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Double asymmetric synthesis: faster reactions are more selective and a model to estimate relative rate†

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The catalysed reaction of an enantiopure substrate with formation of a new chirality element may result in higher diastereoselectivity with one enantiomer of a catalyst (matched pair) than with the other (mismatched pair). The hypothesis that the matched reaction is faster was investigated using literature examples of kinetic resolution procedures that result in the formation of a new stereogenic centre. With one exception from fifteen examples, the selectivity factor ($s = k_{\text{fast}}/k_{\text{slow}} = k_{\text{matched}}/k_{\text{mismatched}}$). A model to estimate the relative rate of a fast-matched reaction vs. the corresponding slow-mismatched reaction is proposed. This model also provides insight into the basis of the selectivity displayed in the kinetic resolution procedures studied.

Introduction

A common occurrence in asymmetric synthesis is the reaction of an enantiopure substrate [e.g. (*R*)-**1**] using an enantiopure catalyst (or reagent)¹ that results in the formation of a new chirality element (Scheme 1). If the ratio of the resulting diastereoisomers [(*R,R'*)-**2**/(*R,S'*)-**3**] is independent of the configuration of the catalyst employed, the reaction is under complete substrate control. Conversely, if the ratio of diastereoisomers inverts on swapping the catalyst configuration the reaction is under complete catalyst control. In many cases the resulting ratio of diastereoisomers is frequently much higher with one enantiomer of the catalyst than is observed with the opposite enantiomer; the former being matched and the latter mismatched using the terms introduced by Masamune *et al.* in their seminal account on double asymmetric synthesis.^{2,3} Although widely exemplified, an analysis of the relative kinetics of these matched and mismatched reactions was not discussed, as is the case in another review on double asymmetric synthesis,⁴ and in many subsequent publications.⁵ There are some instances where a matched reaction is noted to be faster,^{6,7} but there appear to be just four examples of double asymmetric synthesis where the relative rate of the two diastereomeric reactions has been determined.^{8,9} One of these does not fit the expected outcome, where as noted by Sharpless,

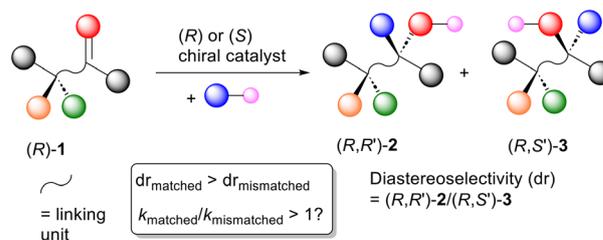
“from a kinetic perspective, one would expect matched double asymmetric reactions, where the intrinsic diastereofacial selectivities of each component are mutually reinforced, to be fast compared to their mismatched counterparts.”⁹

In this paper we describe our investigations to confirm, using multiple examples, this correlation between rate and selectivity in double asymmetric synthesis. The data generated is used to validate a model for the estimation of the relative rate of a matched reaction compared to its mismatched counterpart. In addition, this model may also be used to estimate the selectivity factor (*s*) of a kinetic resolution reaction that results in the generation of a new element of chirality.

Results and discussion

Determination of the rate/selectivity correlation

In light of the paucity of data comparing the rates of matched and mismatched reactions, it was reasoned that the required information may be obtained from kinetic resolution pro-



Scheme 1 Schematic representation of enantiopure substrate (*R*)-**1** and conversion into diastereoisomers (*R,R'*)-**2** and (*R,S'*)-**3**.

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cedures that result in the formation of an additional chirality element (Scheme 2).

In such a reaction, in addition to the recovered enantio-enriched starting material **1** (ee_1), two product diastereoisomers **2** and **3** may be formed (ee_2 and ee_3 respectively). The selectivity factor s (k_{fast}/k_{slow}), readily calculated from a knowledge of conversion C and ee_1 [eqn (1)],^{8a,10} is the same as the relative rate of reaction of a single enantiomer of substrate with both enantiomers of a catalyst or reagent (*i.e.* the relative rate of the more-selective matched and less-selective mismatched outcomes as defined in Scheme 1). In addition, using mass balance equations [eqn (2) and (3)],¹¹ the product diastereomeric ratio ($dr = x_2/x_3$, where x_2 and x_3 are the mole fractions of diastereoisomers **2** and **3** respectively) and the enan-

tiomeric excess of each diastereoisomer (ee_2 and ee_3) may be used to calculate the diastereomeric ratios for the reaction of (*R*)-**1** and (*S*)-**1**. These values are the same as those for the reaction of a single enantiomer of the substrate with both enantiomers of a reagent or catalyst (*i.e.* the dr values for the more-selective matched and less-selective mismatched outcomes as defined in Scheme 1). In this way the correlation between relative rate and diastereoselectivity may be determined.

$$k_{fast}/k_{slow} = s = \frac{\ln[(1-C)(1-ee_1)]}{\ln[(1-C)(1+ee_1)]} \quad (1)$$

$$[R,R']/[R,S'] = dr[(1+ee_2)/(1+ee_3)] \quad (2)$$

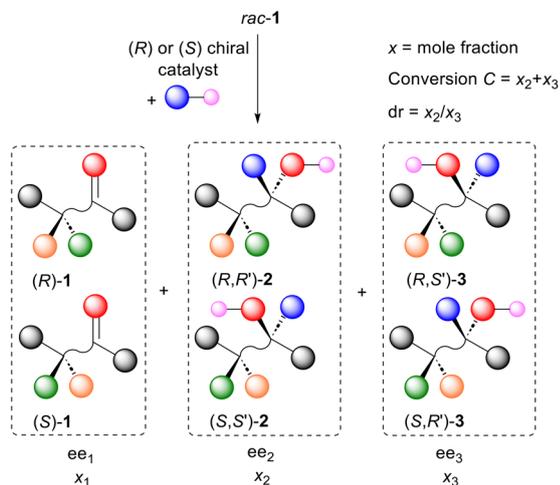
$$[S,S']/[S,R'] = dr[(1-ee_2)/(1-ee_3)] \quad (3)$$

$$Y = x_1ee_1 + x_2ee_2 + x_3ee_3 \quad (4)$$

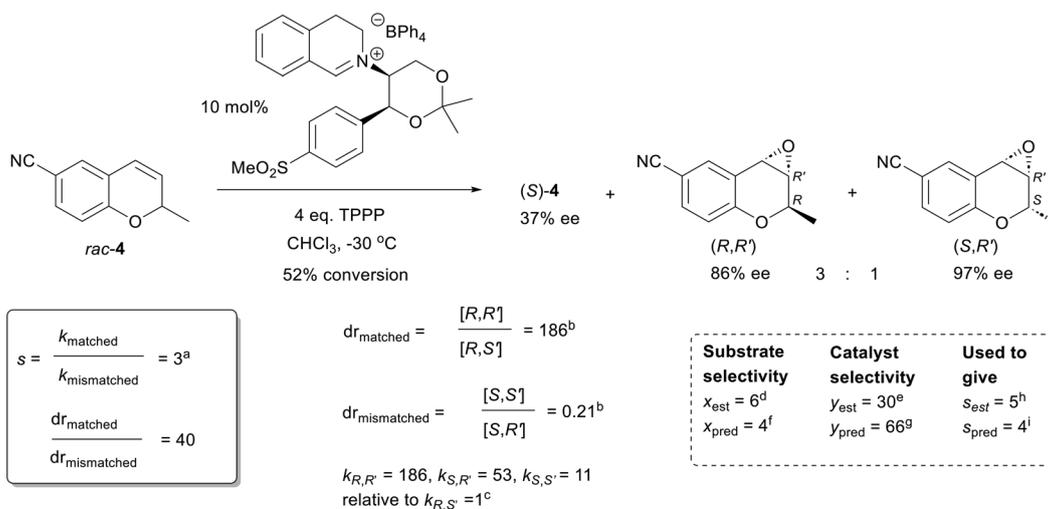
$$x_2ee_2 + x_3ee_3 = 0 \quad \text{when } C = 1 \quad (5)$$

Starting with an examination of the many reviews on kinetic resolution,¹² eleven examples of the procedure outlined in Scheme 2 were identified that contained sufficient data to determine the selectivity factor s , $[R,R']/[R,S']$ and $[S,S']/[S,R']$ (Scheme 3, Table 1, and see ESI†).¹³

As a representative example the asymmetric epoxidation of benzopyran *rac*-**4** with an iminium salt catalyst will be discussed in detail (Scheme 3).¹⁴ At 52% conversion this reaction gave recovered (*S*)-**4** (37% ee) and a 3 : 1 ratio of product diastereoisomers. These diastereoisomers are assigned using first the configuration of the stereogenic centre of the starting material from which it is derived (*R* or *S*), followed by the configuration of the closest new stereogenic centre in the product (*R'* or *S'*). Thus the major diastereoisomer with an ee of 86% is (*R,R'*), and the minor diastereoisomer with an ee of 97% is (*S,R'*). Using the sign convention where the ee value of the



Scheme 2 Schematic representation of the kinetic resolution of *rac*-**1** and conversion into diastereoisomers (*R,R'*)-**2**/*(S,S')*-**2** and (*S,R'*)-**3**/*(S,R')*-**3**.



Scheme 3 A representative kinetic resolution¹⁴ reaction used to study the relationship between s (k_{fast}/k_{slow}) and $k_{matched}/k_{mismatched}$.^aFrom eqn (1) with $C = 0.52$ and $ee_1 = 0.37$ (no sign convention for ee_1 in this calculation).^bFrom eqn (2) and (3) with $ee_2 = 0.86$, $ee_3 = -0.97$ and $dr = 3$.^cDetermined from the values of s , $[R,R']/[R,S']$ and $[S,S']/[S,R']$.^dFrom eqn (10).^eFrom eqn (9).^fFrom eqn (12).^gFrom the er value (66 : 1) obtained using the same catalyst with a related prochiral substrate.^hFrom eqn (8) with x_{est} and y_{est} .ⁱFrom eqn (8) with x_{pred} and y_{pred} .



Table 1 Additional kinetic resolution reactions examined to study the relationship between s ($k_{\text{fast}}/k_{\text{slow}}$) and $k_{\text{matched}}/k_{\text{mismatched}}$ ^{a,b}

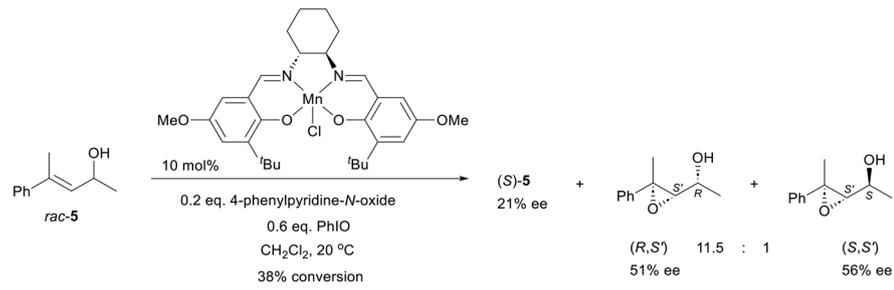
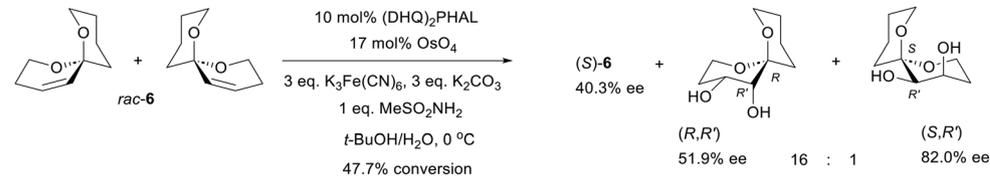
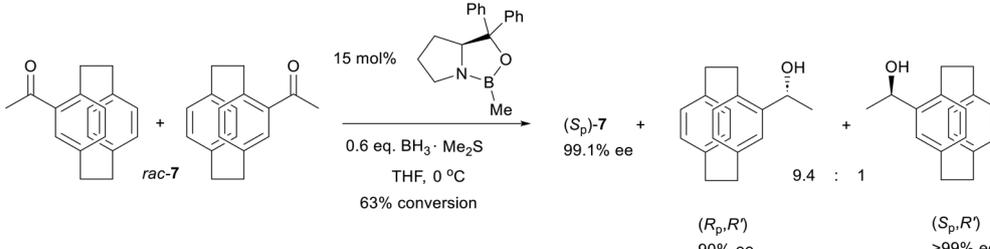
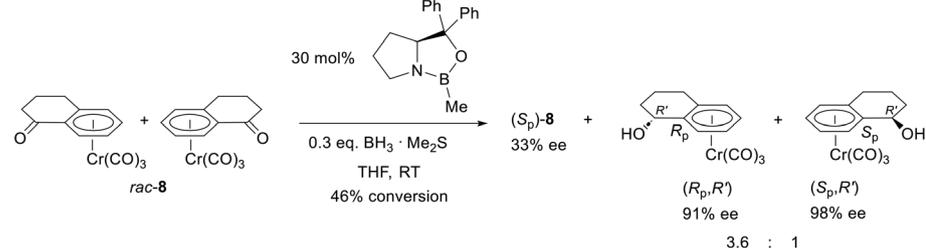
| | | | | | | | | | |
|---|--|-------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|
| <p>Entry 1¹⁶</p>  | | | | | | | | | |
| $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']^c$ | $[S,S']/[S,R']^c$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} |
| 3 | 11 | 0.025 (40) | 0.27 (3.7) | 12 | 12 | 3 | 28 | 3 | 8 |
| <p>Entry 2¹⁷</p>  | | | | | | | | | |
| $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']$ | $[S,S']/[S,R']$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} |
| 4 | 32 | 135 | 4.2 | 24 | 21 | 6 | 2 | 5 | 2 |
| <p>Entry 3¹⁸</p>  | | | | | | | | | |
| $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']$ | $[S,S']/[S,R']$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} |
| 19 | 1332 | 1653 | 1.2 | 45 | 42 | 37 | 56 | 20 | 24 |
| <p>Entry 4¹⁹</p>  | | | | | | | | | |
| $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']$ | $[S,S']/[S,R']^c$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} |
| 3 | 56 | 344 | 0.16 (6) | 8 | 4 | 46 | 56 | 7 | 4 |



Table 1 (Contd.)

| | | | | | | | | | | |
|--|--|-----------------|-----------------------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|--|
| | | | | | | | | | | |
| Entry 5 ²⁰ | | | | | | | | | | |
| $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']$ | $[S,S']/[S,R']^c$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} | |
| 39 | 3447 | 1.05 | 2.8×10^{-4} (3610) | 59 | 75 | 62 | 49 | 30 | 30 | |
| | | | | | | | | | | |
| Entry 6 ²¹ | | | | | | | | | | |
| $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']$ | $[S,S']/[S,R']^c$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} | |
| 16 | 567 | 4.1 | 0.0004 (2352) | 24 | 20 | 99 | 21 | 19 | 10 | |
| | | | | | | | | | | |
| Entry 7 ²² | | | | | | | | | | |
| $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']$ | $[S,S']/[S,R']^c$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} | |
| 9 | 5 | 7.1 | 0.74 (1.4) | 2 | 5 | 3 | 5 | 2 | 3 | |
| | | | | | | | | | | |
| Entry 8 ²³ | | | | | | | | | | |
| $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']$ | $[S,S']/[S,R']$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} | |
| 14 | 51 | 93 | 1.8 | 13 | 29 | 7 | 28 | 5 | 14 | |



Table 1 (Contd.)

Entry 9²⁴

| $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']^c$ | $[S,S']/[S,R']$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} |
|--|--|-------------------|-----------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|
| 16 | 57 | 0.46 (2.2) | 125 | 8 | 20 | 17 | 99 | 5 | 16 |

Entry 10²⁵

| $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']^c$ | $[S,S']/[S,R']$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} |
|--|--|-------------------|-----------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|
| 36 | 44 | 0.017 (59) | 1.3 | 7 | 31 | 9 | 199 | 4 | 26 |

^a Values of s , $[R,R']/[R,S']$, $[S,S']/[S,R']$, x_{est} , y_{est} , x_{pred} , s_{est} and s_{pred} determined as given in Scheme 3, and details of the determination of the values for y_{pred} are given in the ESI.[†] ^b Selectivity factor s quoted to nearest integer for values <50 .²⁶ ^c For values <1 the inverse value is shown in parenthesis.

starting material and compounds derived from it is +ve if R , and -ve if S , $ee_1 = -0.37$, $ee_2 = 0.86$ and $ee_3 = -0.97$, with $x_1 = 0.48$, $x_2 = 0.39$ and $x_3 = 0.13$. The validity of these data was checked using eqn (4),¹¹ a further mass balance relationship where ideally $Y = 0$. In this instance $Y = 0.03$, and for all the examples used in this study $Y \leq \pm 0.05$. From these data application of eqn (1) with $C = x_2 + x_3$ gave $s = 3$, application of eqn (2) with $dr = x_2/x_3$ gave $[R,R']/[R,S'] = 186$, and application of eqn (3) gave $[S,S']/[S,R'] = 0.21$. Thus the faster reacting (R) enantiomer is significantly more selective ($dr = 186:1$) than the slower reacting (S) enantiomer ($dr = 4.8:1$, i.e. $1/0.21:1$) such that $k_{\text{matched}}/k_{\text{mismatched}} = s$ (with $dr_{\text{matched}}/dr_{\text{mismatched}} = 40$).

This positive correlation between rate and diastereoselectivity was observed in all the other ten examples studied (Table 1).^{16–25} In many cases the example used (Scheme 3 and Table 1 entries 1, 2, 5 and 10) is one of several related kinetic resolution procedures. These were also analysed and found to give the same positive correlation (32 examples in total, see ESI[†]).

The assumptions made in this analysis are those required for the application of eqn (1) for the calculation of s : namely that each reaction proceeds with pseudo first-order kinetics in the substrate, there are no non-linear effects, and that no side reactions take place (none are reported for the examples used in Scheme 3/Table 1).²⁷ Reactions of this type have been classified by Kagan as 'divergent reactions on a racemic mixture'.^{11b}

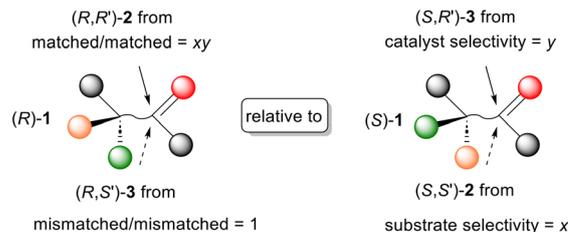
If run to completion the minor diastereoisomer will have the higher ee, a consequence of mass balance as formulated by the Horeau equation, eqn (5).²⁸ In a kinetic resolution procedure this is not necessarily so and the minor diastereoisomer may have the lower ee (e.g. see entries 7 and 10). Using the calculated values for s , $[R,R']/[R,S']$ and $[S,S']/[S,R']$, the relative rate of formation of each stereoisomer may be determined. For the example illustrated in Scheme 3 these values are: $k_{R,R'} = 186$, $k_{S,R'} = 53$ and $k_{S,S'} = 11$, relative to $k_{R,S'} = 1$. In turn this may be used to predict reaction mixture composition as a function of conversion.²⁹

As a hypothetical example of the alternative scenario where the matched reaction is slower ($k_{\text{matched}}/k_{\text{mismatched}} = 1/s$), the progress of *rac*-4 epoxidation (Scheme 3) was calculated with the same value of s (3) but where $[R,R']/[R,S'] = 1/([S,S']/[S,R'])$ and $[S,S']/[S,R'] = 1/([R,R']/[R,S'])$. This revealed that at 52% conversion, in addition to remaining (*S*)-4 (37% ee), the major (*R,R'*, 99% ee) and minor (*S,R'*, 47% ee) products would form with $dr = 1.3:1$. Thus in addition to the same enantiomer of recovered starting material, kinetic resolution where the matched reaction is slower may also result in the same major and minor product diastereoisomers, albeit with different product ee and dr values to that of the actual case where the matched reaction is faster. This highlights the viability of such an outcome, and the significance of the positive correlation between rate and selectivity observed in all the examples summarised in Scheme 3 and Table 1.



A model to account for the rate/selectivity correlation

Underpinning the concept of double asymmetric synthesis were studies on the stereoselectivity of the two corresponding single asymmetric syntheses;² specifically the diastereoselectivity ($x : 1$) of the reaction of a chiral substrate (*e.g.* (*R*)-1) with an achiral catalyst (Scheme 4(i)), and the enantioselectivity ($y : 1$) of the reaction of a related prochiral substrate (*e.g.* 15) with an enantiopure catalyst (Scheme 4(ii)). The differences in the free energy of activation giving rise to these selectivities may be expressed as $\Delta\Delta G_1^\ddagger$ and $\Delta\Delta G_2^\ddagger$, respectively. Then for a double asymmetric reaction, the selectivity of the matched pair ($\Delta\Delta G_1^\ddagger + \Delta\Delta G_2^\ddagger$) = xy and the mismatched pair ($\Delta\Delta G_1^\ddagger - \Delta\Delta G_2^\ddagger$) = x/y . The additional perturbation terms ΔG_{12}^\ddagger and $\Delta G'_{12}^\ddagger$ of eqn (6) and (7) account for conformational differences in the transition states of the double asymmetric reactions compared to the corresponding single asymmetric reactions.² Provided these are relatively small, summation and subtraction of the values for $\Delta\Delta G_1^\ddagger$ and

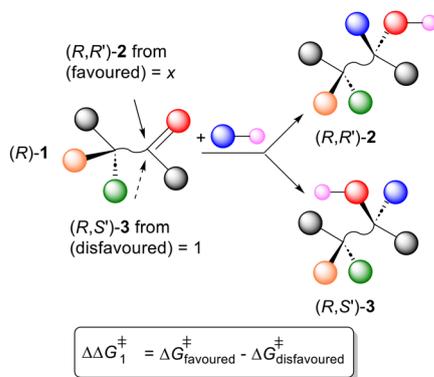


Scheme 5 Schematic representation of the reaction of (*R*) and (*S*)-1 with an enantiopure catalyst and the resulting relative rates as a function of substrate (x) and catalyst (y) selectivities.

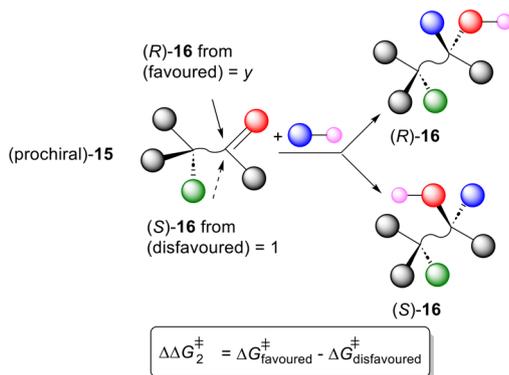
$\Delta\Delta G_2^\ddagger$ works well for the prediction of the diastereoselectivities observed in the matched and mismatched double asymmetric syntheses.

Extension to the reaction of (*R*)-1/(*S*)-1 with an enantiopure catalyst gives four scenarios, exemplified by the formation of (*R,R'*)-2, (*S,S'*)-2, (*R,S'*)-3 and (*S,R'*)-3 (where (*R*)-1 is the fast reacting enantiomer favouring (*R,R'*)-2, Scheme 5).

(i) Substrate selectivity [$dr = x : 1$ ($x > 1$)]



(ii) Chiral catalyst selectivity [$er = y : 1$ ($y > 1$)]



$$\Delta\Delta G^\ddagger (\text{matched}) = \Delta\Delta G_1^\ddagger + \Delta\Delta G_2^\ddagger + \Delta G_{12}^\ddagger \quad \text{eq. (6)}$$

$$\Delta\Delta G^\ddagger (\text{mismatched}) = \Delta\Delta G_1^\ddagger - \Delta\Delta G_2^\ddagger + \Delta G_{12}^\ddagger \quad \text{eq. (7)}$$

Scheme 4 Schematic representation of the reactions of (i) (*R*)-1 with an achiral catalyst and (ii) (prochiral)-15 with an enantiopure catalyst, giving rise to the substrate (x) and catalyst (y) selectivity values.

$$s = \frac{k_{R,R'} + k_{R,S'}}{k_{S,S'} + k_{S,R'}} = \frac{k_{\text{matched}}}{k_{\text{mismatched}}} \approx \frac{xy + 1}{x + y} \quad \text{eq. (8)}$$

$$x = \text{substrate } dr \ (x : 1) \quad y = \text{catalyst } er \ (y : 1)$$

$$y_{\text{est}} = \sqrt{a/b} \quad \text{eq. (9)} \quad x_{\text{est}} = a/y_{\text{est}} \quad \text{eq. (10)}$$

If the substrate diastereoselectivity $dr = x : 1$,³⁰ and the catalyst enantioselectivity $er = y : 1$ (x and $y > 1$), then to a first approximation the relative rates of reaction to give the following are: (*R,R'*)-2 = xy , (*R,S'*)-3 = 1, (*S,S'*)-2 = x and (*S,R'*)-3 = y . The $\Delta\Delta G^\ddagger$ value of the matched/matched reaction is given by the sum of the $\Delta\Delta G_1^\ddagger$ and $\Delta\Delta G_2^\ddagger$ values (Scheme 4) relative to $\Delta\Delta G^\ddagger = 0$ for the mismatched/mismatched reaction. Then the relative rate of reaction of (*R*)-1 and (*S*)-1 is given by eqn (8), such that then $s = k_{\text{matched}}/k_{\text{mismatched}} > 1$. The faster double asymmetric synthesis reaction is more selective.

Determination of the substrate and catalyst selectivity terms

x_{est} and y_{est}

By extension from eqn (8), then $[R,R']/[R,S'] = xy/1$ and $[S,S']/[S,R'] = x/y$, and from these are derived³¹ eqn (9) and (10). The values of x and y calculable from these equations are designated as x_{est} and y_{est} , *i.e.* estimated values for the contributing substrate and catalyst stereoselectivities, respectively. For the example in Scheme 3, the already determined values of $[R,R']/[R,S'] = 186$ ($= a$) and $[S,S']/[S,R'] = 0.21$ ($= b$) are used in eqn (10) and (9) to give $x_{\text{est}} = 6$ and $y_{\text{est}} = 30$. This reveals that the substrate facial selectivity is relatively low (6 : 1), but the catalyst facial selectivity is high (30 : 1). From these x_{est} and y_{est} values, use of eqn (8) gives s_{est} , an estimated value of the selectivity factor, which for this example results in $s_{\text{est}} = 5$. This, and several of the examples in Table 1 approximate to this model ($s \approx s_{\text{est}}$, entries 1–6), in other cases the selectivity

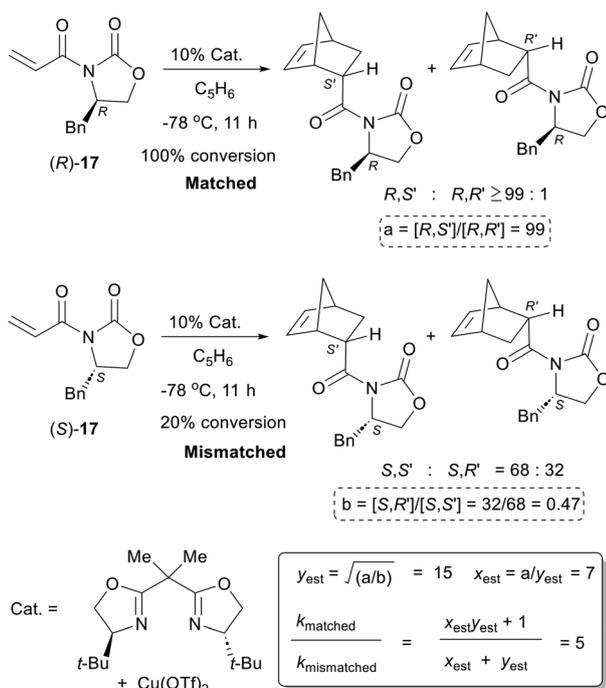


factor is significantly higher than that estimated using eqn (8)–(10) (entries 7–10).³²

$$\frac{dr_{\text{matched}}}{dr_{\text{mismatched}}} = y_{\text{est}}^2 \quad (\text{where } x_{\text{est}} > y_{\text{est}}) \quad (11)$$

$$\text{or } x_{\text{est}}^2 \quad (\text{where } y_{\text{est}} > z_{\text{est}})$$

From the model the ratio $dr_{\text{matched}}/dr_{\text{mismatched}}$ is given by eqn (11),³³ and higher values of this ratio correspond to higher values of s (Scheme 3 and Table 1, entries 1–6), although again this is less apparent where $s > s_{\text{est}}$ (Table 1, entries 7–10). The catalyst selectivity term y_{est} is the same as the ‘average diastereofacial selectivity’ of a chiral reagent proposed by Roush for the analysis of tartrate allylboronate addition to chiral alkoxy-substituted aldehydes.³⁴ As eqn (10) provides, additionally, the corresponding value for a chiral substrate (x_{est}), extension to eqn (8) allows $k_{\text{matched}}/k_{\text{mismatched}}$ to be estimated simply from the matched and mismatched dr values of a double asymmetric procedure. For example, (*S,S*)-bisoxazoline-copper catalysed Diels–Alder reaction of (*R*)-17 and (*S*)-17 with cyclopentadiene are stereochemically matched and mismatched, respectively (Scheme 6).^{6a} The values of $y_{\text{est}} = 15$ [from eqn (9)] and $x_{\text{est}} = 7$ [from eqn (10)] derived from the diastereomeric ratios may be used with eqn (8) to give $k_{\text{matched}}/k_{\text{mismatched}} = 5$. This difference in rate is in approximate agreement with the conversion values of 100% and 20% noted for the matched and mismatched reactions, respectively. In this paper it is noted that in the mismatched example the cycloadduct is derived from a catalyst-dominated rather than a substrate-dominated process.



Scheme 6 Matched and mismatched (*S,S*)-bisoxazoline-copper catalysed Diels–Alder reactions of (*R*) and (*S*)-17 with cyclopentadiene, and estimation of the relative rate.

This is now captured by the larger value of the catalyst selectivity term y_{est} compared to the substrate selectivity term x_{est} .

Determination of the substrate and catalyst selectivity terms

x_{pred} and y_{pred}

As an alternative to estimating the substrate selectivity term using dr values with eqn (9) and (10), it may be determined using eqn (12) from the experimentally determined relative rate values for $k_{R,R'}$, $k_{S,R'}$ and $k_{S,S'}$, with $k_{R,S'} = 1$. This provides a *predictive* value for x , designated x_{pred} . Here x_{pred} is equal to the diastereoselectivity at the start of the reaction (*i.e.* conversion $\ll 1\%$, before any significant kinetic resolution can take place), a value which is the same as the diastereoselectivity resulting from the reaction of the racemic catalyst with either the racemic or non-racemic substrate (where kinetic resolution cannot take place).³⁰ In an ideal case $k_{S,S'} = x_{\text{est}} = x_{\text{pred}}$ ³⁵ and $k_{S,R'} = y_{\text{est}}$. However, as x_{pred} captures deviations from ideality³⁶ it may be used in eqn (8) to provide s_{pred} , a *predictive* value of the selectivity factor. For this calculation an experimentally determined value of y_{pred} is required, and this is provided by the known product ratio resulting from the reaction of a closely related prochiral substrate with the same catalyst. For the example in Scheme 3, use of the same catalyst and conditions with 6-cyano-2,2-dimethylbenzopyran, a prochiral substrate similar to **4**, resulted in an er of 98.5 : 1.5.¹⁵ Thus $y_{\text{pred}} = 66$, and with $x_{\text{pred}} = 4$, then use of eqn (8) gives $s_{\text{pred}} = 4$. Unlike s_{est} , which can underestimate the selectivity factor s in some cases (entries 7–10), the value of s_{pred} is in good agreement with s in most cases. Overall, this analysis reveals that the use of eqn (8), with x and y values as defined in Scheme 5, is applicable as at least an approximate model for the relative kinetics of the matched and mismatched reactions arising from a double asymmetric synthesis procedure.

$$x_{\text{pred}} = \frac{k_{R,R'} + k_{S,S'}}{k_{R,S'} + k_{S,R'}} \quad (12)$$

Understanding the outcome of a kinetic resolution using substrate and catalyst selectivity terms

A successful kinetic resolution, where reaction of the substrate results in an additional chirality element in the product, requires not only a high level of catalyst selectivity, but also a high level of substrate selectivity. Dihydroxylation of *rac*-**6** (Table 1, entry 2) proceeds with a high level of substrate control ($x_{\text{est}} = 24$, $x_{\text{pred}} = 21$) but with less selective catalyst control ($y_{\text{est}} = 6$). Therefore the relative inefficiency of this kinetic resolution is a consequence of *cis*-alkenes being comparatively poor substrates for Sharpless asymmetric dihydroxylation.³⁷

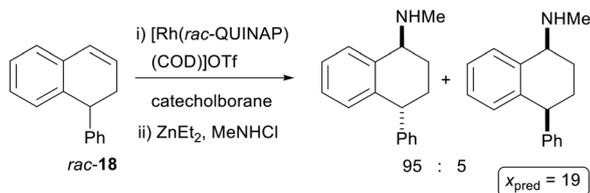
It is instructive to compare two examples of the kinetic resolution of a planar chiral aryl/methyl ketone by CBS catalysed reduction. Table 1, entry 3 summarises the use of a [2.2] paracyclophane substrate *rac*-**7**,¹⁸ and Table 1, entry 4 the use of 1-tetralone- $\text{Cr}(\text{CO})_3$ *rac*-**8** as substrate.¹⁹ With prochiral aryl/alkyl ketones the CBS catalyst results in high reduction



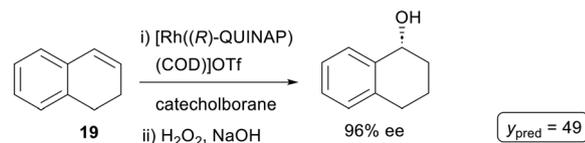
enantioselectivity ($y_{\text{pred}} = 56$ from the 96.5% ee observed with acetophenone),³⁸ and a high level of catalyst control is maintained in the two planar chiral examples ($y_{\text{est}} = 37$ and 46, entries 3 and 4). In contrast, the reaction of *rac*-7 is much more diastereoselective than the reaction of *rac*-8 ($x_{\text{est}} = 45$ vs. 8 and $x_{\text{pred}} = 42$ vs. 4) accounting for the inefficient kinetic resolution of the latter. As discussed above, the value x_{pred} corresponds to the diastereomeric ratio resulting from the reaction of a chiral substrate with a racemic catalyst.³⁰ Therefore a diastereomeric ratio of 4 : 1 is expected for the reduction of **8** with racemic CBS. This is in contrast to the very high diastereoselectivity observed with this substrate on reduction with LiAlH_4 or NaBH_4 (also favouring formation of the *cis*-product).³⁹ This highlights that the diastereoselectivity with a racemic chiral catalyst or reagent can be significantly different to that of an achiral alternative.⁴⁰

The predictive use of this analysis is further illustrated by studies on dihydronaphthalene hydroboration. Regioselective reaction of racemic **18** with *rac*-QUINAP/Rh followed by amination gave a 19 : 1 ratio of product diastereoisomers such that $x_{\text{pred}} = 19$ (Scheme 7(i)).⁴¹ The corresponding reaction of the related prochiral substrate 1,2-dihydronaphthalene **19** with (*R*)-QUINAP resulted, after H_2O_2 oxidation, in the (*R*)-alcohol with an er of 98 : 2, such that $y_{\text{pred}} = 49$ (Scheme 7(ii)).⁴² Thus for the kinetic resolution of **18**, using these data with eqn (8) gives $s_{\text{pred}} = 14$. These data can also be used to predict the dr ratio

(i) Determination of x_{pred} with the racemic catalyst⁴⁰



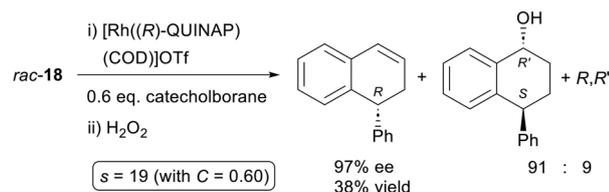
(ii) Determination of y_{pred} with the enantiopure catalyst with a related prochiral substrate⁴¹



(iii) Kinetic resolution⁴⁰

$$\text{Calculation from } x_{\text{pred}} \text{ and } y_{\text{pred}}: s_{\text{pred}} = \frac{x_{\text{pred}} y_{\text{pred}} + 1}{x_{\text{pred}} + y_{\text{pred}}} = 14$$

Experimental⁴⁰



Scheme 7 Hydroboration of *rac*-**18** – determination of s_{pred} and kinetic resolution.

and ee values for the products.⁴³ For comparison, from the experimental kinetic resolution of *rac*-**18** with (*R*)-QUINAP/Rh,⁴¹ using the reported value for ee₁ and an approximate value of *C* (0.60), the selectivity factor calculated with eqn (1) is 19 (Scheme 7(iii)). This example further illustrates that provided a catalyst is known to result in high enantioselectivity with a related prochiral substrate, x_{pred} , the substrate selectivity term, may be used to provide a good indication of the suitability of a racemic substrate for divergent kinetic resolution.

Additional examples

We next applied this model to the four reactions mentioned in the introduction for which the relative rate of the matched/mismatched reactions have been determined, in these instances due to the selectivity factor *s* having been calculated for the kinetic resolution of the racemic substrate.^{8,9} For these examples, the $[R,R']/[R,S']$ and $[S,S']/[S,R']$ ratios were obtained by either reaction of one enantiomer of the substrate with both enantiomers of the catalyst, or by reaction of one enantiomer of the catalyst with both enantiomers of the substrate (Table 2).

The efficient kinetic resolution of *rac*-**20**^{8a} and *rac*-**21**^{8b} (entries 1 and 2) is in part a consequence of the excellent diastereoselectivity of the reactions used with these substrates ($x_{\text{pred}} = 38$ and 55 respectively). Indeed, the DHQD/anthracene based ligand used for the dihydroxylation of **21** was designed to achieve high diastereoselectivity with chiral allylic 4-methoxybenzoates.^{8b} For entry 3 the $[S,S']/[S,R']$ and $[R,R']/[R,S']$ values used are the ratio of products obtained from the reaction of (*R*)-**22** with AD-mix- α and AD-mix- β , these containing quasi-enantiomeric (DHQ)₂PHAL and (DHQD)₂PHAL ligands respectively.^{8c} This difference results in two *s* values for the kinetic resolution of *rac*-**22** with these mixtures, and in turn two values for x_{pred} and s_{pred} (entry 3). Similarly, two *s* values were obtained for the kinetic resolution of *rac*-**23** by Sharpless asymmetric dihydroxylation, with AD-mix- β again being more efficient (entry 4).⁹ In this work the two enantiomers of **23** were also dihydroxylated with both AD-mix- α and β revealing essentially complete catalyst control and therefore no expected kinetic resolution ($s_{\text{est}} \approx 1$).

The exception to the rule

In light of this dichotomy we reinvestigated these reactions, first by performing the dihydroxylation of *rac*-**23** with a reaction mixture containing quinuclidine in place of the cinchona alkaloid-based ligands. This resulted in a 1 : 5.3 ratio of diastereoisomers **24** and **25** (previous report (ref. 9) = 1 : 6) with equatorial dihydroxylation dominating. Kinetic resolution of *rac*-**23** with AD-mix- α gave (*R*_a)-**23** (93% ee, *C* = 0.90, *s* = 3) and with AD-mix- β gave (*S*_a)-**23** (98% ee, *C* = 0.85, *s* = 5). In our hands subsequent use of both enantioenriched substrates with AD-mix- α and β revealed much lower levels of diastereoselectivity than reported previously (Table 2, entry 5). Significantly, a degree of substrate control was observed with (*R*_a)-**23**/ α and (*S*_a)-**23**/ β = matched (**24**:**25** \approx 1 : 8 dr) and (*S*_a)-**23**/ α and (*R*_a)-**23**/ β = mismatched (**24**:**25** \approx 3 : 1 dr). Unexpectedly, the more selective combi-



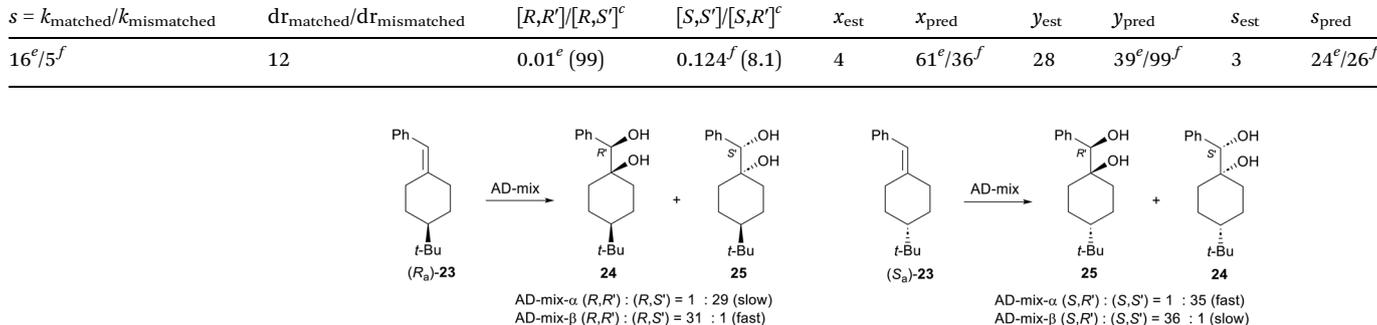
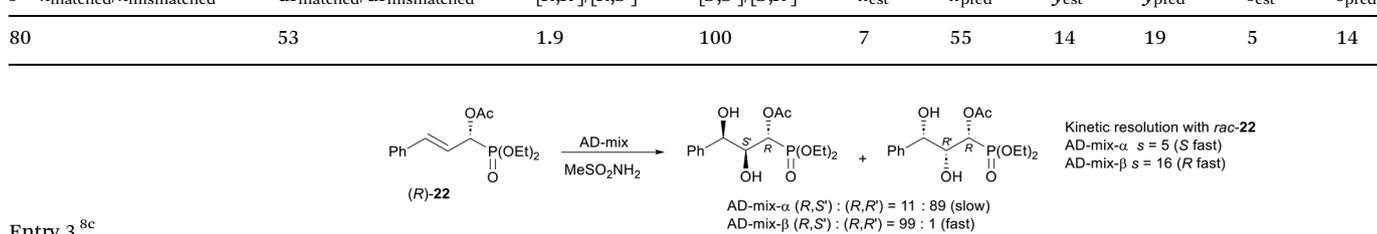
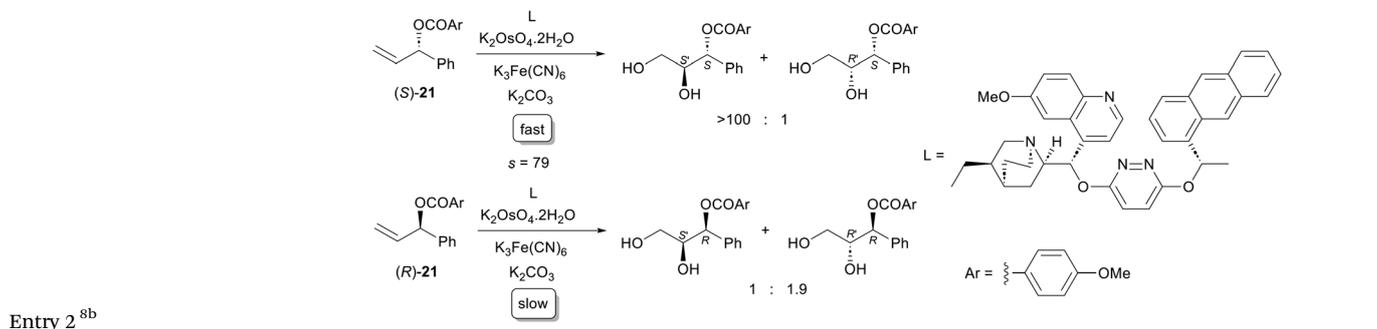
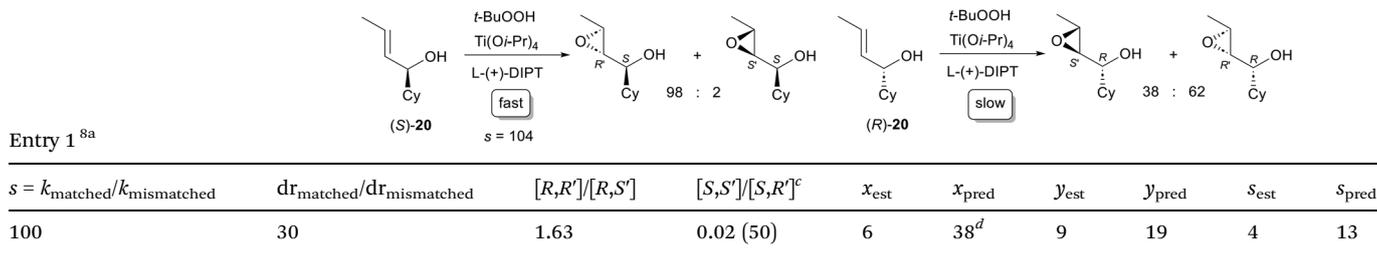
Table 2 Additional examples used to study the relationship between s ($k_{\text{fast}}/k_{\text{slow}}$) and $k_{\text{matched}}/k_{\text{mismatched}}$ where the $[R,R']/[R,S']$ and $[S,S']/[S,R']$ ratios were determined from the reaction of single enantiomer substrates^{a,b}

Table 2 (Contd.)

Kinetic resolution with *rac*-23 AD-mix- α $s = 3$ (S_a fast) AD-mix- β $s = 5$ (R_a fast)

| Entry 5 | $s = k_{\text{matched}}/k_{\text{mismatched}}$ | $dr_{\text{matched}}/dr_{\text{mismatched}}$ | $[R,R']/[R,S']^c$ | $[S,S']/[S,R']^c$ | x_{est} | x_{pred} | y_{est} | y_{pred} | s_{est} | s_{pred} |
|----------------|--|--|-------------------|-------------------|------------------|-------------------|------------------|-------------------|------------------|-------------------|
| 5 ^e | 0.3 | | 2.4 | 0.123 (8.1) | 0.54 | 1.6 | 4.4 | 24 ^e | 0.7 | 1.5 |
| 3 ^f | 0.4 | | 0.13 (7.5) | 2.8 | 0.61 | 1.4 | 4.6 | 24 ^g | 0.7 | 1.4 |

^a Values of s , x_{est} , y_{est} , x_{pred} , s_{est} and s_{pred} determined as given in Scheme 3, and details of the determination of the values for y_{pred} are given in the ESI.† ^b Selectivity factor s quoted to nearest integer for values <50 and to the nearest 10 for values between 50–200, except for entries 4 and 5.²⁶ ^c For values <1 the inverse value is shown in parenthesis. ^d Diastereoselectivity measured in the early stages of the reaction = 32 : 1. ^e AD-mix- β . ^f AD-mix- α . ^g Value for AD-mix- α not available therefore value obtained with AD-mix- β used.

nations were slower ($s_{\text{est}} = 0.7$ for both α and β). In the previous investigation into this reaction it was noted that the fastest forming diol in the kinetic resolution experiments is the axial diastereoisomer **24**, *i.e.* the alternative to that formed preferentially using quinuclidine as ligand.⁴⁴ As the ratio of diols formed is a function of conversion in the kinetic resolutions,⁴⁵ this axial preference may be quantified by the values of x_{pred} (1.4 and 1.6 for AD-mix- α and β respectively). This low diastereoselectivity explains, at least in part, the poor efficiency of the corresponding kinetic resolution procedures. It is possibly significant that this one exception to the rule of ‘matched reactions are faster’ is in an example where the diastereoselectivity inverts on changing from a catalyst with an achiral ligand to a catalyst containing a related chiral ligand.

Conclusions

The reaction of an enantiopure substrate with formation of a new chirality element results in a fast-matched outcome with one enantiomer of a catalyst, and a slow-mismatched outcome with the other enantiomer of the catalyst, when not under complete catalyst or substrate control. This was established primarily by examination of known literature kinetic resolution procedures that result in the formation of a new stereogenic centre. A model is proposed accounting for the fast-matched/slow-mismatched outcomes, and from the diastereomeric ratio values (relative to 1) of these two reactions the individual substrate (x_{est}) and catalyst (y_{est}) selectivity contributions may be estimated. These values may then be used to estimate the relative rate of the two reactions ($k_{\text{matched}}/k_{\text{mismatched}} = s_{\text{est}}$), and in the context of kinetic resolution the values for x_{est} and y_{est} provide insight into the efficiency of this process. Also of utility is the additional substrate selectivity number (x_{pred}), a value which is also the diastereomeric ratio for the reaction of

the racemic catalyst with the substrate. Use of this, in conjunction with the enantiomeric ratio for the reaction of a related prochiral substrate with the enantiopure catalyst (y_{pred}), provides a good prediction of the kinetic resolution selectivity factor (s_{pred}). Values obtained for x_{est} and x_{pred} highlight the change in diastereoselectivity that can occur by switching from an achiral catalyst or reagent to a chiral counterpart.

Experimental

General information

Silica gel (60 Å pore size, 40–63 μm technical grade) was used for chromatography. Compound *rac*-23 was prepared essentially as reported previously.⁴⁶

Dihydroxylation of *rac*-23 with quinuclidine-based AD-mix

Quinuclidine (29.2 mg, 0.26 mmol, 0.1 eq.) was added to a stirred light-brown solution of $\text{K}_2\text{OsO}_4 \cdot 2\text{H}_2\text{O}$ (19.4 mg, 0.053 mmol, 0.02 eq.) in H_2O (33 mL) at room temperature. The resulting cloudy-white brown solution was stirred for 15 min, then *t*-BuOH (33 mL), $\text{K}_3\text{Fe}(\text{CN})_6$ (865.9 mg, 2.63 mmol, 1.0 eq.), K_2CO_3 (363.2 mg, 2.63 mmol, 1.0 eq.) and MeSO_2NH_2 (250 mg, 2.63 mmol, 1.0 eq.) were added simultaneously. After 5 min, *rac*-23 (600 mg, 2.63 mmol, 1.0 eq.) was added to the yellow solution which was then stirred for 48 h at room temperature. The resulting mixture was concentrated *in vacuo* (40 torr, 50 °C) to dryness and the crude material was purified by silica gel chromatography using 20% EtOAc/hexane. Compound *rac*-24 and *rac*-25 were isolated together in a 1 : 5.3 ratio as a crystalline colourless solid (400 mg, 1.52 mmol, 58% yield). Further purification by silica gel chromatography using 5–10% EtOAc/hexane enabled the isolation of both diastereoisomers as a colourless solid.



Data for *rac*-**24**:⁴⁷ Mp: 162–168 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.28 (m, 5H), 4.37 (s, 1H), 2.48 (s, 1H), 1.82–1.78 (m, 1H), 1.72 (s, 1H), 1.56–1.46 (m, 2H), 1.44–1.39 (m, 1H), 1.32–1.13 (m, 5H), 0.76 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 140.4, 127.9, 127.8, 127.7, 81.4, 73.4, 47.7, 34.8, 32.4, 32.2, 27.5, 22.2, 22.0. IR (cm⁻¹) ν: 3407, 2933, 2864, 2359, 1450, 1389, 1012. HRMS (ASAP-TOF) *m/z*: [M + H]⁺ calcd for C₁₇H₂₆O₂ 262.1933; found 262.1930.

Data for *rac*-**25**: Mp: 162–168 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.36–7.22 (m, 5H), 4.77 (d, *J* = 6.0 Hz, 1H), 2.37–2.31 (m, 2H), 1.89 (s, 1H), 1.77–1.70 (m, 1H), 1.56–1.50 (m, 1H), 1.48 (s, 1H), 1.37–1.02 (m, 5H), 0.83 (s, 9H). ¹³C NMR (101 MHz, CDCl₃) δ 140.6, 128.3, 128.0, 127.6, 77.2, 74.0, 47.3, 35.8, 35.7, 32.8, 27.6, 24.2, 23.8. IR (cm⁻¹) ν: 3333, 2941, 2865, 2360, 1453, 1364, 1061, 1042.

Kinetic resolution of *rac*-**23** with AD-mix-α

AD-mix alpha (5.00 g, 0.0016 eq. Os) was added all at once to a stirred solution of *rac*-**23** (1.000 g, 4.38 mmol, 1.0 eq.) and methanesulfonamide (1.000 g, 10.51 mmol, 2.40 eq.) in *t*-BuOH/H₂O (1 : 1) (300 mL) at room temperature. The resulting yellow solution was stirred at room temperature for 14 days. The reaction was monitored by HPLC and stopped when the ee of **23** reached 93% ee. The solvents were removed *in vacuo* (40 torr, 50 °C) and the crude material was purified using 0–20% EtOAc/hexane. Compound (*R*_a)-**23** was obtained as a light-yellow oil (75 mg, 0.33 mmol, 7.5% yield, 93% ee) and compounds **24** and **25** were obtained as a colourless solid as a ≈ 1 : 1 mixture of diastereoisomers (0.82 g, 3.125 mmol, 71% yield). Conversion ≈ 90%, *s* = 3 (valid for a conversion range of 87–94%). The absolute configuration of (*R*_a)-**23** was confirmed by polarimetry [α]_D²² = -15.4 (*c* 0.13, CHCl₃) [Lit.⁴⁷ = -37.4 (*c* 0.59, MeOH)].

Kinetic resolution of *rac*-**19** with AD-mix-β

AD-mix beta (5.00 g, 0.0016 eq. Os) was added all at once to a stirred solution of *rac*-**23** (1.000 g, 4.38 mmol, 1.0 eq.) in *t*-BuOH/H₂O (1 : 1) (300 mL) at room temperature. The resulting yellow solution was stirred at room temperature for 7 days. The reaction was monitored by HPLC and stopped when the ee of **21** reached 98% ee. The solvents were removed *in vacuo* (40 torr, 50 °C) and the crude material was purified using 0–20% EtOAc/hexane. Compound (*S*_a)-**23** was obtained as a light-yellow oil (122 mg, 0.534 mmol, 12% yield, 98% ee) and compounds **24** and **25** were obtained as a colourless solid as a ≈ 1 : 1 mixture of diastereoisomers (0.78 g, 2.97 mmol, 68% yield). Conversion ≈ 85%, *s* = 5 (valid for conversion range of 82–86%). The absolute configuration of (*S*_a)-**23** was confirmed by polarimetry [α]_D²² = +28.6 (*c* 0.84, CHCl₃) [Lit.⁴⁸ = +32.8 (*c* 1.39, MeOH)].

General procedure for the dihydroxylation of (*R*_a)-**23** and (*S*_a)-**23**

AD-mix-α or β (150 mg, 0.0016 eq. Os) was added all at once to a stirred solution of either (*R*_a)-**23** or (*S*_a)-**23** (30 mg, 0.13 mmol, 1.0 eq.) and methanesulfonamide (30 mg,

0.32 mmol, 2.4 eq.) in *t*-BuOH/H₂O (1 : 1) (10 mL) at room temperature. The resulting yellow solution was stirred at room temperature for 3 days. After the reaction had reached completion, the solvent was removed *in vacuo* (40 torr, 50 °C) and the crude material was purified using 0–20% EtOAc/hexane to give a mixture of **24** and **25** as a colourless solid.

Using AD-mix-α and (*R*_a)-**23** (93% ee) gave **24** and **25** as a 1 : 7.5 mixture of diastereoisomers (29 mg, 0.111 mmol, 84% yield).

Using AD-mix-β and (*R*_a)-**23** (93% ee) gave **24** and **25** as a 2.4 : 1 mixture of diastereoisomers (30 mg, 0.114 mmol, 85% yield).

Using AD-mix-α and (*S*_a)-**23** (98% ee) gave **24** and **25** as a 2.8 : 1 mixture of diastereoisomers (20 mg, 0.076 mmol, 58% yield).

Using AD-mix-β and (*S*_a)-**23** (98% ee) gave **24** and **25** as a 1 : 8 mixture of diastereoisomers (18 mg, 0.069 mmol, 53% yield).

Author contributions

The manuscript was written through contributions of all authors.

Conflicts of interest

There are no conflicts to declare.

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 - 32 In these cases $k_{R,R'}$ is larger than expected relative to $k_{S,R'}$ and $k_{S,S'}$. This could be due to additional factors favouring formation of the *R,R'* isomer, or disfavoured the reaction of the *S* substrate (to give *S,R'* and *S,S'* products), or a combination of the two.
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- 44 It was this observation that dihydroxylation of the fast reacting olefin in the kinetic resolution is preferentially from the “intrinsically disfavored diastereoface” that lead to the statement quoted in the introduction to this paper.⁹
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