67	6.78
Kcd	*p*-MeO	*p*-NO_2	4.97	42.88	8.62
Kce	*p*-MeO	*m*-NO_2	3.16	24.93	7.89

[a] K_{XY} from the DCL without a template is included for comparison.

Table 6
Benzylidene exchange reactions of INOAr-H (R = *p*-$MeOC_6H_4$) with Y-ArCHO

Y	[Y-ArCHO][a] (M)	[H-ArCHO][a] (M)	[INOAr-Y] (M)	[INOAr-H] (M)	K_{XY}
H					1.00E+00
p-Cl	0.017	0.0033	0.0033	0.0167	3.90E−02
p-MeO	0.0165	0.0035	0.0035	0.0165	4.50E−02
p-NO_2	0.0082	0.0118	0.0118	0.0082	2.07E+00
m-NO_2	0.0100	0.0100	0.0100	0.0100	1.00E+00

[a] The concentrations of the aldehydes (M) were measured using GC–MS. The integral areas were corrected using butylhydroxytoluene as internal standard.

The library constructed by addition of aldehydes Y-ArCHO (Y = *p*-Cl, *p*-MeO, *p*-NO_2 and *m*-NO_2) to INOAr-H in the presence of CF_3SO_3H revealed that under these conditions all the aldehydes are more reactive than benzaldehyde (Table 7). The reactivity order of the aldehydes in the latter DCL is *p*-NO_2 > *m*-NO_2 > *p*-MeO > *p*-Cl > *p*-H. *p*-Methoxybenzaldehyde became more reactive than *p*-chlorobenzaldehyde probably because of protonation of the methoxy group by the strong acid.

Thus, the benzylidene exchange reactions of ring-chain-ring tautomeric mixtures (INOAr-X(Y)) allow the construction of more complete DCLs since the library members exist as multiple tautomers, thus increasing the diversity of the system, and therefore allowing for the greater possibility of different interactions with a template. The discussions on the probable mechanism of the benzylidene exchange reaction in the DCL were supported with Hammett type correlation analyses. The correlations of $\log K_{XY}$ with σ_{dif} produced a more general and more useful equation for the predictions of unknown K_{XY}, namely $\log K_{XY} = \rho\sigma_{dif}$, than the correlations with σ_Y alone.

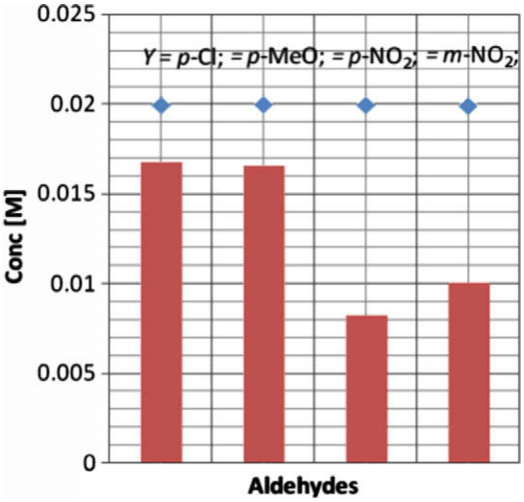


Figure 3. Comparison of the benzylidene exchange reactions of INOAr-H with Y-ArCHO; (◆) and (🟥) denote the concentrations of the aldehydes before and after treatment with INO-Ar-H and CF_3SO_3H, respectively.

Nitrone **1a** was prepared in 50% yield according to a previously reported procedure[13] and converted to INOAr-H by reduction with $NaBH_4$ in THF at reflux.[7] *3,6-Diphenyl-5-p-methoxyphenyl-1,2,5-oxadiazinane* **5a**: Yield 90%. Mp 150–150.3 °C. IR (KBr) ν_{NH} 3255 cm^{-1}. The spectrum was obtained from the crystalline product immediately upon dissolution in $CDCl_3$. The solution consisted of **2a** (9%), **4a** (12%) and **5a** (78%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.75 (3H, s), 3.85–3.93 (1H, m), 4.04 (1H, br s), 4.51 (1H, dd, *J* = 12.0; 6.4 Hz), 5.61 (1H, s), 6.49 (2H, d, *J* = 9.2 Hz), 7.03 (2H, d, *J* = 9.2 Hz), 7.25–7.38 (10H, m). Anal. Calcd for $C_{22}H_{22}N_2O_2$ (346.42) C, 76.28; H, 6.40; N, 8.09. Found: C, 76.32; H, 6.43; N, 8.15.

C-Phenyl-N-(1-phenyl-2-p-methoxyphenylaminoethyl) nitrone **2a**: The spectrum was obtained from an equilibrated tautomeric mixture containing **2a** (69%), **4a** (18%) and **5a** (12%). ^1H NMR (400 MHz, $CDCl_3$): δ 3.61 (1H, dd, *J* = 14.4; 4.0 Hz), 3.76 (3H, s), 4.04 (1H, br s), 4.30 (1H, dd, *J* = 14.4; 10.0 Hz), 5.20 (1H, dd, *J* = 10.0; 4.0), 6.62 (2H, d, *J* = 9.2 Hz), 6.79 (2H, d, *J* = 9.2), 7.36–7.41 (7H, m), 7.57–7.59 (2H, m), 8.19–8.22 (2H, m).

Preparation of INOAr-X(Y) DCL: To a solution of INO-ArH (0.2 mmol, 0.0693 g) in THF (4.8 mL), $NH_2OH{\cdot}HCl$ (0.2 mmol, 0.0135 g) dissolved in MeOH (0.2 mL) was added and the reaction mixture was stirred at 25 °C for 4 h. Completion of the reaction was confirmed by ^1H NMR. A solution of aromatic aldehydes Y-ArCHO was prepared by dissolving 0.8 mmol of each aldehyde in 20 mL of THF. The same solution was used to obtain calibration curves

Table 7
Concentrations of the aldehydes and INOAr-X(Y) in the DCL at 25 °C in THF with CF_3SO_3H

2–5	X(Y)	[(Y)X-ArCHO][a] (M)	STDEV[b]	[INOAr-X(Y)][a] (M)
a	H	0.0212	0.0016	−0.0012
b	*p*-Cl	0.017	0.0010	0.003
c	*p*-MeO	0.0162	0.0013	0.0038
d	*p*-NO_2	0.0122	0.0016	0.0078
e	*m*-NO_2	0.0133	0.0012	0.0067

[a] The concentrations of the aldehydes and INOAr-X(Y) were determined as mentioned in the legend of Table 1.

[b] STDEV = standard deviation.

for the chromatographic analyses as well as for the syntheses of DCL. The concentrations used for the calibration curves were 0.04, 0.02 and 0.01 M. Five millilitres from the 0.04 M solution of aldehydes were added to the in situ formed aminohydroxylamine **3** and the library was left to equilibrate for 20 h at 25 °C. The aldehyde content of the DCL was analyzed by GC–MS. $ZnBr_2$ (0.2 mmol, 0.0450 g) was added to the equilibrated DCLs which were then stirred at 25 °C for 20 h.

Aldehyde exchange reactions of INOAr-H with Y-ArCHO in the presence of CF_3SO_3H : To a solution of the aromatic aldehyde (0.02 mmol) in 1 mL of THF, INOAr-H (0.02 mmol, 0.0069 g) was added. CF_3SO_3H (0.02 mmol, 0.003 g) was added and the reaction mixture was stirred at 25 °C for 20 h. The amounts of the aldehydes were determined by GC–MS. The concentrations used for the calibration curves were 0.02, 0.01 and 0.005 M.

Acknowledgement

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9. In a separate experiment, the ratio of the aldehydes in the DCL were measured from the integral areas of the corresponding aldehyde proton signals in the ^1H NMR spectra of the mixture at different times. After 15 hours, the values did not deviate significantly and thus we assumed that the exchange reactions in the library had reached an equilibrium.
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12. The correlations with $\sigma_{sum} = \sigma_X + \sigma_Y$ produced the equations $\log K_{XY} = \rho\sigma_{sum} +$ intercept where the intercept are ca. $2\log K_{XY(Y=H)}$. The predicting power of the latter is not higher than the equations from the correlations with σ_Y.
13. (a) Coşkun, N.; Sümengen, D. *Synth. Commun.* **1993**, *23*, 1699–1706; (b) Coşkun, N.; Asutay, O. *Chim. Acta Turc.* **1997**, *25*, 69–71; (c) Coşkun, N.; Asutay, O. *Chim. Acta Turc.* **1999**, *27*, 17–23.