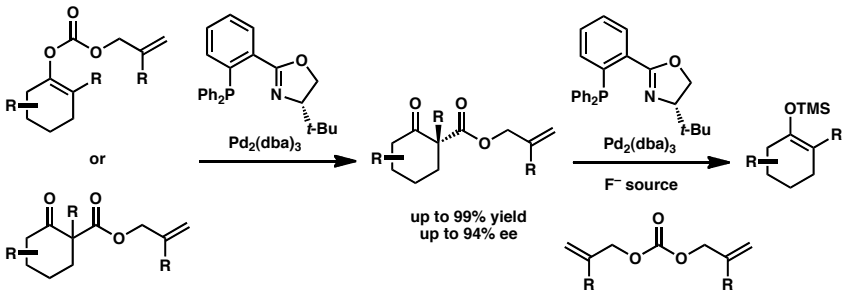
APPENDIX 5

Nonlinear Effect Experiment on Palladium-Catalyzed Decarboxylative Allylic Alkylation

A5.1 INTRODUCTION AND BACKGROUND

We have recently developed a series of palladium-catalyzed decarboxylative enantioselective allylic alkylation reactions of cyclic ketone enolates, such as allyl carbonates, β-ketoesters, and silyl enol ethers (Scheme A5.1).[1] These reactions proceed in the presence of steric hindrance, are compatible with a variety of functional groups, and demonstrate a high tolerance to water. These experimental observations support an inner-sphere mechanism, by which a palladium-bound enolate is operative. However, these studies do not discount the possibility of a bimetallic mechanism, wherein one palladium delivers the enolate to another palladium π-allyl complex. To probe the molecularity of the catalytically active species, we performed a nonlinear experiment.

Scheme A5.1 Palladium-catalyzed enantioselective decarboxylative allylic alkylation reactions of ketone enolates

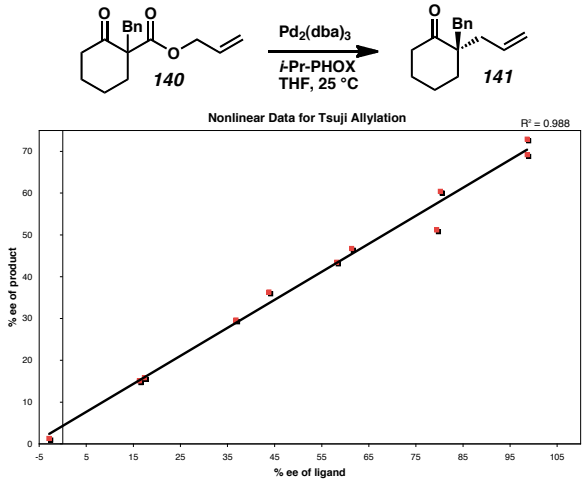


Pioneered by Kagan, the relationship between the enantiomeric excess of the chiral ligand and the enantiomeric excess of the product can provide mechanistic insight into the structure of the catalytically active species in asymmetric reactions.[2] When the relationship between the enantiomeric excess of the ligand and the enantiomeric excess of the product deviates from linearity, the phenomenon is described as a nonlinear effect. Nonlinear effects arise when the chiral catalyst undergoes aggregation at some stage of the reaction.

A5.2 NONLINEAR EFFECT EXPERIMENT

The decarboxylative asymmetric allylation of benzyl β-ketoester **140** was studied by using different enantiomeric purities of the *i*-Pr-PHOX ligand. Comparison of the enantiomeric excess of the product versus the enantiomeric excess of the *i*-Pr-PHOX ligand revealed a linear relationship (Scheme A5.2). The absence of a nonlinear effect suggests that the catalytically active species in our decarboxylative system involves one molecule of *i*-Pr-PHOX, thus one palladium metal center. Furthermore, the absence of a nonlinear effect does not support a mechanism that involves a bimetallic rate determining step where one palladium delivers the enolate to another palladium π-allyl complex.

Scheme A5.2 Nonlinear experiment on palladium-catalyzed decarboxylative allylic alkylation



A5.3 CONCLUSION

Probing the palladium-catalyzed decarboxylative allylic alkylation developed by our laboratories revealed a linear relationship between the enantiomeric excess of the ligand and the enantiomeric excess of the product, which suggests that the catalytically active species is a single ligand-bound palladium complex. The results of this study have contributed to the general understanding of the operative mechanism.[3]

A5.4 EXPERIMENTAL SECTION

A5.4.1 Materials and Methods

Unless otherwise stated, reactions were performed in flame-dried glassware under argon atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. Tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) was purchased from Strem and stored in a desiccator under argon atmosphere prior to use. (*S*)-*t*-Bu-PHOX, (*S*)-*i*-Pr-PHOX, (*R*)-*i*-Pr-PHOX, and substrate were prepared by our previously reported methods.[1] Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed by using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching or anisaldehyde. ICN silica gel (particle size 0.032-0.063 mm) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC, utilizing a Chiracel OJ column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd with visualization at 254 nm. Analytical achiral GC was performed with an Agilent 6850 GC utilizing a DB-WAX column (30 mm x 0.24 mm with 1.0 mL/min carrier gas flow).

A5.4.2. General Procedures for Nonlinear Experiments

THF stock solutions with the desired enantiomeric excess of *i*-Pr-PHOX were freshly prepared prior to each experiment. The enantiomeric excess of the *i*-Pr-PHOX delivered was confirmed by chiral HPLC analysis with a Chiracel OJ column using 1% ethanol in hexanes (1.0 mL/min) as eluent on the stock solution ((*S*)-*i*-Pr-PHOX: 13.16 min and (*R*)-*i*-Pr-PHOX: 7.60 min).

A 1-dram vial equipped with a stirbar was flame-dried twice under vacuum. After cooling under nitrogen, $Pd_2(dba)_3$ (4.6 mg, 0.005 mmol) was added. The vial was evacuated for 5 minutes. THF (3 mL total) was added, and then *i*-Pr-PHOX (4.8 mg, 0.0125 mmol) in THF was added via syringe. The contents were allowed to stir for 30 minutes at 25 °C prior to addition of benzyl β-ketoester **140** (27.2 mg, 0.1 mmol) via syringe. The reaction progress was monitored by TLC. Upon completion, the reaction was concentrated and purified via column chromatography (20% ether in pentane). Subsequently, the enantiomeric excess of product **141** was determined by chiral HPLC analysis with a Chiracel OJ column using 1% ethanol in hexanes (1.0 mL/min) as eluent (**141**: 15.942 min and 24.345 min).

A5.5 NOTES AND REFERENCES FOR TEXT

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