Electronic Supplementary Material (ESI) for Organdic and Biomolecular Chemistry

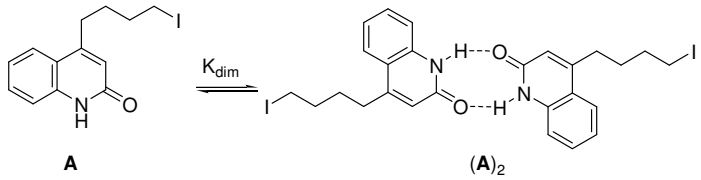
Supplementary Information

Enantioselective radical cyclisation reactions of 4-substituted quinolones mediated by a chiral template

Aline Bakowski, Martina Dressel, Andreas Bauer,* Thorsten Bach*

1. Determination of K_{dim} – NMR-dilution experiment

Dimerisation constants can be obtained from dilution experiments. A number of samples have to be prepared, each with a different concentration of the substrate. The NMR-shift of the most sensitive nucleus (in all described titrations an amide N–H proton) is measured for each sample at the given temperature.



Scheme 1: Dimerisation equilibrium of substrate **6a** (**A**)

In our hands, much better results were obtained, when the individual samples were prepared directly from a stock solution rather than diluting one sample further and further. An additional benefit from this procedure is the fact, that titrations can be performed with identical samples at different temperatures without adjusting the temperature of the NMR probe-head after each sample.

A 2.5 mM stock solution of substrate **6a** (in the following called **A** for simplicity) in toluene-*d8* was diluted with the appropriate amounts of toluene-*d8* to give the concentrations listed in table 1 using microliter syringes (Hamilton, Bonaduz).

Table 1: Dilution experiments for the determination of K_{dim} (T=298 K, 273 K)

Entry	$[A]_0$ [mol/L]	δ_{NH} [ppm] T=298 K	δ_{NH} [ppm] T=273 K
1	7.50E-05	9.040	10.714
2	1.25E-04	9.497	11.185
3	2.50E-04	10.162	11.760
4	3.75E-04	10.572	12.075
5	5.00E-04	10.870	12.275
6	6.25E-04	11.115	12.456
7	1.25E-03	11.740	12.854
8	1.75E-03	12.004	13.010
9	2.50E-03	12.245	13.156

Using equation (6) (annex A) the expected chemical shift for a given set of $[A]_0$, K_{dim}, δ_A and δ_{A_2} can be calculated and compared to the measured values resulting in the respective signal-residuals (see figure 1). By nonlinear regression the sum of residuals is minimized (least square fit, gradient algorithm) using K_{dim}, δ_A and δ_{A_2}.as parameters in the optimisation process. Errors are estimated using the described *Monte-Carlo* approach (*vide infra*).

Table 2: Concentrations and shifts for optimised parameters for the T=298 K experiment K_{dim}=2001 L/mol, δ_A = 7.875 ppm, δ_{A_2}= 13.880 ppm

Entry	$[A]_0$ [mol/L]	[A] [mol/L]	$[A_2]$ [mol/L]	δ_{NH} [ppm] *calc.*	δ_{NH} [ppm] *measured*	$\Delta\delta_{NH}$ [ppm]
1	7.50E-05	6.04E-05	7.30E-06	9.044	9.040	0.004
2	1.25E-04	9.15E-05	1.68E-05	9.484	9.497	-0.013
3	2.50E-04	1.54E-04	4.78E-05	10.169	10.162	0.007
4	3.75E-04	2.06E-04	8.47E-05	10.586	10.572	0.014
5	5.00E-04	2.50E-04	1.25E-04	10.878	10.870	0.008
6	6.25E-04	2.90E-04	1.68E-04	11.098	11.115	-0.017
7	1.25E-03	4.48E-04	4.01E-04	11.729	11.740	-0.011
8	1.75E-03	5.48E-04	6.01E-04	11.999	12.004	-0.005
9	2.50E-03	6.75E-04	9.12E-04	12.258	12.245	0.013

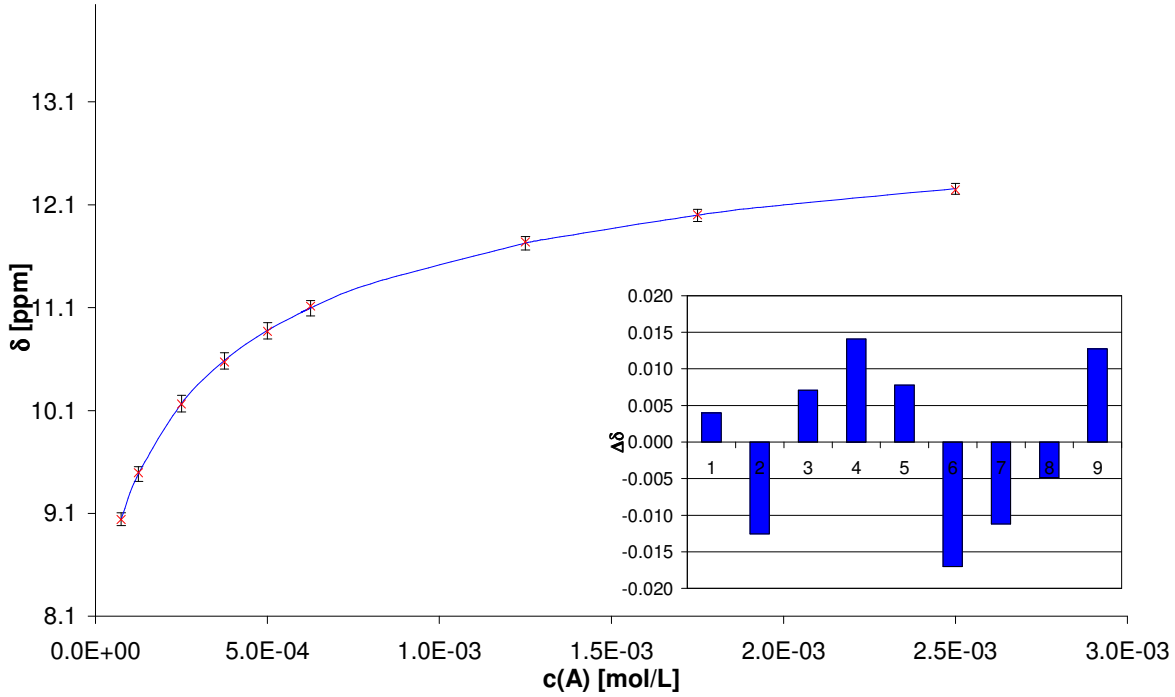
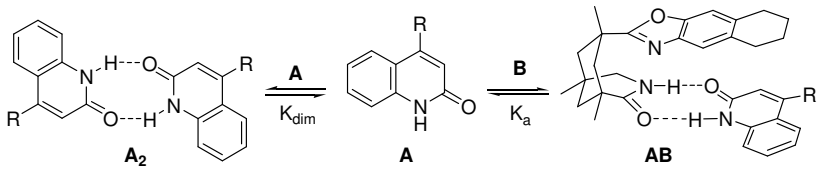


Figure 1: Measured values (red), calculated chemical shift (blue line) and signal residuals for the dilution experiment at 298 K – error bars refer to the largest and smallest shift using the upper and lower limit of the confidence interval.

2. Determination of K_a – NMR-titration of template with substrate

As for the determination of K_{dim}, much better results were obtained, when the samples were prepared each directly from a stock solution rather than diluting one sample further and further. An additional benefit from this procedure is the fact, that titrations can be performed with identical samples at different temperatures without adjusting the temperature of the NMR probe-head after each sample.



Scheme 2: Dimerisation and Association of Substrate **6a** (A) and Template (+)-1 (B)

A 2.5 mM stock solution of substrate **6a** (in the following called **A** for simplicity) containing 0.2 mM of template (+)-**1** (for simplicity called **B**) in toluene-*d8* was added to appropriate amounts of a 0.2 mM solution of template (+1) in toluene-*d8* to give the concentrations listed in table 2 using microliter syringes (Hamilton, Bonaduz).

Table 3: Titration experiments for the determination of K_a (T=298 K, 273 K), $[B]_0$=0.2 mM

Entry	$[A]_0$ [mol/L]	δ_{NH} [ppm] T=298 K	δ_{NH} [ppm] T=273 K
0	0.00E+00	3.874	3.955
1	5.00E-05	4.034	4.295
2	1.00E-04	4.169	4.541
3	1.50E-04	4.273	4.714
4	2.50E-04	4.435	4.970
5	3.75E-04	4.607	5.231
6	6.50E-04	4.889	5.618
7	1.35E-03	5.330	6.173
8	2.50E-03	5.750	6.632

Using equation (13) (annex B) the expected chemical shift for a given set of $[A]_0$, $[B]_0$ K_{dim}, K_a, δ_B and δ_{AB} can be calculated and compared to the measured values resulting in the respective signal-residuals (see figure 2). By nonlinear regression the sum of residuals is minimized (least square fit, gradient algorithm) using K_a and δ_{AB} parameters in the optimisation process. The dimerisation constant K_{dim} is either used as parameter or determined separately (*vide supra*). Errors are estimated using the described *Monte-Carlo* approach (*vide infra*).

Table 4: Concentrations and shifts for optimised parameters for the T=298 K experiment $[B]_0$=0.2 mM, K_{dim}=2000 L/mol, K_a=835 L/mol, δ_{AB} = 9.137 ppm

Entry	$[A]_0$ [mol/L]	[A] [mol/L]	[B] [mol/L]	[AB] [mol/L]	δ_{NH} [ppm] *calc.*	δ_{NH} [ppm] *measured*	$\Delta\delta_{NH}$ [ppm]
0	0.00	0.00	2.00E-04	1.47E-34	3.874	3.874	0.000
1	5.00E-05	3.81E-05	1.94E-04	2.90E-06	4.036	4.034	0.002
2	1.00E-04	6.96E-05	1.89E-04	9.70E-06	4.163	4.169	-0.006
3	1.50E-04	9.72E-05	1.85E-04	1.89E-05	4.269	4.273	-0.004
4	2.50E-04	1.45E-04	1.78E-04	4.19E-05	4.441	4.435	0.006
5	3.75E-04	1.95E-04	1.72E-04	7.60E-05	4.611	4.607	0.004
6	6.50E-04	2.85E-04	1.62E-04	1.63E-04	4.887	4.889	-0.002
7	1.35E-03	4.58E-04	1.45E-04	4.19E-04	5.328	5.330	-0.002
8	2.50E-03	6.64E-04	1.29E-04	8.82E-04	5.751	5.750	0.001

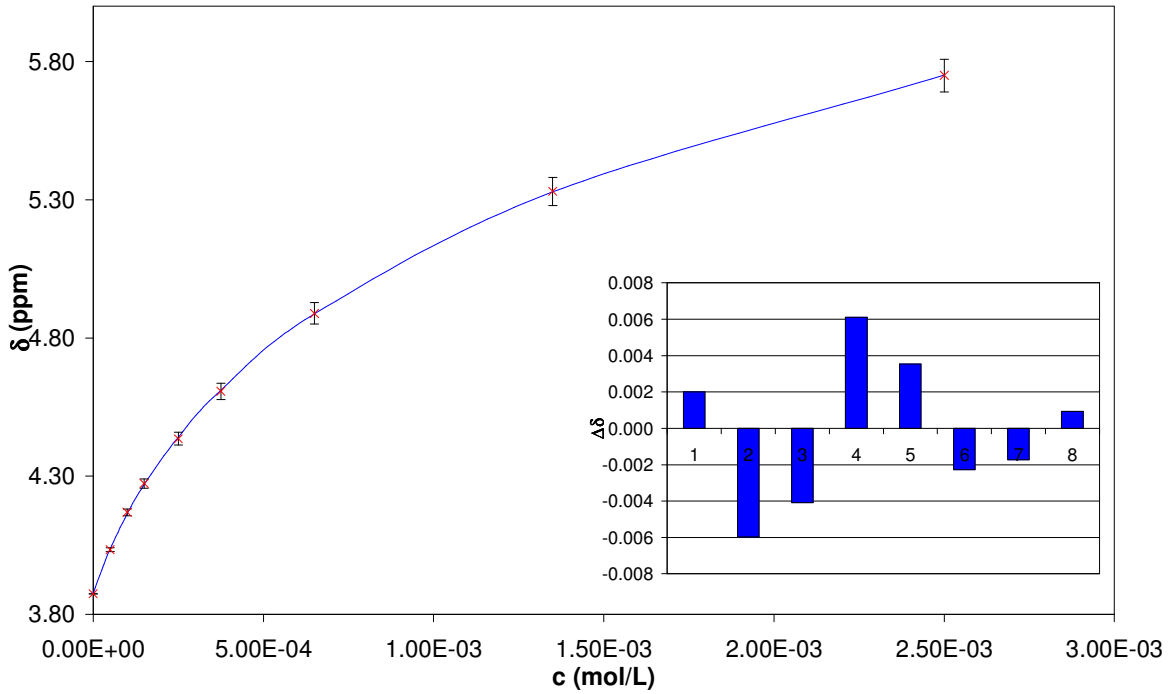


Figure 2: Measured values (red), calculated chemical shift (blue line) and signal residuals for the association experiment at 298 K – error bars refer to the largest and smallest shift using the upper and lower limit of the confidence interval.

3. Monte-Carlo error analysis

Monte-Carlo error analysis can be used as tool to evaluate the quality of a single set of measured data.[1,2] in which the respective input data set is artificially scattered by randomly chosen values which are derived from the maximum signal residual of the initial nonlinear parameter optimisation. With this method, 1000 scattered datasets were refined for each titration experiment to give 1000 binding constants and chemical shifts of the respective complexes. This data can be judged by standard statistical methods, giving access to values like the confidence interval (here 95% confidence level).[2] Figure 3 shows for the 298 K titration experiment a typical distribution of association constants obtained with this method. The applied random scatter ranges from ±0.007 ppm (see manuscript, table 3, entries 1 and 3) to about ±0.015 ppm (see manuscript, table 3, entries 4 to 6).

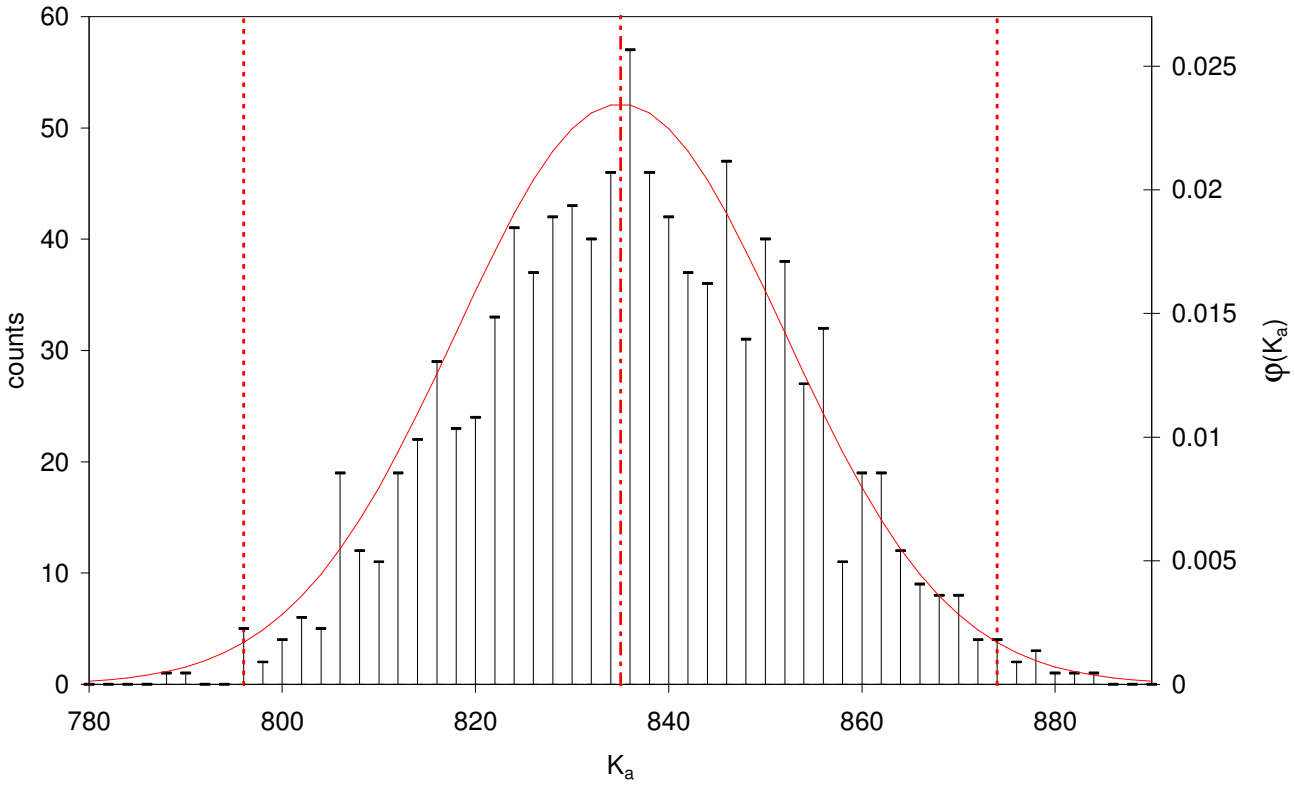
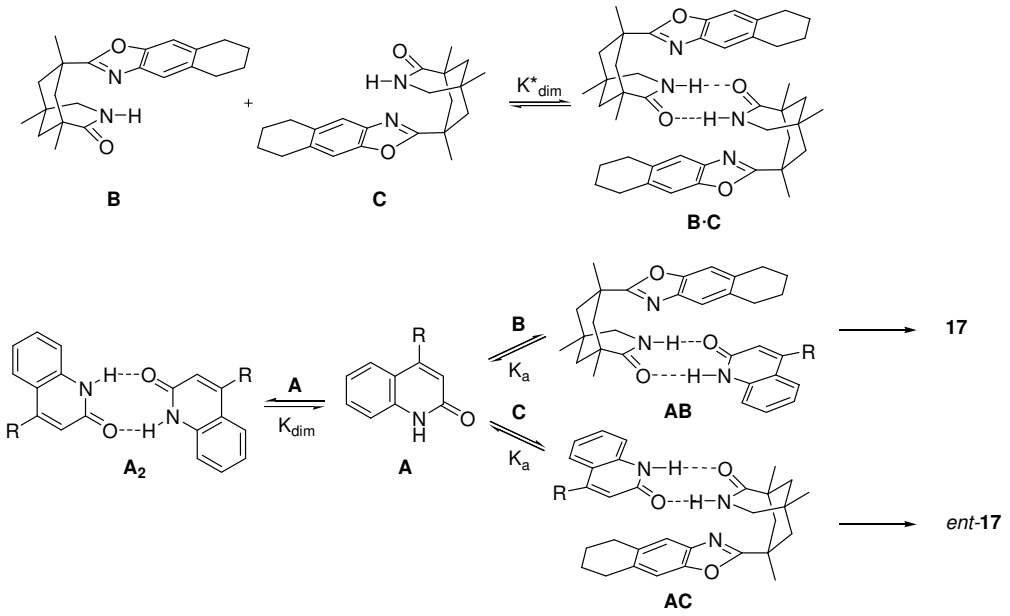


Figure 3: Frequency histogram for 1000 association constants obtained from the randomly scattered dataset of the 293 K titration experiment (see manuscript, table 3, entry 3).
Shown in red: normal distribution (———), mean (— – —) and confidence interval (– – – –)

[1] J. S. Alper, R. I. Gelb, *J. Phys. Chem.* **1990**, *94,* 4741-4151
[2] http://www.graphpad.com/manuals/prism4/regressionbook.pdf

4. Nonlinear dependence of the optical purity of template and product

The nonlinear dependence of the optical purity of template and product has been investigated by performing the radical cyclisation of substrate **6b** in the presence of template **1** with different optical purities.



Scheme 3: Dimerisation (K_{dim}) and Association ($K_{a'}$) of Substrate **6b** (**A**) and Templates (+)-1 (**B**) and (–)-1 (**C**); heterochiral association of the template enantiomers (K^*_{dim})

The respective association constants for these experiments (complexes $(\mathbf{6b})_2$ and **6b**·**1** in trifluorotoluene) have not been determined by titration experiments. Using the obvious assumption, that the dimerisation constant of the substrate **6b** used in this investigation is approximately the same as the dimerisation constant of the substrate **6a** it is possible to calculate a reasonable estimate for the association constant K_a for the complexes **6b**·**1** (equation (12)).

Table 5: Nonlinear relationship between template *ee* and product *ee*

Entry	*ee* **1** [%]	*ee* **17** [%] $K^*_{dim} = 0$[a]	*ee* **17** [%] $K^*_{dim} \rightarrow \infty$[b]	*ee* **17** [%] $K^*_{dim} = 750$[c]	*ee* **17** [%] *found*
1	100	94	94	94	94
2	80	75	90	86	80
3	60	56	81	73	73
4	40	38	63	52	62
5	20	19	35	27	29
6	0	9	0	0	0

[a] trivial case: calculated from $ee_{\mathbf{17}}$(*ee* **1**)=$ee_{\mathbf{17}}$(100% *ee*) · *ee* **1** [b] calculated using equation (12), $[\mathbf{B}]_0 = [(+)\text{-}\mathbf{1}] - [(-)\text{-}\mathbf{1}]$ with (+)-**1** being the major enantiomer. [c] calculated using equation (24).

Annex A – Equations for K_{dim}

$$2\,A \overset{K_{dim}}{\rightleftharpoons} A_2$$

$$K_{dim} = \frac{[A_2]}{[A]^2} \quad \Rightarrow \quad [A_2] = K_{dim} \cdot [A]^2 \qquad (1), (2)$$

Using the boundary $[A]_0 = 2 \cdot [A_2] + [A]$ gives a second order equation in [A] which can be solved as follows.

$$0 = 2 \cdot K_{dim} \cdot [A]^2 + [A] - [A]_0 \qquad (3)$$

$$[A] = \frac{-1 + \sqrt{1 + 8 \cdot K_{dim} [A]_0}}{4 \cdot K_{dim}} \quad \text{or} \quad [A] = \frac{-1 - \sqrt{1 + 8 \cdot K_{dim} [A]_0}}{4 \cdot K_{dim}} \qquad (4), (5)$$

The latter equation results in negative concentration, thus only the first solution has to be considered. As $[A]_0$ is known, this equation has only one Parameter to be optimised (K_{dim}).

The chemical shift of the proton under investigation is described as weighted average of the individual species:

$$\delta_{calc} = \delta_A \cdot \frac{[A]}{[A]_0} + \delta_{A_2} \frac{2 \cdot [A_2]}{[A]_0} \qquad (6)$$

As usually both δ_A and δ_{A_2} are not known, the optimisation has to deal with three parameters: K_{dim}, δ_A and δ_{A_2}.

Annex B – Equations for K_a

$$\mathbf{A_2} \underset{K_{dim}}{\overset{\mathbf{A}}{\rightleftharpoons}} \mathbf{A} \underset{K_a}{\overset{\mathbf{B}}{\rightleftharpoons}} \mathbf{AB}$$

$$K_{dim} = \frac{[A_2]}{[A]^2} \quad \Rightarrow \quad [A_2] = K_{dim} \cdot [A]^2 \qquad (7), (8)$$

$$K_a = \frac{[AB]}{[A] \cdot [B]} \quad \Rightarrow \quad [AB] = K_a \cdot [A] \cdot [B] \qquad (9), (10)$$

Using the boundary $[B]_0 = [B] + [AB]$ an equation for [B](K_a, [A]) can be obtained:

$$B = \frac{[B]_0}{1 + K_a \cdot [A]} \qquad (11)$$

Using the boundary $[A]_0 = 2 \cdot [A_2] + [A] + [AB]$ together with expression (11) a third order equation in [A] can be obtained:

$$0 = 2 \cdot K_{dim} \cdot K_a \cdot [A]^3 + (2 \cdot K_{dim} + K_a) \cdot [A]^2 + (K_a \cdot [B]_0 - K_a \cdot [A]_0 + 1)[A] - [A]_0 \qquad (12)$$

This equation is solved analytically. It can be shown, that for values $K_a > 0$, $K_{dim} > 0$, $[A]_0 > 0$ and $[B]_0 > 0$ only one real solution and two complex solutions exist, the latter being of no relevance to this problem.

The chemical shift of the proton under investigation is described as weighted average of the individual species:

$$\delta_{calc} = \delta_B \cdot \frac{[B]}{[B]_0} + \delta_{AB} \frac{[AB]}{[B]_0} \qquad (13)$$

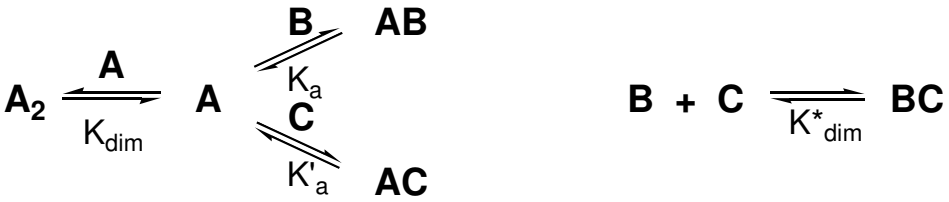
As δ_B is directly accessible (template with the given constant concentration, without substrate) only δ_{AB} is unknown. The optimisation has either to deal with three parameters (K_{dim}, K_a and δ_{AB}) or – if K_{dim} has been determined in a separate experiment – with two parameters (K_a and δ_{AB}) resulting in more accurate results due to significantly more robust optimisation.

In addition, the enantiomeric excess in a reaction of substrate **A** can be calculated.

$$ee_{calc} = \alpha \cdot \frac{[AB]}{[A]_0} \qquad (14)$$

From previous studies using the template **1** it is known, that the efficiency α of the side differentiation is very high and is therefore set to 1.

Annex C: Equations for K^*_{dim}



$$K_{dim} = \frac{[A_2]}{[A]^2} \Rightarrow [A_2] = K_{dim} \cdot [A]^2 \quad (15), (16) \qquad K_a = \frac{[AB]}{[A]\cdot[B]} \Rightarrow [AB] = K_a \cdot [A]\cdot[B] \quad (17), (18)$$

$$K'_a = \frac{[AC]}{[A]\cdot[C]} \Rightarrow [AC] = K'_a \cdot [A]\cdot[C] \quad (19), (20) \qquad K^*_{dim} = \frac{[BC]}{[B]\cdot[C]} \Rightarrow [BC] = K^*_{dim} \cdot [B]\cdot[C] \quad (21), (22)$$

Using the boundary $[B]_0=[BC]+[B]+[AB]$ an equation for $[B]([A],[B]_0,[C],K_a,K^*_{dim})$ can be obtained:

$$B = \frac{[B]_0}{[A]\cdot K_a + [C]\cdot K^*_{dim} + 1} \quad (23)$$

Using the boundary $[C]_0=[BC]+[C]+[AC]$ together with expression (23) a second order equation in [C] can be obtained which delivers two solutions $[C]([A],[B]_0,[C]_0,K_a,K'_a,K^*_{dim})$. Only one of the two solutions gives positive real values. This expression is used to eliminate the variable [C] from equation (23) to an expression $[B]([A],[B]_0,[C]_0,K_a,K'_a,K^*_{dim})$.

The obtained expressions $[B]([A],[B]_0,[C]_0,K_a,K'_a,K^*_{dim})$ and $[C]([A],[B]_0,[C]_0,K_a,K'_a,K^*_{dim})$ together with the boundary $[A]_0=2\cdot[A_2]+[A]+[AB]+[AC]$ give a function in [A] (equation (24))which is solved numerically (Newton):

$$0 = \frac{2\,[A][B]_0 \cdot (2[A]K_aK'_a + K_a + K'_a)}{\sqrt{K_a^2K'^2_a[A]^4 + 2K_aK'_a\cdot(K_a+K'_a)[A]^3 + (2[B]_0K_aK'_aK^*_{dim} + 2[C]_0K_aK'_aK^*_{dim} + K_a^2 + 4K_aK'_a + K'^2_a)[A]^2 + (2K_a + K'_a)([B]_0K^*_{dim} + [C]_0K^*_{dim} + 1)[A] + [B]_0^2K^{*2}_{dim} + 2[B]_0K^*_{dim}(1 - [C]_0K^*_{dim}) + [C]_0^2K^{*2}_{dim} + 2(1 - [C]_0K^*_{dim}) + 1}} \sim$$

$$\sim \frac{}{K_aK'_a[A]^2 + (K_a + K'_a)[A] - [B]_0K^*_{dim} + [C]_0K^*_{dim} + 1} + \frac{[B]_0 - [C]_0}{K'_a[A] + 1} + 2K_{dim}[A]^2 + [A] - [A]_0 - [B]_0 + [C]_0 \quad (24)$$

Using the obtained value for [A] allows to successively calculate all concentrations and deduced values (e.g. *ee*).