

# Expansion of the Concept of Nonlinear Effects in Catalytic Reactions beyond Asymmetric Catalysis



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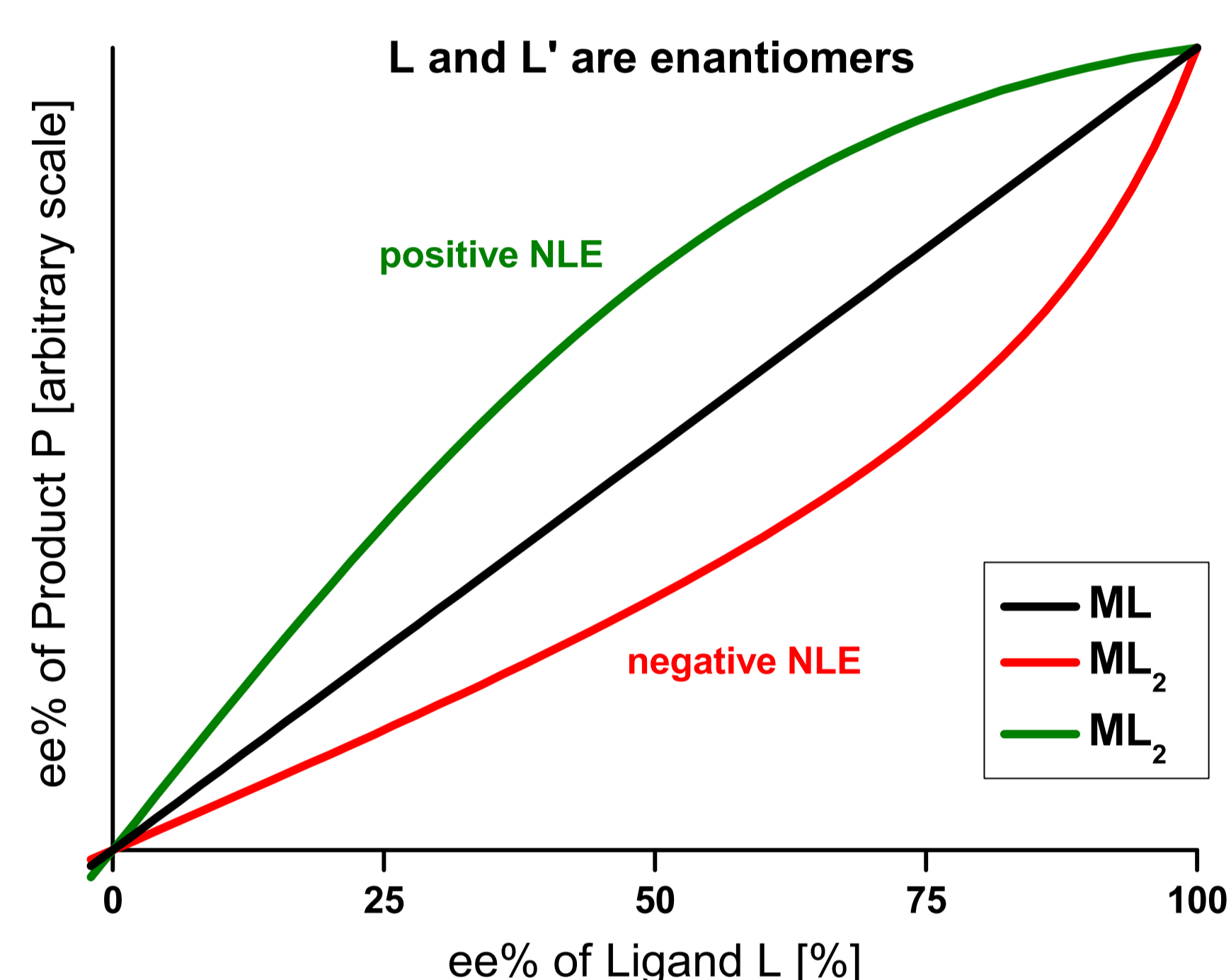
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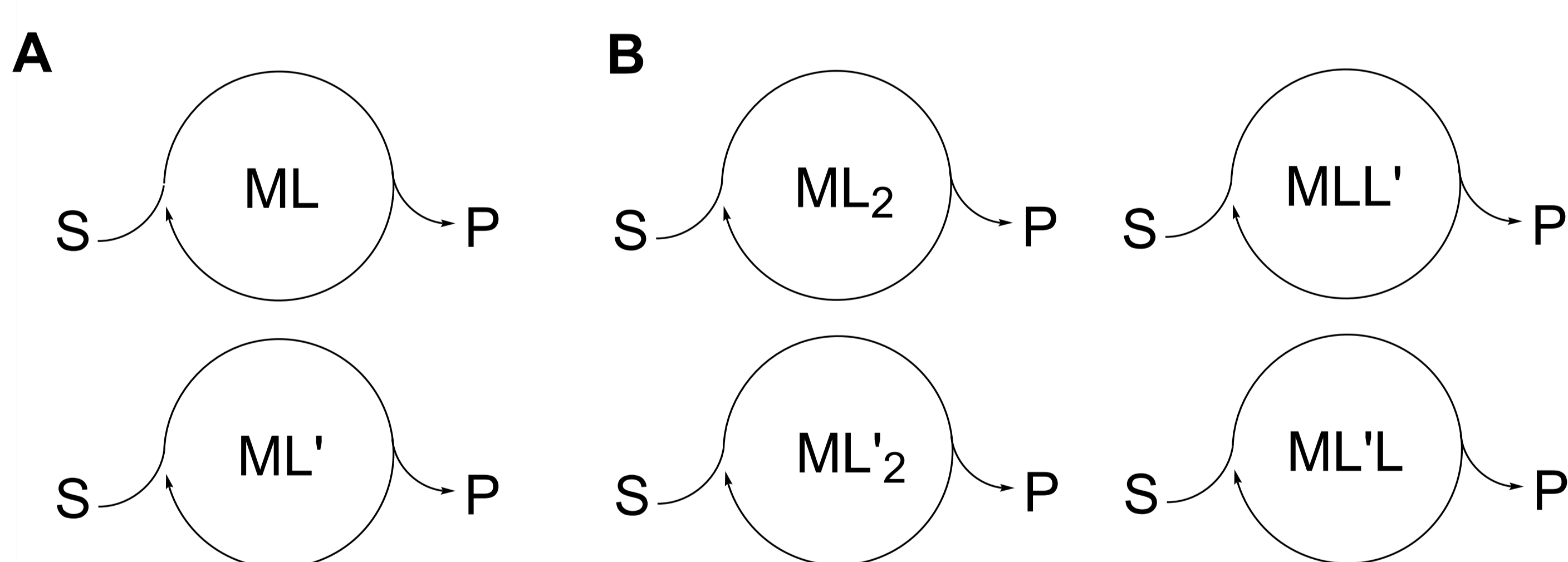
## Introduction

The observation and investigation of nonlinear effects in catalytic reactions provides valuable mechanistic insight. In 1976, Wynberg and Feringa<sup>1</sup> proposed for the first time in literature that using nonenantiopure substrates and reagents in chemical reactions could enable diastereomeric interactions between the respective enantiomers and therefore potentially affect the corresponding reaction both thermodynamically and kinetically even in an achiral environment. The term nonlinear effect (NLE) was later coined by Kagan and coworkers<sup>2</sup> and was defined as the nonlinear dependence of the product enantiopurity on the enantiopurity of a chiral auxiliary utilized in either asymmetric catalysis or asymmetric synthesis. Most of the theoretical foundation and understanding of the investigation of NLEs was developed by Kagan<sup>3</sup> and Blackmond<sup>4</sup> in the following two decades. However, the applicability of this method was, until now, limited to molecules possessing chirality and therefore to asymmetric synthesis. We herein report the expansion of the concept of nonlinear effects to catalytic reactions beyond asymmetric catalysis by using derivatives instead of enantiomers and considering rates instead of enantiomeric excess and its systematic application to investigate the mechanism of catalytic reactions.

## Basics of Nonlinear Effects

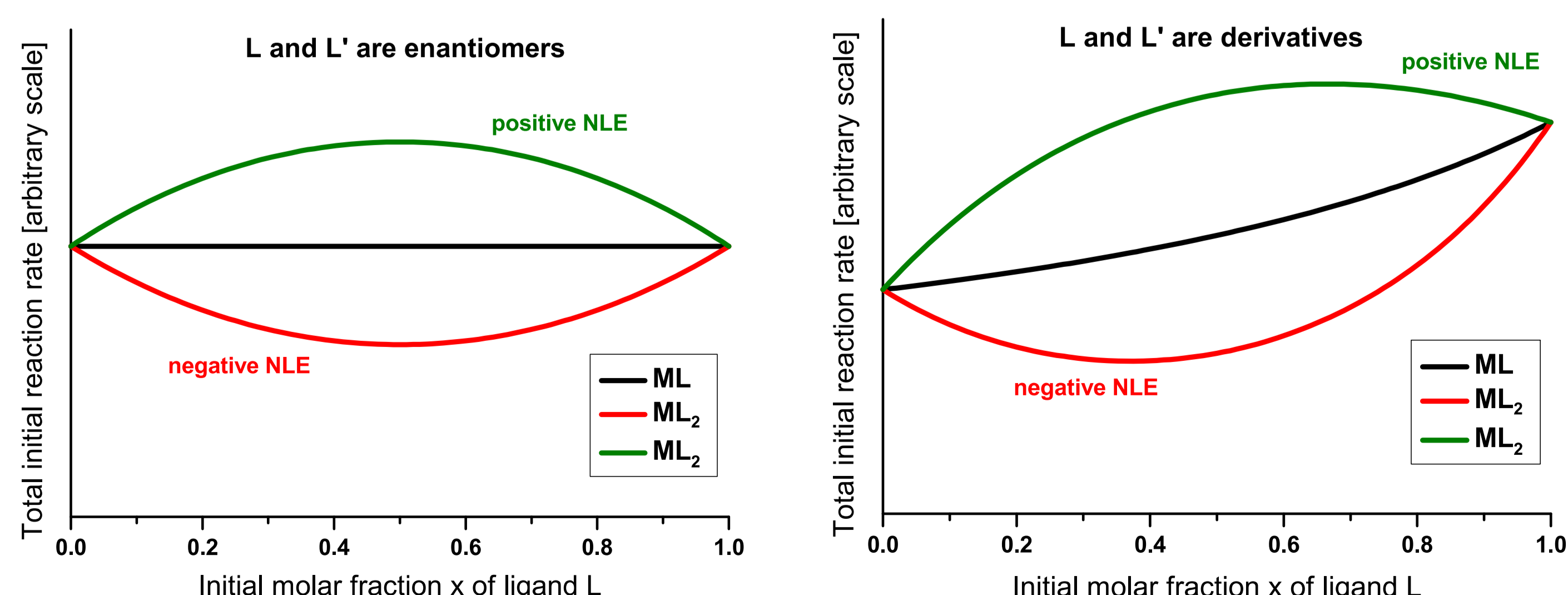


Representative behavior of catalytic model reactions with respect to the variation of the relative amounts of two equivalent ligands L and L' for either catalytically active ML or ML<sub>2</sub> and their dependence of the enantiomeric excess (ee) of the product on the ee of the ligand (L and L' are assumed to be enantiomers). The green curve shows a system with a positive stereochemical NLE (product optical purity higher than with linear behavior), the red curve shows a system with a negative stereochemical NLE (product optical purity lower than with linear behavior).



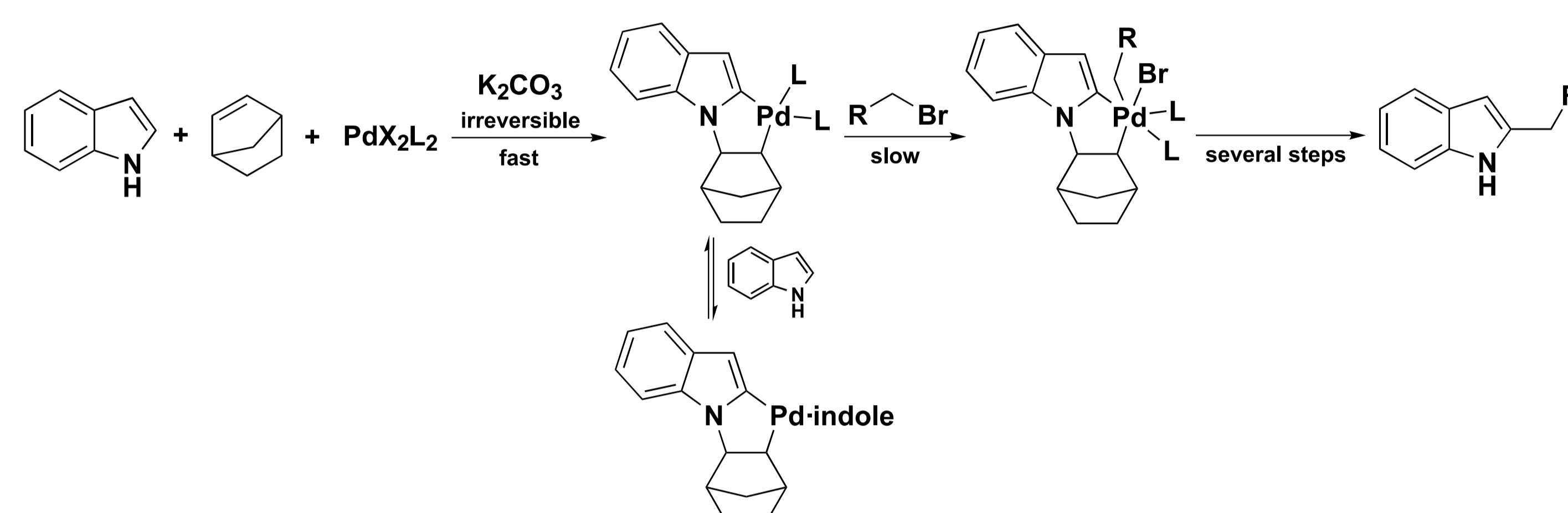
Schematic illustration of the underlying kinetic models for either catalytic ML or ML<sub>2</sub> when two equivalent ligands L and L' are present. Substrate S is converted to product P under catalysis of (A) ML or (B) ML<sub>2</sub>.

## Expansion to Derivatives

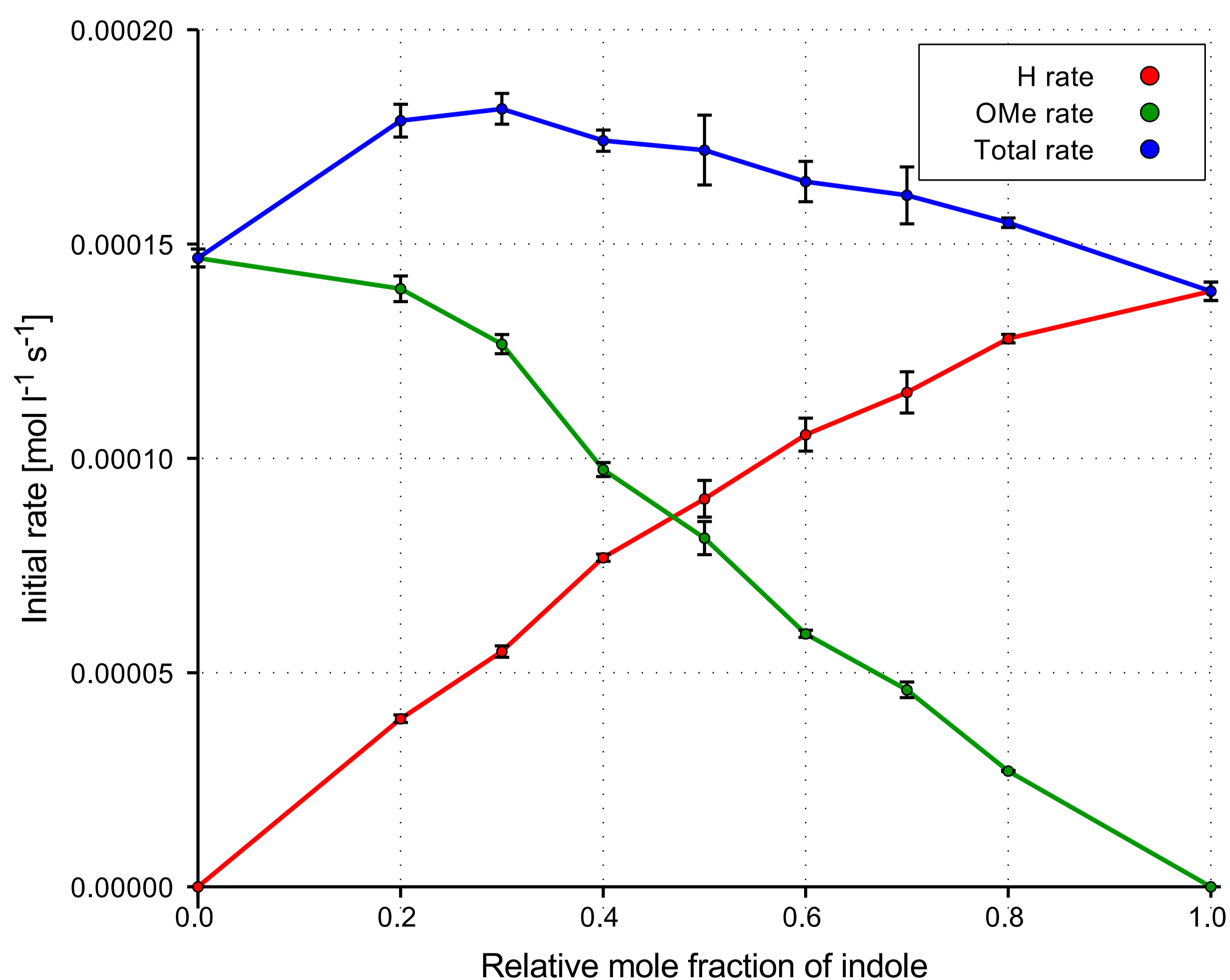
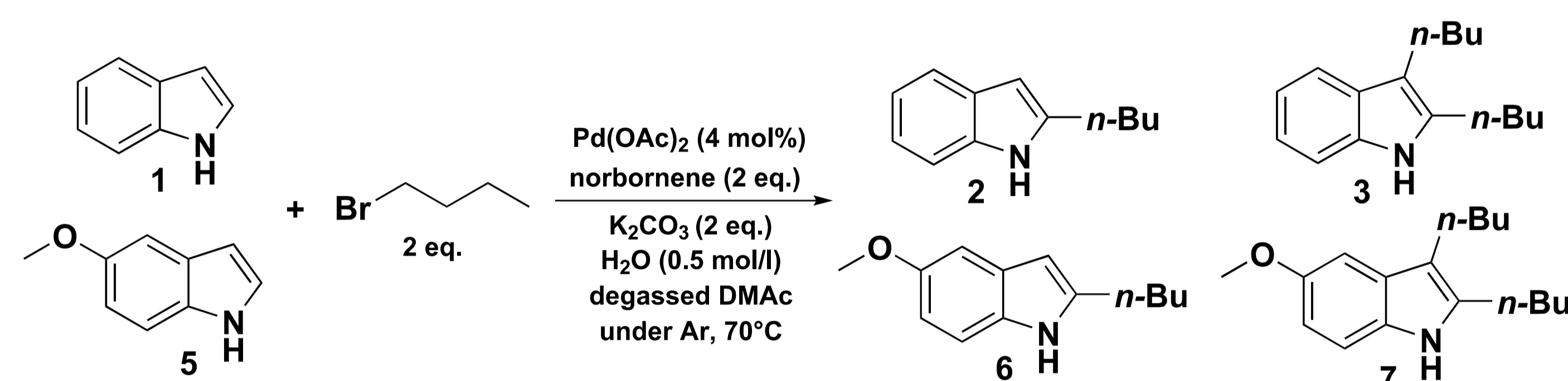


Representative behavior of catalytic model reactions with respect to the variation of the relative amounts of two equivalent ligands L and L' for either catalytically active ML or ML<sub>2</sub> and their dependences of the total initial reaction rates on the initial molar fraction of ligand L with respect to the total amounts of ligands L and L'. In the left diagram the ligands are assumed to be enantiomers, in the right diagram they are assumed to be derivatives. The green curve shows a system with a positive kinetic NLE (rate maximum observed when both ligands are present), the red curve shows a system with a negative kinetic NLE (rate minimum observed when both ligands are present).

## Model Reaction



Proposed kinetic model for the Pd-catalyzed direct alkylation of indoles.<sup>5</sup> The cyclometalated intermediate is in equilibrium with an off-cycle Pd-species coordinated to two molecules of indole. The slow step was proposed to be oxidative addition of the alkylbromide to the cyclometalated intermediate.



Experimental observation of an NLE with respect to two equivalent electronically modified substrates in the Pd-catalyzed direct alkylation of indoles.<sup>5-7</sup> The initial reaction rates when several mixtures of indole and 5-methoxyindole were subjected to the reaction conditions were determined. The colored circles show the experimental values obtained. The rate values of each series are linearly connected as a guide to the eye.

## Conclusion

To conclude, we believe that by expanding the applicability of the investigation of NLEs beyond its previous limitation to asymmetric reactions this method now can reach its full potential as a mechanistic tool. The systematic investigation of the kinetic behavior of catalytic reactions when mixtures of different equivalent (co-)catalysts or substrates are subjected to the reaction conditions is a valuable expansion of the experimental toolbox to study reaction mechanisms and this method enables to gather indirect information about the structure of kinetically relevant catalyst species involved which is in general not readily obtained by alternative methods. In addition, it provides valuable insight into the intrinsic kinetic behavior of the system under investigation and therefore leads to a better understanding of a catalytic reaction.

1) H. Wynberg, B. Feringa, *Tetrahedron* 1976, 32, 2831–2834. 2) C. Puchot, O. Samuel, E. Dunach, S. Zhao, C. Agami, H. Kagan, *J. Am. Chem. Soc.* 1986, 108, 2353–2357. 3) C. Girard, H. B. Kagan, *Angew. Chem. Int. Ed.* 1998, 37, 2922–2959. 4) D. G. Blackmond, *Acc. Chem. Res.* 2000, 33, 402–411. 5) L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* 2012, 134, 14563–14572. 6) L. Jiao, T. Bach, *J. Am. Chem. Soc.* 2011, 133, 12990–12993. 7) L. Jiao, T. Bach, *Synthesis* 2014, 46, 35–41.