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Caution in the Use of Nonlinear Effects as a Mechanistic Tool for Catalytic Enantioconvergent Reactions: Intrinsic Negative Nonlinear Effects in the Absence of Higher-Order Species

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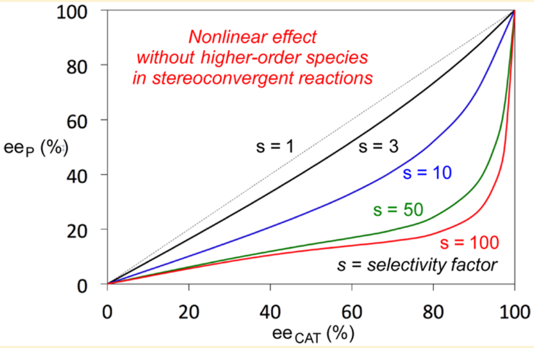
Ⓢ *Supporting Information*

ABSTRACT: Investigation of the dependence of product enantiometric excess (ee) on catalyst ee is a widely used tool to probe the mechanism of an enantioselective reaction; in particular, the observation of a nonlinear relationship is usually interpreted as an indication of the presence of one or more species that contain at least two units of the chiral entity. In this report, we demonstrate that catalytic enantioconvergent reactions can display an *intrinsic* negative nonlinear effect that originates purely from the kinetic characteristics of certain enantioconvergent processes and is independent of possible aggregation of the chiral entity. Specifically, this intrinsic negative nonlinear effect can arise when there is a kinetic resolution of the racemic starting material, and its magnitude is correlated with the selectivity factor and the conversion; the dependence on conversion provides a ready means to distinguish it from a more conventional nonlinear effect. We support our analysis with experimental data for two distinct enantioconvergent processes, one catalyzed by a chiral phosphine and the other by a chiral Pd/phosphine complex.



INTRODUCTION

A nonlinear effect (NLE) in asymmetric catalysis is a deviation from proportionality (linear dependence) between the enantiomeric excess of a chiral product (ee_P) and the enantiomeric excess of a chiral catalyst (ee_{CAT}) used in a reaction (Figure 1).[1] The first instances of such nonlinear effects (positive and negative) were reported by Kagan in 1986.[2] Since this pioneering discovery, a growing number of processes that display positive, negative, or multishape nonlinear effects have been identified.

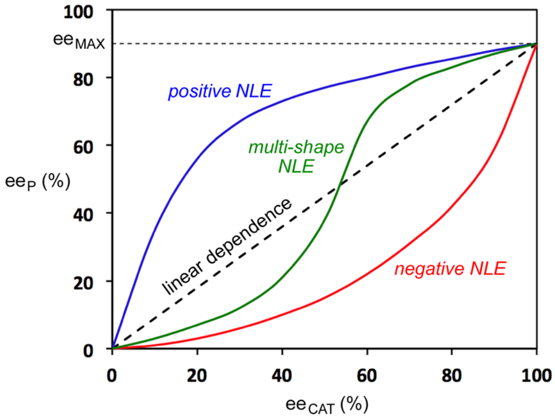


Figure 1. Examples of nonlinear effects in asymmetric catalysis. ee_{MAX} = ee provided by enantiopure catalyst.

Since 1986, nonlinear effects have attracted considerable attention, both for practical reasons and from the perspective of understanding reaction mechanisms.[1] In the latter case, an adherence to or a departure from a linear relationship can provide insight into the composition of species that are present in a reaction mixture. Thus, the observation of a nonlinear effect in a homogeneous reaction[3] can be an indication of the presence of a catalyst (or other species) that contains two or more units of the chiral entity (e.g., multiple chiral ligands bound to a transition metal), and models for various scenarios have been developed, e.g., ML_n models for catalysts and a reservoir model. Due in part to the experimental simplicity of NLE investigations relative to many other types of mechanistic studies, the determination of the relationship between product ee and catalyst ee has become a standard tool for obtaining insight into new catalytic asymmetric processes.

As indicated above, the observation of a nonlinear correlation between product ee and catalyst ee is typically interpreted as evidence for the presence of one or more species that contain multiple units of the chiral entity. In this report, we demonstrate that a nonlinear effect can be observed in the absence of such

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higher-order speciation; specifically, we provide a model and experimental data that illustrate that a (negative) nonlinear effect can occur in certain enantioconvergent reactions.

RESULTS AND DISCUSSION

Analysis. In the case of simple (nondynamic) kinetic resolutions of racemic compounds (Figure 2), the ee of the product varies intrinsically as a function of conversion,[4] which complicates the use of conventional NLE studies (e.g., Figure 1) as a mechanistic probe. Nevertheless, investigations (both theory and experiment) of such kinetic resolutions using enantiomerically impure catalysts have been described, usually focusing on the impact on the ee of the unreacted, enantioenriched starting material,[5] which is often the "desired product" in simple kinetic resolutions.

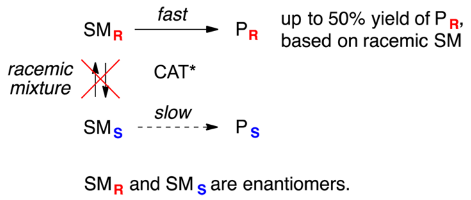

Figure 2. Simple (nondynamic) kinetic resolution.

Racemic compounds can serve as useful substrates not only for simple kinetic resolutions, but also for stereoconvergent reactions, wherein both enantiomers of the racemic starting material are converted into a particular enantiomer of the product, thereby making full use of the substrate (Figure 3).[6−8]

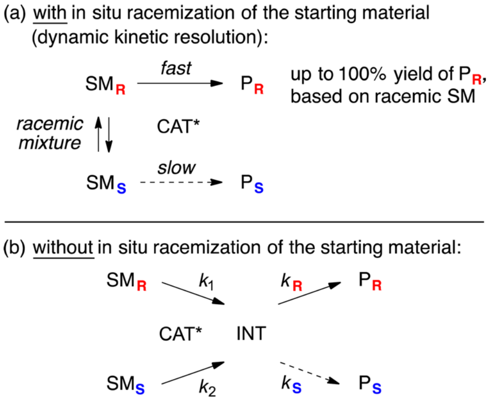

Figure 3. Illustrative examples of enantioconvergent processes: (a) *with* in situ racemization of the starting material; (b) *without* in situ racemization of the starting material.

Enantioconvergence can be achieved with (e.g., dynamic kinetic resolution)[6] or without[7] in situ racemization of the starting material.[9] In such reactions, the ee of the product need not vary as a function of conversion or of the stereochemical composition of the starting material.

Although nonlinear effects have been investigated in the context of certain kinetic resolutions,[5] to the best of our knowledge, nonlinear effects in *enantioconvergent* processes of the type depicted in Figure 3b have not been mathematically analyzed;[10] building on important earlier studies,[5] we focus on this topic in the context of product ee.

For the sake of illustration, we examine the simplest scenar- io, wherein the catalyst is fully selective (i.e., $k_S = 0$ in Figure 3b). In this case, CAT_R produces only P_R, and the enantioconvergent reaction may be represented by eqs 1 and 2.[11] If the catalyst is scalemic, as in an NLE study, then two additional pathways must also be considered (eqs 3 and 4), which have the same pair of rate constants as for eqs 1 and 2 (k_1 and k_2), due to symmetry.

$$SM_R \xrightarrow[k_1]{CAT_R} P_R \qquad (1)$$

$$SM_S \xrightarrow[k_2]{CAT_R} P_R \qquad (2)$$

$$SM_R \xrightarrow[k_2]{CAT_S} P_S \qquad (3)$$

$$SM_S \xrightarrow[k_1]{CAT_S} P_S \qquad (4)$$

SM_R and SM_S are enantiomers.
CAT_R and CAT_S are enantiomers.
P_R and P_S are enantiomers.

where SM_R and SM_S are enntiomers, CAT_R and CAT_S are enantiomers, and P_R and P_S are enantiomers.

Within this model, consider the case in which $k_1 \gg k_2$ (i.e., there is a substantial kinetic resolution of the starting material) and the catalyst is scalemic ($[CAT_R] > [CAT_S]$). At the beginning of the reaction, eq 1 is therefore dominant, leading to the preferential formation of P_R and *the corresponding depletion of* SM_R relative to SM_S. As the reaction progresses, because $[SM_S] > [SM_R]$, eq 4 becomes increasingly significant, leading to an erosion in product ee.[12] Of course, this parallels the behavior of product ee in a simple kinetic resolution, i.e., it decreases as the reaction proceeds.

Figure 4 illustrates numerical simulations of the model that is shown in eqs 1−4. At the outset of the reaction, the product ee (ee_P) is equal to the catalyst ee (ee_{CAT}); as the reaction progresses, the product ee decreases from that initial value (Figure 4a). The magnitude of this effect increases as the selectivity factor increases (Figure 4b).

The calculated dependence of product ee on catalyst ee as a function of the selectivity factor at 10% and at 90% conversion is provided in Figures 5a and 5b, respectively. These figures illustrate that, for enantioconvergent processes of the type analyzed herein, *a negative nonlinear effect is expected* ***without the intervention of higher-order species***.

At 10% conversion, the "intrinsic" negative nonlinear effect is very small even for reactions with a high selectivity factor (Figure 5a). This is because, at low conversion, the unreacted starting material is virtually racemic, and the ee of the product therefore largely reflects the ee of the catalyst (left side of Figure 4a) and the inherent selectivity of the catalyst (left side of Figure 4b).

On the other hand, at 90% conversion, the intrinsic nonlinear effect is much more pronounced and is discernible even in the case of a low selectivity factor (e.g., $s = 3$; Figure 5b). This is because, at high conversion, the unreacted starting material may be substantially enantioenriched, and the ee of the product therefore deviates from that expected based on the ee of the catalyst (Figure 4a: "expected" = left side; observed = right side) and the inherent selectivity of the catalyst (Figure 4b: "expected" = left side; observed = right side).

Because the magnitude of this intrinsic nonlinear effect for such enantioconvergent processes is dependent on the conversion, investigations of nonlinear effects for these reactions should be conducted at low and at high conversion. In order to

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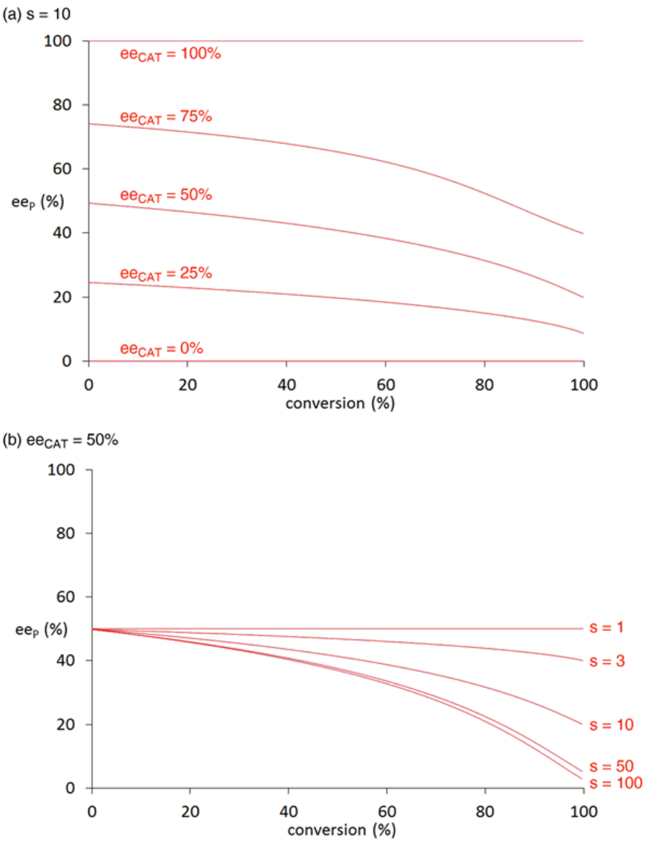


Figure 4. Mathematical simulations of product ee (ee$_P$) as a function of conversion, starting from a racemic starting material. Variation of (a) ee$_{CAT}$, with a constant *s* (10); (b) *s*, with a constant ee$_{CAT}$ (50%).

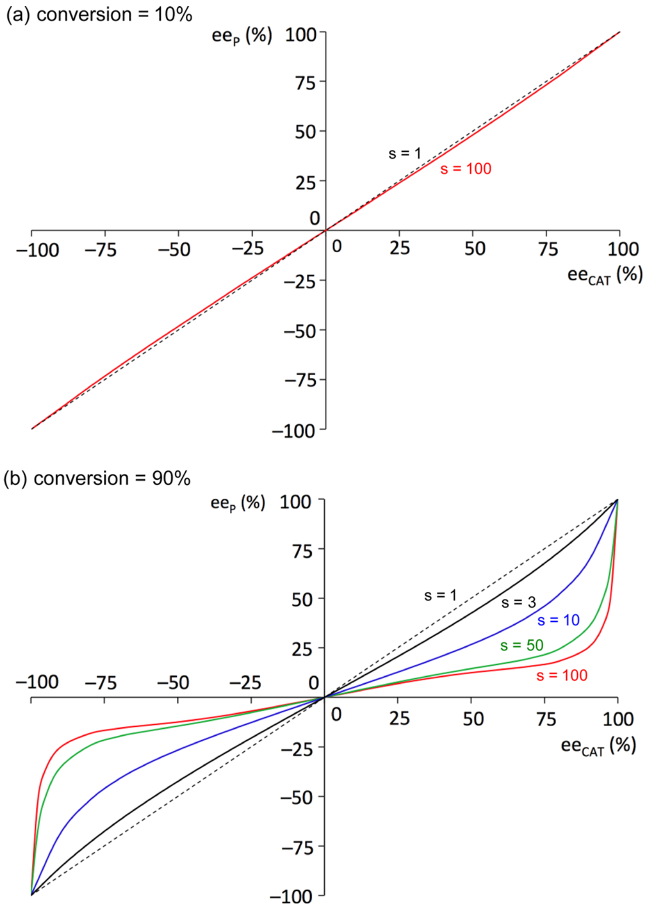


Figure 5. Mathematical simulations of product ee (ee$_P$) as a function of catalyst ee (ee$_{CAT}$), starting from a racemic starting material. Variation of *s* at: (a) 10% conversion; (b) 90% conversion.

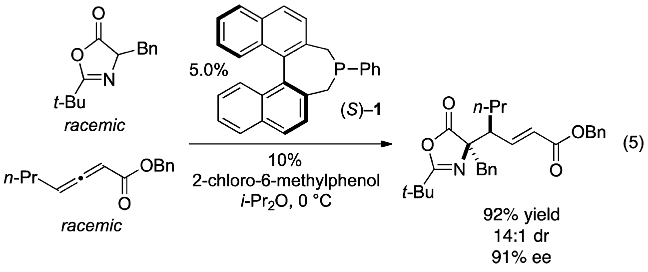
assess the possible presence of higher-order species that contain the chiral entity, an NLE study carried out at low (and consistent) conversion will minimize the impact of the intrinsic negative nonlinear effect (Figure 5a). Comparison of the low-conversion and the high-conversion data can then provide insight into the contribution of the intrinsic nonlinear effect. From a practical point of view, the graph in Figure 5b shows that, for enantioconvergent reactions that proceed with a high selectivity factor, it can be important to employ catalyst of very high ee, because even modest impurities can lead to a substantial erosion in product ee (Figure 5b: ee$_{CAT}$ = 95%, $s = 50 \Rightarrow$ ee$_P$ = 50%).

It is important to note that many of our conclusions have analogy with Blackmond, Singleton, Kagan, and Ismagilov's analyses of the use of enantiomerically impure catalysts in simple kinetic resolutions.[5] However, due to the nature of simple kinetic resolutions (product ee decreases as the conversion increases), they are not typically subjected to classical NLE studies of product ee versus catalyst ee.

Thus, enantioconvergent reactions can display an intrinsic negative nonlinear effect that originates from the inherent kinetics of the system and not from the intervention of higher-order species that include the chiral entity. This effect can occur when there is a kinetic resolution of the chiral substrate that is (at least partly) the turnover-limiting step of the overall catalytic cycle.

Experimental Data. We have examined nonlinear effects for two distinct enantioconvergent processes, one that is catalyzed by a phosphine and one that is catalyzed by a transition metal. For each reaction, we have investigated the impact of catalyst ee on product ee at low and at high conversions of the starting material.

First, we investigated the enantioselective addition of 1,3-oxazol-5(4*H*)-ones to racemic allenes catalyzed by chiral phosphepine **1** (eq 5).[13] Mechanistic studies of this and of related phosphine-catalyzed γ additions are consistent with the mechanism outlined in Figure 6.[13,14]



The coupling is stereoconvergent with respect to both of the racemic starting materials. With regard to the 1,3-oxazol-5(4*H*)-one, because it undergoes rapid deprotonation/racemization under the reaction conditions and the achiral conjugate base serves as the partner in the coupling process, its chirality does not impact our analysis. With regard to the allene, it does not racemize during the reaction, and a modest kinetic resolution is observed ($s \sim 4$). The rate law for the coupling is first-order in the catalyst and in the allene, and it is zeroth-order in the nucleophile and the phenol. Furthermore, the resting state of the catalyst

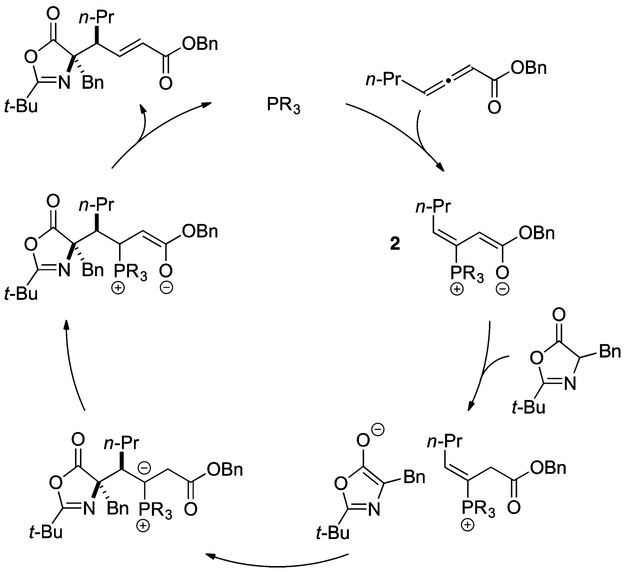


Figure 6. Outline of the proposed mechanism for the enantioconvergent γ addition of 1,3-oxazol-5(4*H*)-ones to racemic allenes catalyzed by chiral phosphepine **1**.

during the reaction is the free phosphine. Collectively, these data are consistent with the formation of intermediate **2** being the rate-determining step of the catalytic cycle (Figure 6).[13] In this step, the two enantiomers of the allene react with the chiral catalyst to form a common intermediate in which the axial chirality of the starting allene has been ablated.

As illustrated in Figure 7, when this phosphine-catalyzed γ addition is examined at low conversion, no nonlinear effect is evident (~10% conversion; blue squares). In contrast, when the reaction is allowed to proceed to high conversion, a negative nonlinear effect is observed (>90% conversion; red circles). Because no nonlinear effect is detected at low conversion, we conclude that the observed negative nonlinear effect at >90% conversion is due to the intrinsic kinetics of this enantioconvergent process, as predicted by the model, rather than the presence of species that contain more than one unit of the chiral phosphine. The magnitude of the intrinsic nonlinear effect is small, due to the modest selectivity factor ($s \sim 4$) in the kinetic resolution of the chiral allene.

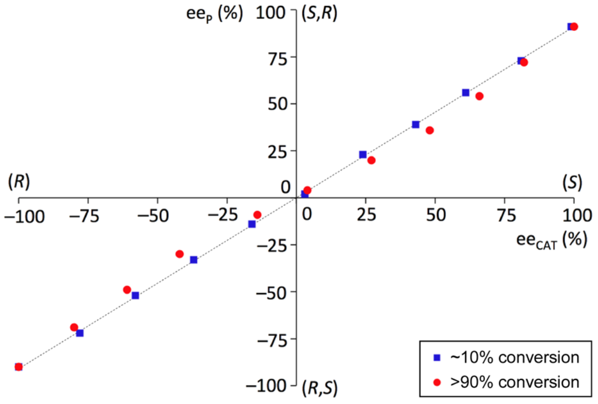
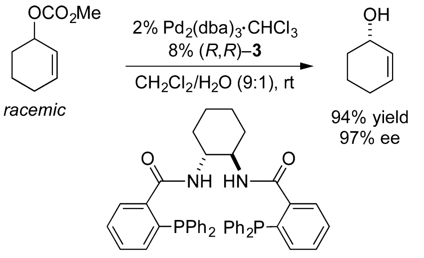


Figure 7. Product ee (major diastereomer) as a function of catalyst ee for a phosphine-catalyzed enantioconvergent coupling (eq 5).

Next, we chose to investigate a mechanistically distinct enantioconvergent process wherein the intrinsic negative nonlinear effect should be more apparent, due to a more efficient kinetic resolution. Specifically, we examined the palladium-catalyzed enantioconvergent conversion of racemic allylic carbonates into allylic alcohols, under the conditions described by Gais and Lüssem (eq 6).[15]



(*R*,*R*)-**3** (6)

An outline of the proposed mechanism,[15] which follows the generally accepted pathway for allylic substitutions catalyzed by palladium(0) complexes,[16] is provided in Figure 8. In the first step, the two enantiomers of the allylic carbonate react with the chiral catalyst to form a common intermediate (**4**), resulting in enantioconvergence of the racemic starting material. Our own investigation establishes that the starting allylic carbonate is configurationally stable under the reaction conditions and that it is resolved with a high selectivity factor ($s \sim 70$).[17]

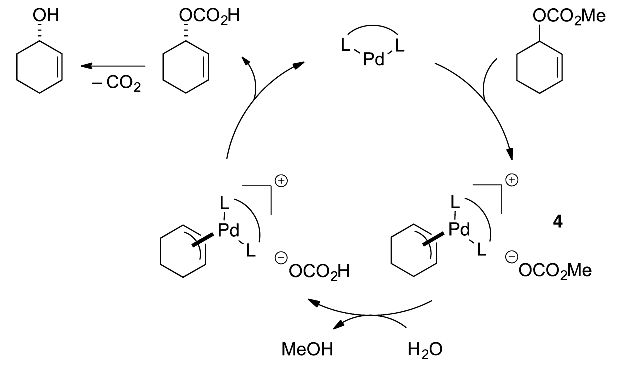


Figure 8. Outline of the proposed mechanism for the enantioconvergent conversion of racemic allylic carbonates into allylic alcohols catalyzed by a chiral palladium/phosphine complex.

When we conduct an NLE study of this palladium-catalyzed enantioconvergent process, essentially no nonlinear effect is evident at low conversion (blue squares; Figure 9), whereas we observe a substantial negative nonlinear effect for reactions that proceed to high conversion (red circles). Again, this is consistent with our model and with the conclusion that the negative nonlinear effect at high conversion is due to the intrinsic kinetics of the enantioconvergent reaction, not to higher-order species that contain the chiral ligand.[18]

■ CONCLUSIONS

Although the observation of a nonlinear effect (ee$_P$ versus ee$_{CAT}$) in a catalytic asymmetric reaction is often cited as evidence for the presence of at least one species that contains multiple units of the chiral entity, we have identified a particular family of processes that can display a negative nonlinear effect in the absence of such higher-order species. Thus, enantioconvergent reactions wherein there is a kinetic resolution of the racemic starting material in the (at least partially) rate-determining step can exhibit a negative nonlinear effect due to the intrinsic kinetics

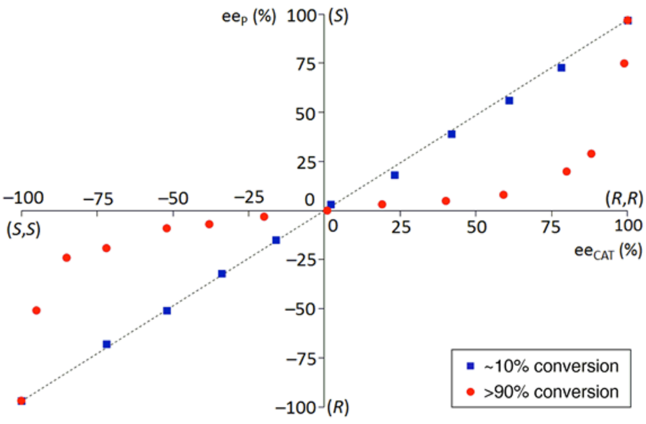


Figure 9. Product ee as a function of catalyst ee for a palladium-catalyzed enantioconvergent coupling (eq 6).

of such transformations. In the context of two previously reported enantioconvergent processes, we have demonstrated that, by investigating the relationship between ee$_P$ and ee$_{CAT}$ both at low and at high conversion, it is possible to gain insight into the origin of a nonlinear effect, i.e., due to higher-order species versus intrinsic.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b01826.

Mathematical analysis and experimental procedures (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews and leading references, see: (a) Satyanarayana, T.; Abraham, S.; Kagan, H. B. *Angew. Chem., Int. Ed.* **2009**, *48*, 456−494. (b) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402−411. (c) Heller, D.; Drexler, H.-J.; Fischer, C.; Buschmann, H.; Baumann, W.; Heller, B. *Angew. Chem., Int. Ed.* **2000**, *39*, 495−499.

(2) Puchot, C.; Samuel, O.; Dunach, E.; Zhao, S.; Agami, C.; Kagan, H. B. *J. Am. Chem. Soc.* **1986**, *108*, 2353−2357.

(3) For an example of a study of a heterogeneous system, see: Klussmann, M.; Iwamura, H.; Mathew, S. P.; Wells, D. H., Jr.; Pandya, U.; Armstrong, A.; Blackmond, D. G. *Nature* **2006**, *441*, 621−623.

(4) Kagan, H. B.; Fiaud, J. C. In *Topics in Stereochemistry*; Eliel, E. L., Wilen, S. H., Eds.; John Wiley & Sons: Hoboken, NJ, 1988; Vol. *18*, pp 249−330.

(5) For pioneering studies, see: (a) Ismagilov, R. F. *J. Org. Chem.* **1998**, *63*, 3772−3774. (b) Luukas, T. O.; Girard, C.; Fenwick, D. R.; Kagan, H. B. *J. Am. Chem. Soc.* **1999**, *121*, 9299−9306. (c) Johnson, D. W., Jr.; Singleton, D. A. *J. Am. Chem. Soc.* **1999**, *121*, 9307−9312. (d) Blackmond, D. G. *J. Am. Chem. Soc.* **2001**, *123*, 545−553.

(6) Pellissier, H. *Chirality from Dynamic Kinetic Resolution*; Royal Society of Chemistry: London, 2011.

(7) For two very recent examples of catalytic enantioconvergent reactions (not DKR), see: (a) Terada, M.; Ota, Y.; Li, F.; Toda, Y.; Kondoh, A. *J. Am. Chem. Soc.* **2016**, *138*, 11038−11043. (b) Kainz, Q. M.; Matier, C. M.; Bartoszewicz, A.; Zultanski, S. L.; Peters, J. C.; Fu, G. C. *Science* **2016**, *351*, 681−684. In addition to the mechanisms illustrated in Figure 3, other pathways for enantioconvergence are possible (e.g., *interconverting* intermediates).

(8) For overviews and leading references, see: (a) Rachwalski, M.; Vermue, N.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2013**, *42*, 9268−9282. (b) Steinreiber, J.; Faber, K.; Griengl, H. *Chem. - Eur. J.* **2008**, *14*, 8060−8072. (c) Wolf, C. *Dynamic Stereochemistry of Chiral Compounds*; Royal Society of Chemistry: Cambridge, 2008.

(9) Stereoconvergence can also be achieved without the formation of an intermediate; however, such processes are rare. For example, see: Ito, H.; Kunii, S.; Sawamura, M. *Nat. Chem.* **2010**, *2*, 972−976.

(10) For examples of catalytic enantioconvergent reactions for which an NLE study has been reported, see: (a) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293−12297. (b) Wang, X.; Guo, P.; Han, Z.; Wang, X.; Wang, Z.; Ding, K. *J. Am. Chem. Soc.* **2014**, *136*, 405−411. (c) Jin, M.; Adak, L.; Nakamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 7128−7134. (d) Nakajima, K.; Shibata, M.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2015**, *137*, 2472−2475. The possible complication of an *intrinsic* (vide infra) nonlinear effect was not discussed in these reports.

(11) Our conclusions also apply when the reaction proceeds via the two-step mechanism shown in Figure 3b and the catalyst is *not* 100% selective. For a more detailed analysis, see the Supporting Information.

(12) The instantaneous enantioselectivity in the model described by eqs 1−4 is given by eq a (see the Supporting Information for details). Thus, if ee$_{SM}$ > 0, then $X < 1$, which leads to product enantioselectivity that is lower than er$_{CAT}$.

$$\frac{\frac{d[\mathrm{P_R}]}{dt}}{\frac{d[\mathrm{P_S}]}{dt}} = \frac{s+1+ee_{SM}(1-s)}{s+1+ee_{SM}(s-1)}\cdot\frac{1+ee_{CAT}}{1-ee_{CAT}} = \frac{s+1+ee_{SM}(1-s)}{s+1+ee_{SM}(s-1)}\cdot er_{CAT} = X\cdot er_{CAT} \qquad \text{(a)}$$

s = selectivity factor
P_R = major enantiomer of product
er_{CAT} = enantiomeric ratio of the catalyst (≥ 1)
ee_{SM} = ee of starting meterial at a given time
($0 \leq ee_{SM} \leq 1$)

(13) Kalek, M.; Fu, G. C. *J. Am. Chem. Soc.* **2015**, *137*, 9438−9442.

(14) For leading references, see: Fan, Y. C.; Kwon, O. *Chem. Commun.* **2013**, *49*, 11588−11619.

(15) Lüssem, B. J.; Gais, H.-J. *J. Am. Chem. Soc.* **2003**, *125*, 6066−6067.

(16) For a review with leading references, see: Moreno-Manas, M.; Pleixats, R. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 2, pp 1707−1767.

(17) Our observed selectivity factor ($s \sim 70$) for the reaction in eq 6 is comparable to that reported for the kinetic resolution of this allylic carbonate by this chiral catalyst ($Pd_2(dba)_3{\cdot}CHCl_3$/ligand **3**) with 2-mercaptopyrimidine as the nucleophile: Gais, H.-J.; Jagusch, T.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Chem. - Eur. J.* **2003**, *9*, 4202−4221.

(18) The NLE that we observe (Figure 9) is not due to an interaction between the enantioenriched product and the catalyst. Thus, addition of enantiopure product, at the outset of the reaction, has no effect on the course of the reaction.