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Letter to the Editor

In the recent paper of Meier et al. [1], the origin of the rate acceleration in asymmetric heterogeneous catalysis (i.e., enhancement of the reaction rate in the presence of a chiral modifier) was investigated using transient experiments in a fixed-bed reactor. Rate acceleration is a central mechanistic feature of the Orito reaction [2] and has been the subject of extensive investigation and debate. The increased turnover rate over modified sites has been considered a key mechanistic feature of reactant–modifier interactions, supported by the experimentally observed correlation of modifier concentration, enantiomeric excess (ee), and reaction rate, as well as the up to 100-fold-higher hydrogenation rate in the presence of modifier. The increased turnover rate mechanism has been challenged by recent experimental observations [3–8], however. Ligand acceleration is readily observed in homogeneous catalysis, and in enantioselective hydrogenation over heterogeneous catalysts is associated mainly with ethyl pyruvate (EP) hydrogenation over cinchonidine (CD)-modifier Pt catalysts (Orito reaction) [2], whereas for other reactants the reaction rate does not differ much in racemic and enantioselective reactions and sometimes even rate deceleration is observed [9]. It is worth emphasizing that recent publications also have reported a lack of rate acceleration and high ee in liquid-phase EP [3–6] and gas-phase methyl pyruvate [7] hydrogenations. These are important experimental observations, and a detailed understanding of them plays a very important role in the development of mechanistic models for asymmetric heterogeneous catalysis. These experimental observations should be dealt with objectively.

Meyer et al. [1] made two references to our previously published work that were clearly erroneous/misinterpretations; we would like to comment on these. First, they stated the following: "Recently, Toukoniitty and Murzin [61] lent support to Jenkins' proposal on the inverted effect of the alkaloid modifier. They carried out experiments in toluene in a continuous-flow reactor and concluded that the rate enhancement achieved by addition of CD would be due to suppression of catalyst deactivation. Interestingly, they did not acknowledge that 2 years earlier, they had arrived at the opposite conclusion—that CD would always lead to rate deceleration [62]." This is an oversimplification and misinterpretation of our two publications. We carried out a systematic study [5] of EP hydrogenation over a commercial Pt/Al_2O_3 catalyst over a broad reactant and modifier concentration range in a batch reactor. We could demonstrate that by using low EP concentrations (0.01–0.1 mol L^{-1}) in a batch reactor, two mechanistic cornerstones for the Orito reaction were no longer valid—that is, the reaction rate was not proportional to the modifier concentration, and a high ee could be obtained with no rate acceleration or even in the presence of rate deceleration. These experimental observations lend support to the hypothesis proposed by Jenkins et al. [8] that rate acceleration is due to increased number sites rather than to increased turnover frequencies in a small amount of sites. Rate acceleration could be observed in our batch reactor experiments at higher reactant concentrations (0.3–2.0 mol L^{-1}), in line with numerous previous reports on rate acceleration. This study ([5]; Ref. 61 in [1]) was a continuation of our previous investigation using a Pt/SiO_2 fiber catalyst, reported 2 years earlier. In that investigation, we noted that under our experimental conditions in a continuous fixed-bed reactor, the presence of CD induced *ee* and rate deceleration, whereas the presence of trace amounts of oxygen induced increases in both ee and reaction rate. Already in this first paper ([6]; Ref. 62 in [1]), we discussed the role of catalyst deactivation in the widely reported ligand acceleration phenomena and acknowledged the low reactant concentrations as one plausible explanation for the lack of rate acceleration. Therefore, [5] and [6] are not contradictory—both reports emphasize the role of catalyst deactivation at high reactant concentrations in ligand acceleration phenomena.

Furthermore, in [5] we reported additional continuous fixed-bed experiments that confirmed that the initial (first minutes) deactivation rate was higher at higher EP concentrations (0.01–0.05 mol L^{-1}), and that the presence of modifier decreased the catalyst deactivation rate and was able to even restore the initial catalyst activity of an already deactivated catalyst.

To elucidate the importance of the concentration domain, we have carried out experiments with rather low concentrations of EP [6] and demonstrated the absence of any rate acceleration. In a subsequent study [5], we hydrogenated EP in the presence and absence of CD over a broader EP concentration range (0.01–2.0 mol L^{-1}) using a commercial 5% Pt/Al_2O_3 catalyst. We explicitly stated in the abstract of [5] that ligand acceleration (LA) could be observed at higher concentration range (0.3–2.0 mol L^{-1}) (see also Fig. 1), whereas at lower concentration ranges, enantioselective and racemic reactions have equal reaction rates.

Typically, experiments with EP are carried out at higher reactant concentrations or under the high concentration domain under which rate acceleration is readily observed. In fact, we also reported [5] rate acceleration at EP concentrations >0.1 mol L^{-1} (Fig. 1). We also would like to point out that the time-on-stream catalyst deactivation exhibits, according to our experience, often an exponential decay type of dependency;

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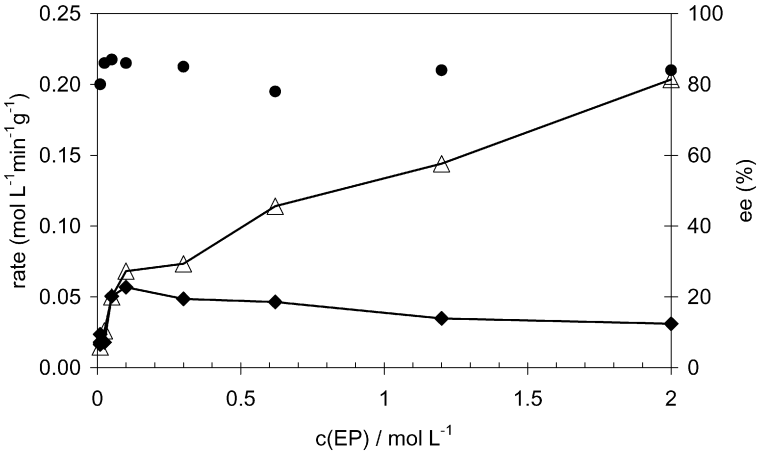

Fig. 1. Initial hydrogenation rates of enantioselective (△) and racemic hydrogenation (◆) and the enantiomeric excess (●) [5].

that is, deactivation is rapid during the first moments of reaction (few minutes of time on stream) and then attains a steady state. The steady state is also attained faster at higher EP concentrations and the initial deactivation rate is faster at higher EP inlet concentrations. Therefore, care should be taken when carrying continuous fixed-bed experiments at high inlet concentrations of EP and making observations about catalyst deactivation. There may be a risk of concluding a lack of deactivation based on steady-state catalyst activity, while disregarding the rapid initial deactivation occurring during the first seconds or minutes of TOS.

A second reference to our work was made by Meyer et al. [1]: "This assumption is supported by other work from the same group involving the hydrogenation of another α-ketoester substrate, ethyl benzoylformate, that found no deactivation in acetic acid in a continuous flow reactor but a rapid loss of activity in toluene [36], exactly in line with our proposal concerning the solvent effect on catalyst deactivation." We would like to point out that there is an error in the reference to our work ([10]; Ref. 36 in [1])—we have not reported the aforementioned solvent effects on catalyst deactivation. Namely, our experimental data do not exhibit lack of deactivation in acetic acid and rapid deactivation in toluene as they claimed [1]. In fact, we observed catalyst deactivation regardless of the solvent used in continuous fixed-bed reactor hydrogenation of ethyl benzoylformate.

We should stress, therefore, that contrary to the report of Meyer et al. [1], there are no contradictions in our reports [4,5], showing that ligand acceleration is not necessarily an intrinsic feature of enantioselective hydrogenation, but rather is specific to the substrate and even the substrate concentration. The differences in the rates of racemic and enantioselective hydrogenation depending on the reactant concentration domain were attributed in [5] to deactivation, caused by side reactions of EP, which are faster at higher reactant concentrations. In the context of this letter, the key mechanistic questions are whether the intrinsic catalyst activity was increased by the modifier–reactant interactions by a factor of 50–500, as it should have been to account for the experimentally observed rate accelerations, and whether the racemic reaction in the absence of modifier is a bad reference point, suffering from notable side reactions that cause rapid catalyst deactivation. From an experimentalist's viewpoint, it is much easier to deactivate the catalyst rather than to increase the activity of an optimized catalyst by one or two orders of magnitude. The actual molecular-level origin of the rate acceleration in the Orito reaction remains an open question that merits an objective evaluation of experimental observations.

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