Testing Racemic Chiral Catalysts for Kinetic Resolution Potential**

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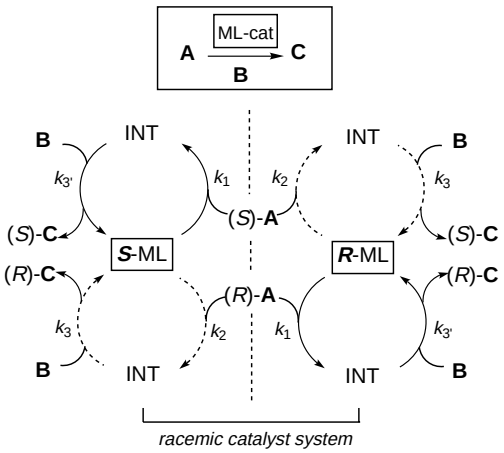
Development of methods for accelerated discovery of asymmetric catalysts has been the subject of much recent attention.[1] Most methods[2] are underpinned by two tactics: 1) the synthesis of diverse sets ("libraries") of novel chiral ligands and 2) rapid ("high-throughput") screening to distinguish selective from nonselective catalysts.

Kinetic resolution is a well known and utilized process in asymmetric catalysis[3] and several novel methods have emerged for rapid screening. Recent examples include the mass spectrometric analysis of pseudoenantiomers[4] and the detection of differential rates between racemic/enantiomerically pure substrates by IR thermography[5] or thermionic resistors.[6]

Despite such advances, a common restriction in the discovery of novel chiral catalysts is the dependence on chiral pool, preexisting asymmetric methodologies, or classical resolution.[7] This reinforces the relationship between ready availability and application. Herein we report on "proof-of-concept" studies for a method that *predicts* whether a catalyst will display significant selectivity in a kinetic resolution reaction. We do this by testing the racemic form, without the need for the preparation of scalemic or enantiomerically pure catalyst.[8] This method differs substantially from asymmetric deactivation ("poisoning"),[9] activation,[10] or complexation[11] of racemic catalysts, since the active catalyst system is racemic.[12]

Kinetic resolution reactions operate through a kinetic match/mismatch relationship (often quantified as "s" $= k_{fast}/k_{slow}$) between the two enantiomers of the substrate and the catalyst. Consider the enantiomeric processes (*R*)-**A** + **B** $\rightarrow$(*R*)-**C**; (*S*)-**A** + **B** $\rightarrow$(*S*)-**C**, where **A** is substrate, **B** is an achiral reagent, and their reaction to give **C** is catalyzed by "ML", a metal complex bearing chiral ligand L (Scheme 1). If there is kinetic diastereoselection between the reaction of "ML" with enantiomers of **A** (i.e. $k_1/k_2\,(=s) > 1$), then kinetic resolution of (±)-**A** will occur if *enantiomerically enriched or pure* "ML" is employed to facilitate turnover of either the left-hand or the right-hand pair of cycles.[13] However, with the racemic catalyst "(±)-ML", enantiomeric catalytic cycles (Scheme 1) will turn over at equal rates and there will be no kinetic resolution.[14]

On the surface it thus appears that the racemic catalyst cannot be tested. However, on closer inspection it emerges that if the reaction velocity does not display a *direct* relationship with the concentration of **A**,[15] then one may gain access to qualitative information regarding the magnitude of s by employing a *scalemic* ($0 < ee < 100$) sample of **A** and monitoring the change in the enantiomeric excess (*ee*) of **A** with conversion. For example, if the catalyst is "perfect" in its selectivity (i.e. $s = \infty$), then enantiomeric catalytic cycles will react exclusively with enantiomeric substrate (**A**). Under a kinetic regime that is pseudo zero-order in [**A**],[15] the enantiomeric catalytic cycles consume **A** at essentially equal rates (i.e. net-*racemic* **A** is converted to **C**) until all of the minor enantiomer of **A** is consumed. Thus the *ee* of the remaining unreacted **A** *increases* throughout reaction[16] and eventually becomes 100 %. In contrast, if there is no catalyst selectivity ($s = 1$), then both enantiomers of catalyst react equally proficiently with both enantiomers of substrate. Consequently, the relative rate of consumption of (*R*)-**A** versus that of (*S*)-**A** is solely dependent on their relative concentration (i.e. the enantiomeric ratio) and the *ee* of **A** will remain constant throughout reaction.



Scheme 1. Hypothetical reaction in which (*R*)-**A** is matched with catalyst (*R*)-ML and mismatched with (*S*)-ML (and vice versa for (*S*)-**A**) for conversion to **C** by reaction with **B**. When pure (*R*)-ML or pure (*S*)-ML is employed, kinetic resolution of (±)-**A** will occur.

For the method to be of practical utility, the *ee* of remaining **A** must be measured with reasonable accuracy and thus monitoring changes in *ee* (Δ_{ee}) at lower conversions is preferred. Prior to conducting experiments, we simulated[17] the system in Scheme 1 to study the change in *ee* of **A** with conversion under ideal conditions. The simulation on the left-hand side of Figure 1 indicates that for initial substrate *ee* values (ee_{init}) of 20, 40, 60, and 80 %, a selective ($s = 10$),[3c] but

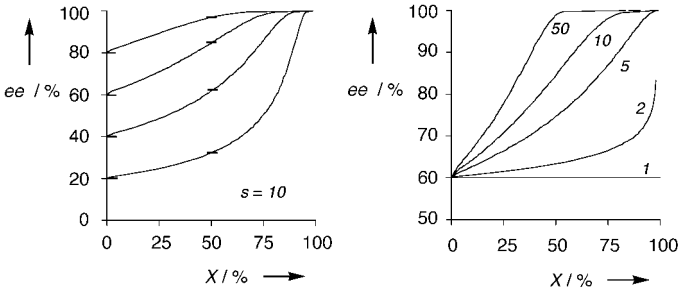


Figure 1. Predicted[17] *ee* of **A** (y axis) as a function of conversion (x axis; X = conversion of **A**) on reaction with **B** catalyzed by racemic catalyst (±)-ML as in Scheme 1. Left-hand graph: $s = 10$ and ee_{init} variable; right-hand graph: $ee_{init} = 60$ % and s variable.

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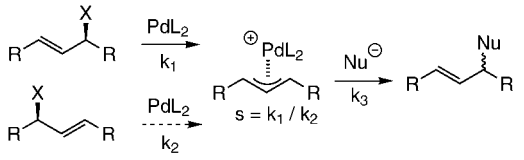
racemic, catalyst system will induce Δ_{ee} values of 12, 21, 24, and 16% respectively after 50% conversion of **A**. For the example of an ee_{init} value of 60%, the right-hand simulation explores the relationships between *ee* and conversion predicted for different selectivity (*s*) values. These simulations demonstrate that it should be feasible to compare racemic catalysts under such conditions and gain some indication of their relative selectivities.

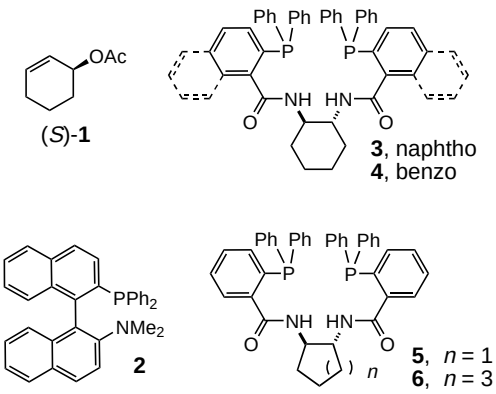
There has recently been considerable interest in Pd-catalyzed kinetic resolution of allylic electrophiles, [Eq. (1)].[18] Since it is common that the rate-limiting step



(1)

involves attack of the nucleophile (most often a stabilized carbanion) on a Pd^{II}-π-allyl intermediate,[19] one may envisage that a pseudo zero-order regime in allylic substrate will hold through a wide range of conversion. Therefore, such a process (e.g. that in Scheme 1, **A** = allylic electrophile; **B** = nucleophile) appeared to be a good candidate for a "proof-of-concept" study in which the *ee* value of an initially scalemic sample of allyl substrate should rise throughout reaction if $s > 1$.

The change in *ee* value of samples of (*S*)-cyclohex-2-enyl acetate (*S*)-**1** (62–64% *ee*) with conversion upon Pd-catalyzed reaction with [$NaCH(CO_2Me)_2$], by employing three well known, but racemic ligands **2**,[20a] **3**,[20b] and **4**,[20c] is given in the left-hand graph in Figure 2. It is evident by comparison with the curves predicted in Figure 1 that the system deviates from ideality. Nonetheless, the magnitude of the Δ_{ee} value does predict **4** to be superior to **2** or **3**. This was indeed found to be the case: the *s* values independently determined under identical conditions with enantiomerically pure samples of (*S*)-**2**, (*R*,*R*)-**3**, and (*R*,*R*)-**4** were 2, 10, and 45 respectively.



To demonstrate the utility of this method, we have prepared and tested analogues of the Trost modular ligand **4**. Unlike *trans*-1,2-diaminocyclohexane (used for the construction of **4**), neither diamine required for construction of ligands **5** and **6** is

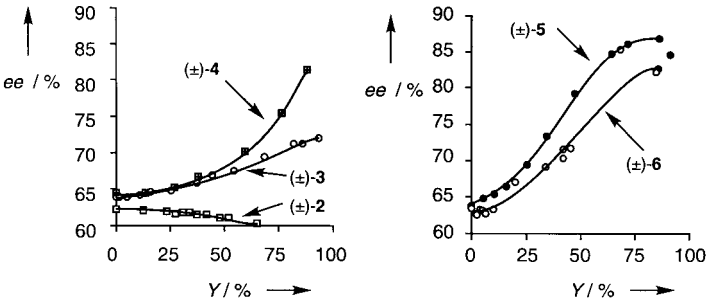


Figure 2. Experimentally observed changes in *ee* (*y* axis) as a function of conversion (*x* axis; *Y* = conversion of **1**) for the Pd-catalyzed reaction of (*S*)-cyclohex-2-enyl acetate ((*S*)-**1**; 62–64% *ee*) with $NaCH(CO_2Me)_2$ in THF at 25 °C. Left-hand graph: using known ligands (±)-**2**, (±)-**3**, and (±)-**4**; right-hand graph: using novel ligands (±)-**5** and (±)-**6**.

commercially available. However, racemic ligands (±)-**5** and (±)-**6** were readily prepared in a few steps from cyclopentene and cycloheptene, respectively, and then screened (see right-hand graph in Figure 2). The results clearly suggest that cyclopentyldiamine-derived ligand **5** may have potential utility in enantiomerically pure form.[21]

In summary, we have demonstrated that the potential efficacy of an enantiomerically pure ligand for a transition metal catalyzed kinetic resolution reaction can be tested by monitoring the reaction of a scalemic substrate by employing a catalyst generated from racemic ligand under pseudo zero-order conditions. The ability to test a racemic ligand *before* enantioselective ligand synthesis or resolution need be developed may prove of significant utility in novel ligand architecture based on axial, planar, helical, or heteroatom (e.g. P) chirality.

Experimental Section

[{Pd(η^3-C_3H_5)Cl}$_2$] (1 mg, 2.5 mmol) and (±)-**5** (5 mg, 7.5 mmol) were dissolved in anhydrous THF (1 mL) and stirred at 25 °C for 15 min to afford a pale yellow solution. In a separate Schlenk tube, (*S*)-**1** (76 mg, 0.50 mmol; 63% *ee*) was added to a solution of dimethylmalonate (164 mg, 1.25 mmol), NaH (60% dispersion in mineral oil, 50 mg, 1.25 mmol), and 4-methylacetophenone (internal standard) in THF (20 mL), immediately followed by the catalyst solution. Aliquots (100–200 μL) of the reaction mixture were periodically withdrawn by cannula, quenched with saturated aqueous NH_4Cl, dried ($MgSO_4$), filtered through a plug of silica, and then analyzed for conversion and *ee* by GC (30 m Chiraldex β-dm column, 123 KPa, 1.4 $cm^3 min^{-1}$, ID 0.25 mm, 90 °C, (*R*)-**1** 9.2 min, (*S*)-**1** 9.5 min) data obtained as shown in Figure 2.

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[7] See, for example, catalysts for asymmetric acylation: a) G. C. Fu, *Pure Appl. Chem.* **2001**, *73*, 347 – 349; b) A. Spivey, A. Maddaford, T. Fekner, A. J. Redgrave, C. S. Frampton, *J. Chem. Soc. Perkin Trans. 2* **2000**, 3460 – 3468.

[8] As noted by a referee, the method demands availablity of asymmetric protocols for preparation of the enantiomerically enriched substrate and is unsuitable for parallel screening of ligand libraries. However, we envisage that the method will find most utility in screening single novel ligands (in racemic form) in *benchmark* reactions.

[9] See, for example: a) J. W. Faller, D. W. I. Sams, X. Liu, *J. Am. Chem. Soc.* **1996**, *118*, 217 – 218; b) J. W. Faller, *Tetrahedron Lett.* **1993**, *34*, 7359 – 7362.

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[11] See, for example: J. M. Brown, P. J. Maddox, *Chirality* **1991**, *3*, 345 – 354.

[12] We note that most (but not all) nonlinear effects arise through active "monomer" and inactive aggregate. Leading references: a) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088 – 3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2923 – 2959; b) H. B. Kagan, *Synlett* **2001**, 888 – 899.

[13] For leading references and discussions of the implications of scalemic catalysts in kinetic resolution, see: a) D. G. Blackmond, *J. Am. Chem. Soc.* **2001**, *123*, 545 – 553; b) T. O. Luukas, C. Girard, D. R. Fenwick, H. B. Kagan, *J. Am. Chem. Soc.* **1999**, *121*, 9299 – 9306; c) D. W. Johnson, D. A. Singleton, *J. Am. Chem. Soc.* **1999**, *121*, 9307 – 9312; d) R. F. Ismagilov, *J. Org. Chem.* **1998**, *63*, 3772 – 3774.

[14] Irrespective of the order of "**A**" in the rate equation, comparison of rates of racemic "(±)-**A**" versus enantiomerically pure, for example (*S*)-**A**, will not usually distinguish whether $s > 1$.

[15] "Saturation" or "pseudo zero-order" conditions are quite common in kinetic resolutions (see ref. [3b]). If $k_1[\mathbf{A}][\mathrm{ML}] > k_2[\mathbf{A}][\mathrm{ML}] \gg k_3[\mathbf{B}][\mathrm{INT}]$, Scheme 1, then the "resting state" is INT, $\mathrm{d}[\mathbf{A}]/\mathrm{d}t \propto [\mathbf{B}][\mathrm{INT}]$ and, irrespective of *s*, the *ee* value of **A** will not affect turnover rates.

[16] If the reaction is stereospecific (e.g. (*R*)-**A** gives (*R*)-**C**) then $ee\,\mathbf{C}_{init} < ee\,\mathbf{C}_{final}$ ($= ee\,\mathbf{A}_{init}$).

[17] MacKinetics v0.9.1b, Leipold Associates, USA, **1997**, Scheme 1: $[\mathbf{A}]_0 = [\mathbf{B}]_0 = 1.0$, $[(\pm)\text{-ML}]_0 = 0.02$; $k_1 = 100$, $k_2 = k_1/s$; $k_3 = 1$.

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[21] (*R*,*R*)-**5** was subsequently prepared and tested in the kinetic resolution of (±)-**1** (15 data points, $c = 0 \rightarrow 51\,\%$). Nonlinear regression of $s = \ln[(1-c)(1-ee)]/\ln[(1-c)(1+ee)]$ gave $s = 120 \pm 30$; however, the selectivity increases as the reaction proceeds; for example, $c = 50.7\,\%$; *ee* (**1**) = 99 %; $s = 263$. This selectivity ($s > 100$) is significantly higher than any reported to date in Pd-catalyzed allylic alkylation.[18] We are currently evaluating **5** in other reactions.