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Catalyst Selection Based on Intermediate Stability Measured by Mass Spectrometry

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1. Introduction

1-1. Catalyst development

a) Rational catalyst design

b) Generation of diversity followed by selection

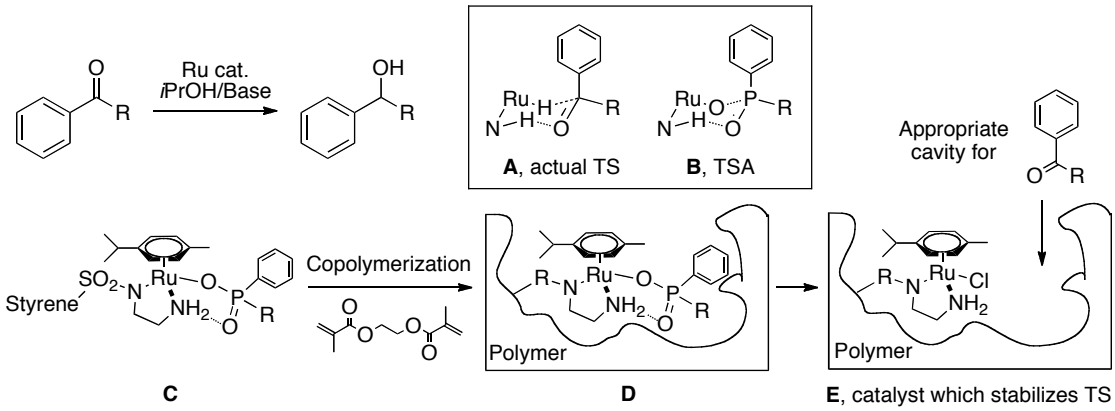
Enzyme	Combinatorial methods
◎ nature's most successful catalyst ◎ natural selection: "survival of the fittest"	○ availability of large ligand libraries × all library members have to be evaluated individually

➔ Efficient selection method capable of selecting the best catalyst from a mixture is desirable.

1-2. Exapmles of reported selection method: How to select the best catalyst (reaction rate, stereoselectivity, etc.)

a) Select the catalyst which lowers the activation barrier

Scheme 1. *Molecular imprinting with TSA in Ru-catalyzed transfer hydrogenation of ketones*



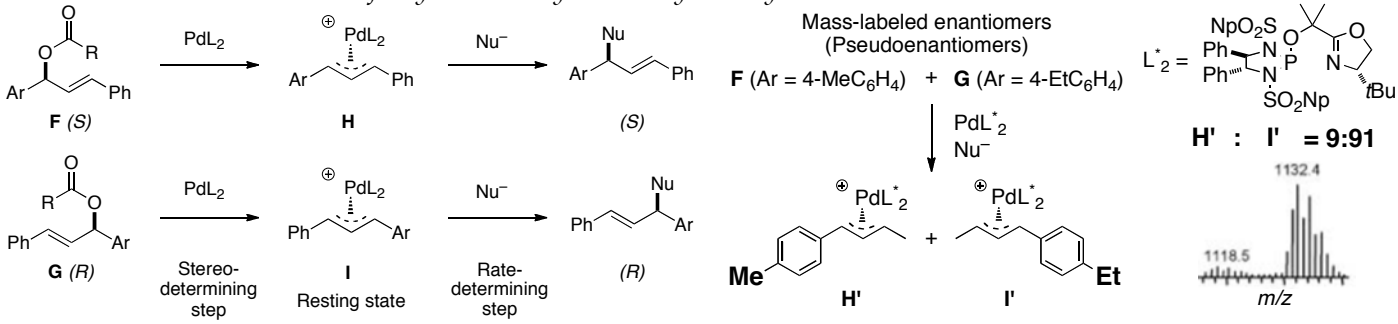
• In one example, phosphinato complex **B** was utilized as transition state analogue (TSA) of actual TS **A** in Ru-catalyzed transfer hydrogenation of ketones (Scheme 1).[1]

• Complex **C** having TS-like structure was copolymerized to give the highly crosslinked jet porous polymer **D**, whose phosphinato moiety was subsequently cleaved off to give polymer **E**, which has an cavity with the appropriate shape for the reaction of the corresponding ketone.

• The transfer hydrogenation reaction using polymer **E** was more active, and substrate-selective for the ketone used for molding than the polymer without such a cavity.

b) Selection method by examining catalytic intermediates

Scheme 2. *Kinetic resolution of allylic esters by Pd-catalyzed allylic substitution*



• In one example, ESI-MS was used to determine the ligand with the highest kinetic resolution ability in Pd-catalyzed allylic substitution reaction (Scheme 2).[2]
• Oxidative addition of a racemic mixture of **F** and **G** to PdL_2 affords Pd-allyl complexes **H** and **I**, whose ratio reflects the catalyst's ability to discriminate between two enantiomers **F** and **G**.
• In order to distinguish **H** and **I** in ESI-MS measurement, mass-labeled psesudoenantiomers **H'** and **I'**, which possess a substituent with a different mass in the position too far from the reactive part to affect the reaction were employed.
• Analysis of the reaction mixture by ESI-MS successfully predicted the resolution ability of a chiral ligand.

➔ Generally speaking, the selection method based on property of intermediate is more convenient because it is much easier to understand intermediates than more elusive transition states.

1-3. This work

Authors have developed a new catalyst selection method which focuses on the stability of catalytic intermediates equilibrated in a mixture using electrospray ionization mass spectrometry (ESI-MS), and applied it for the ligand optimization of Pd-catalyzed allylic alkylation reactions.

2. Results and Discussion

2-1. Author's assumption: relationship between stability of intermediate and activation energy

• Higher reaction rate = lower activation energy (E_a) is achieved by
a) stabilization of transition state
b) destabilization of reactant (this work)

• According to Marcus theory, TS is affected to a less extent, when the reactant is raised or lowered in energy, especially if it is late TS ($|E_2 - E_1| > |E_{TS2} - E_{TS1}|$).

➔Relative stability of reactant rather than TS determines E_a.
• When E_2 is less stable ($E_2 > E_1$), E_{a2} is lower ($E_{a2} < E_{a1}$).

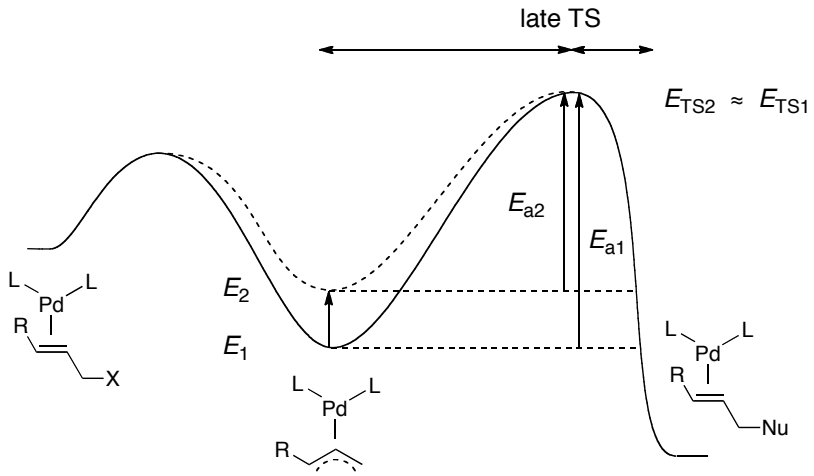


Figure 1. *Potential energy diagram of Pd-catalyzed allylic alkylation*

2-2. Proof of Principle: Pd-catalyzed allylic alkylation

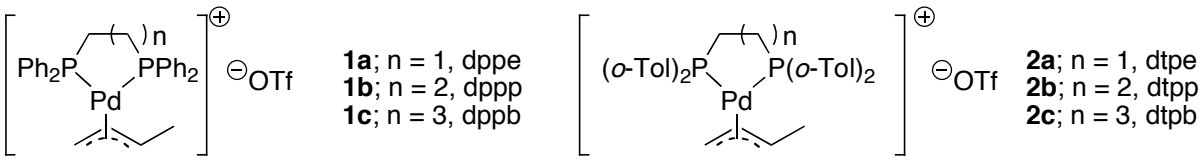
• Rate-determining step in Pd-catalyzed allylic alkylation is nucleophilic attack to Pd–π-allyl intermediate with late TS.[3]

➔The reaction fulfills the conditions outlined above (*2-1*).

• The least stable Pd–π-allyl intermediate should lead to the most active catalyst: "survival of the weakest".

2-2-1. New catalyst selection method using ESI–MS

• 6 diphosphine ligands with different bite angles and steric properties were used to prepare the corresponding Pd complexes **1a–1c** and **2a–2c**.



• One equivalent of **1a** was mixed with equimolar amounts of dppp and dppb to generate a dynamic library of Pd-allyl intermediates (Scheme 3).

• In order to exclude the trapping of kinetic mixtures, experiments starting with **1b** and **1c** were also conducted to give the identical data.

Scheme 3. *Dynamic library of Pd-allyl intermediates in equilibrium*

1a + dppp + dppb
or
dppe + **1b** + dppb
or
dppe + dppp + **1c**

1 h, dichloromethane →

X **1a** + Y **1b** + Z **1c**
(1–X) dppe + (1–Y) dppp + (1–Z) dppb
(X + Y + Z = 1, 0 ≤ X, Y, Z ≤ 1)

• The resulting equilibrium mixture was analyzed by ESI-MS (Figure 2).

Abundance:	**1a** > **1b** > **1c**	**2a** > **2b** > **2c**
Stability:	**1a** > **1b** > **1c**	**2a** > **2b** > **2c**
Expected reactivity:	**1c** > **1b** > **1a**	**2c** > **2b** > **2a**

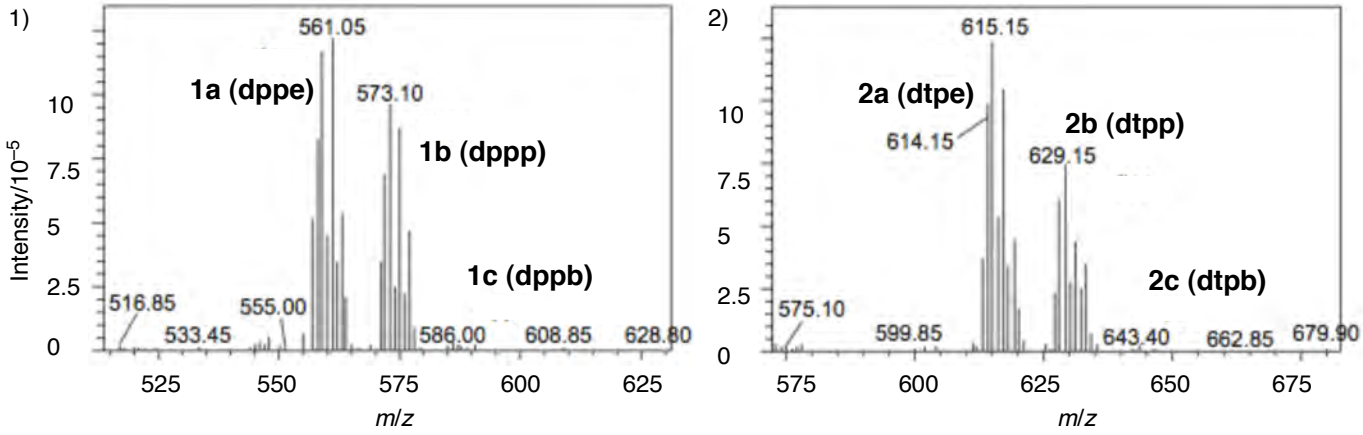
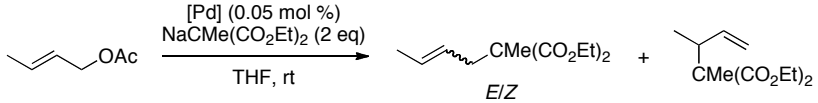


Figure 2. *ESI-MS spectrum of a dynamic library of Pd-allyl complexes for the ligand series 1)* ***1a–1c*** *and 2)* ***2a–2c***

2-2-2. Catalytic reaction with Pd complexes

Table 1. *Pd-catalyzed allylic alkylation of crotyl acetate*



catalyst	TOF[a]	*linear/branch*	*E/Z*
1a	**2.0**	80/20	86/14
1b	**2.9**	83/17	92/8
1c	**8.9**	82/18	96/4
2a	**0.7**	91/9	71/29
2b	**1.5**	96/4	67//33
2c	**3.8**	98/2	87/13

[a] Turnover frequency determined at 20% conversion in h^{-1}.

• The trend in reaction rate (**1c** > **1b** > **1a**, **2c** > **2b** > **2a**) is consistent with that obtained by the ESI-MS selection method.

2-2-3. Thermodynamic parameters

a) Experimental relative energy of Pd- allyl complex: $\Delta G_{MS} = -RT \ln(I_A / I_B)$ (I: intensity of ESI-MS)

b) Experimental relative activation energy: $\Delta E_a = -RT \ln(k_A / k_B)$ (k: turnover frequency)

c) Theoretical relative energy of Pd-allyl complex: ΔE_{DFT}

• Experimental ΔG_{MS} values correspond well with theoretical ΔE_{DFT} values.

• The degree to which ΔE_a is lowered is much smaller than the effect on the ΔG_{MS} ($|\Delta G_{MS}| > |\Delta E_a|$).

➔ Consistent with the initial assumption based on Marcus theory.

Tabel 2. *Relative energies*

Pd–allyl	ΔG_{MS} (kcal mol^{-1})	ΔE_{DFT}[a] (kcal mol^{-1})	ΔE_a (kcal mol^{-1})
1a	0.0	0.0	0.0
1b	0.4	0.4	–0.3
1c	2.8	3.9	–0.9
2a	0.0	–	0.0
2b	0.6	–	–0.5
2c	2.9	–	–1.0

[a] In the absence of OTf^- counterion at ZORA-BLYP/TZ2P level.

2-4. Application to another reaction

• Pd-catalyzed asymmetric allylic alkylation of *rac*-diphenylpropenyl acetate with IndolPhos was performed (Scheme 4).

• Equimolar amounts of five IndolPhos ligands **3a–3e** with different steric and electronic properties were mixed with 1 equivalent of a precursor, $[Pd(\eta^3\text{-}1,3\text{-}Ph_2\text{-allyl})(MeCN)_2]PF_6$.

• After equilibration for 3 days, relative abundance **3a** < **3b** < **3c** < **3d** < **3e** was determined by ESI-MS.

• The order of TOF **3a** > **3b** > **3c** > **3d** > **3e** determined by GC monitoring correlates inversely with relative stablitiy (Figure 3).

➔ Author's concept "survival of the weakest" was again supported.

Scheme 4. *IndolPhos–Pd catalyzed allylic alkylation*

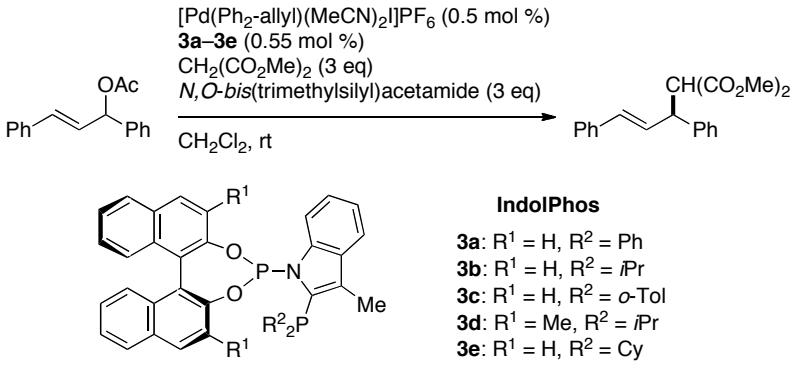
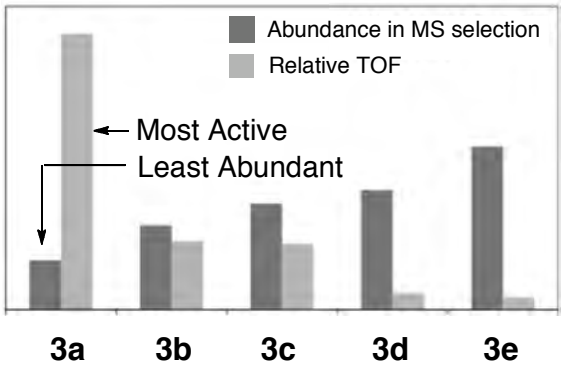


Figure 3*. Relative abundance and TOF*



3. Conclusion

Authors developed a new technique to select the most active catalyst from a dynamic mixture of Pd complexes for allylic alkylations. The selection method only requires an ordinary ESI-MS and can screen several ligands at the same time, making it simple and efficient.

4. References

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[3] a) Granberg, K. L.; Backvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858–6863. b) Evans, L. A.; Fey, N.; Harvey, J. N.; Hose, D.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G.; Osborne, R.; Owen-Smith, G. J. J.; Purdie, M. *J. Am. Chem. Soc.* **2008**, *130*, 14471–14473. c) Helmchen, G.; Dahnz, A.; Dübon, Pierre.; Schelwies M.; Weihofen, R. *Chem. Commun.* **2007**, 675–691.