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Is It Possible To Estimate the Enantioselectivity of a Chiral Catalyst from Its Racemic Mixture?

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In recent years, parallel synthesis and screening technologies have increasingly been applied to the discovery of chiral catalysts.[1−3] The evaluation of enantioselective catalysts in a parallel fashion is necessary to avoid the cancellation of opposing enantioselectivities that would result from combined screening. It would be extremely useful to directly measure the enantioselectivity of the component enantiomers of a racemic catalyst without first having to resolve or prepare the individual catalyst enantiomers.[4−8] In this Communication, we report and discuss our finding that the diastereoselectivity observed upon sequential transformation of an achiral substrate bearing two remote prochiral centers can sometimes be used to calculate catalyst enantioselectivity.

There are many reports of the reaction of an enantiopure reagent or catalyst with an achiral substrate bearing multiple prochiral centers.[9−14] Scheme 1 illustrates the simple case of a symmetrical diketone **1** with remote carbonyls that is quantitatively reduced in the presence of a chiral catalyst to afford a mixture of the three stereoisomers of diol **3**. For a reaction utilizing an enantiopure catalyst, it is easy to establish that if one defines ee_1 as the enantioselectivity of the first step (formation of intermediate ketol, **2**) and de_2 as the diastereoselectivities of the second step (assumed identical), then de_{homo}, the preference for formation of the homochiral versus meso diastereomer, is simply the product of ee_1 and de_2 (eq 1).[15] The observed diastereoselectivity, de_{homo}, is large when the stereoselectivities (ee_1 and de_2) are both high. In the special case where the stereoselectivities of the two steps are identical, de_{homo} is given simply as the square of ee_1 (eq 2). Consequently, the easily measured de_{homo} can be used to calculate ee_1, the enantioselectivity of the first step.

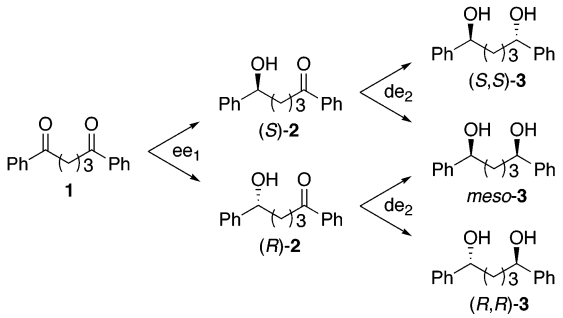
$$ee_1 de_2 = de_{homo} \qquad (1)$$

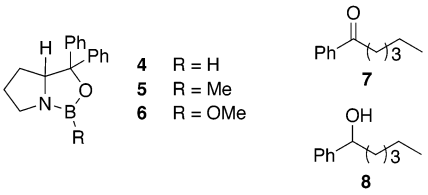
$$ee_1^{\,2} = de_{homo} \qquad (\text{if } ee_1 = de_2) \qquad (2)$$

The situation becomes more complex for racemic catalysts, as the second reaction step may involve a catalyst molecule that is the enantiomer of the one used in the initial step. In such instances where substantial catalyst "scrambling" occurs, de_{homo} will be nil, whatever the ee_1. In the special case where the same enantiomer of the catalyst is involved in both steps, the above discussion shows that eqs 1 and 2 remain valid, and $de_{homo} > 0$ will be observed. In other words, a racemic catalyst is expected to produce a low level of the meso product diastereomer whenever a single catalyst molecule with high enantioselectivity performs both steps on a bifunctional substrate. We report here on such a case involving a catalyst−substrate system in which the second reaction is fast relative to release of the initial product−catalyst complex.

To ensure that ee_1 and de_2 are the same, it is necessary to design a bifunctional substrate where the reactive centers are sufficiently separated so as to minimize substrate control in the second reaction. Otherwise, eq 2 becomes invalid, and one must use eq 1 where the desired information ee_1 is obscured by the presence of de_2 (a composite of catalyst and substrate control).[15] As a first check on the validity of the above ideas, we investigated diketone **1**, which afforded a nearly statistical 1:2:1 ratio of diol **3** stereoisomers (i.e., no diastereoselectivity) when reduced by a variety of achiral reagents.[16−18] Enantioselective borane reductions catalyzed by chiral oxazaborolidines (OABs) derived from 2,2-diphenylprolinol were initially considered. Catalysts such as **4**−**6** are often used in asymmetric catalysis.[19]

Scheme 1. Diagram of the Product Distribution in Two Consecutive Asymmetric Reactions with an Enantiopure Catalyst





Ketone **7** was selected as a model for study of the enantioselectivity of the monoreduction of **1**. Its reduction to alcohol **8** by 0.75 equiv of $BH_3{\cdot}SMe_2$ under various conditions in the presence of OAB catalysts gave enantioselectivities close to 90% ee. Reduction of diketone **1** by enantiopure catalysts **4**−**6** afforded the chiral diol **3** in very high ee (close to 99%). The diastereoselectivity de_{homo} is quite good, and the relationship between de_{homo} and ee_{homo} is accurately described by

$$ee_{homo} = 2(de_{homo})^{1/2}/(1 + de_{homo}) \qquad (3)$$

established when $ee_1 = de_2$.[15]

We were pleased to observe that reduction of diketone **1** with the corresponding racemic catalysts **4**−**6** also afforded diol **3** with high diastereoselectivity (de_{homo}).

As shown in Table 1, use of eq 2 to calculate ee_1 on the basis of measured de_{homo} values gave results similar to those obtained by

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Table 1. Diastereoselectivity and Enantioselectivity in the Reduction of Diketone **1** in THF[a,b]

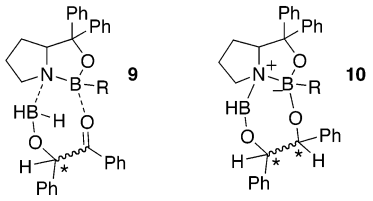
catalyst	% de_{homo}[c]	% ee_1[d] (% ee of **8**)[c]
(*R*)-**4**[e]	87	93 (82)
(*R*)-**4**[f]	86	93 (79)
rac-**4**[e]	56	75 (82)
rac-**4**[f]	86	93 (79)
(*S*)-**5**[e]	81	90 (87)
(*S*)-**5**[f]	72	85 (83)
rac-**5**[f]	83	91 (83)
(*R*)-**6**[e]	89	94 (−)[g]
rac-**6**[e]	82	91 (−)[g]

[a] 10 mol % of catalyst unless otherwise stated. [b] Addition of a solution of **1** in 1 h to a solution of catalyst and BH_3·SMe_2 (2.5 equiv). Reaction time: 1 h, unless otherwise stated. Quantitative conversion of **1**. More details in Supporting Information. [c] Measured by chiral SFC (Chiralcel OD-H). (*R*)-OAB catalysts give (*S*,*S*)-diol **3**. [d] Calculated from eq 2. [e] 0 °C. [f] 66 °C. [g] Not measured.

reduction of model ketone **7**. Comparable results were obtained using toluene as a reaction solvent (see Supporting Information).

Two additional catalytic systems were investigated, hydrosilylation (α-naphthylphenylsilane) catalyzed by [RhCl(diop)(cod)][20] and hydrogen transfer from 2-propanol catalyzed by a chiral ruthenium complex generated in situ from [{$RuCl_2$(*p*-cymene)}$_2$], ephedrine, and KOH.[21] The enantio- and diastereoselectivities of these reactions were studied using the enantiopure catalysts and are in good agreement with eqs 3 and 2. However, no diastereoselectivity is observed with the racemic catalysts, suggesting that significant catalyst scrambling has occurred.

What then makes the OAB catalysts so special? To answer this question, it is helpful to consider the mechanism of the reaction.[19] It has been observed that two hydrogen atoms from BH_3 are used in ketone reductions, the second hydrogen being delivered in a faster reaction.[22] In the present case, the half-reduced species **9** contains an N-coordinated $ROBH_2$ moiety that can serve as an excellent hydride donor. Consequently, intramolecular hydride delivery to form **10** occurs rapidly, the large size of the chelation ring ensuring that the first stereocenter does not influence the stereochemical outcome of the second reduction.[23] Instead, product stereochemistry is controlled predominantly by the chiral oxazaborolidine system.



Additional support for this interpretation is provided by some experiments with (*S*)- or (*R*)-ketol **2** (98% ee), prepared by reduction of **1** by (+)- or (−)-Ipc_2BBr, respectively. The reduction of (*S*)- or (*R*)-**2** by a stoichiometric amount of (*R*)-OAB **5** (in situ complexed by 1 mol equiv of borane)[24] gave a large amount of homochiral (*S*,*S*)-diol **3** ((*S*,*S*):*meso* = 96:4) or *meso*-diol **3** (*meso*:(*R*,*R*) = 93:7), respectively, clearly establishing that the stereochemical outcome of the second reduction step is under catalyst control, with the (*R*)-catalyst affording the (*S*)-stereocenter in both the matched and the mismatched cases.[25] This suggests that ee_1 and de_2 are indeed equivalent and that the use of eq 2 to calculate ee_1 is justified.

In conclusion, these results demonstrate that, at least in some specialized cases, it is possible to evaluate the enantioselectivity of racemic catalysts without the need for resolution. One can envision additional strategies to counteract the escape of the catalyst before the second reaction has taken place. We are presently investigating these approaches in an effort to expand the generality of this method of using easily measured diastereoselectivity as an indicator of the enantioselectivity of the component enantiomers of a racemic catalyst.

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Supporting Information Available: Experimental procedure for reduction of various diketones and ketones, results of OAB reductions of **1** in toluene, data concerning diols **3** and ketol **2**, equations and mathematical treatment, catalytic cycle and chromatograms of some ee measurements (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) An achiral oxazaborolidine (10 mol % equiv prepared in situ from 2-aminoethanol and borane) used as a catalyst gives a low diastereoselectivity (% de_{homo} = 28, THF, 66 °C), ruling out a strong substrate control in the second reduction (for details, see Supporting Information).
(24) In the catalytic reaction of ketol (*R*)-**2** with (*S*)-OAB **5** in THF at 0 °C, the de_{homo} is quite low (51%) because of the competitive direct formation of monoalkoxyborane, followed by uncatalyzed intramolecular reduction.
(25) This was confirmed by the partial conversion (35%) of racemic ketol **2** in the presence of (*R*)-**5**, and BH_3 (THF, 0 °C). Ketol **2** was recovered (racemic), and a 1:1 mixture of (*S*,*S*)-**3** (92% ee) and *meso*-**3** was obtained.

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