A data-intensive approach to mechanistic elucidation applied to

chiral anion catalysis

Anat Milo, Andrew J. Neel, F. Dean Toste, Matthew S. Sigman

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## 1. Introduction

1-1. How do you improve your reaction?

a) Optimize the catalyst by the screening

   - Huge number of the candidates and difficult to determine the crucial parameter

b) Expand the scope of the reaction by using the standard condition

   - No one can know that this standard condition can apply to every substrate or not

⇒ We need the hypothesis rely on the experimental data

Previous work: Show the Gibbs free energy as the function of "quantifiable" parameter (Sterimol[1] and vibration[2]) in asymmetric reaction.

This work: **Combine the "measurable" outcomes and "quantifiable" properties**

1-2. Choice of case study

catalyst	conversion (%)	ee (%)
1	91	80
2	88	41
3	93	45
4	86	−8
5	95	−16
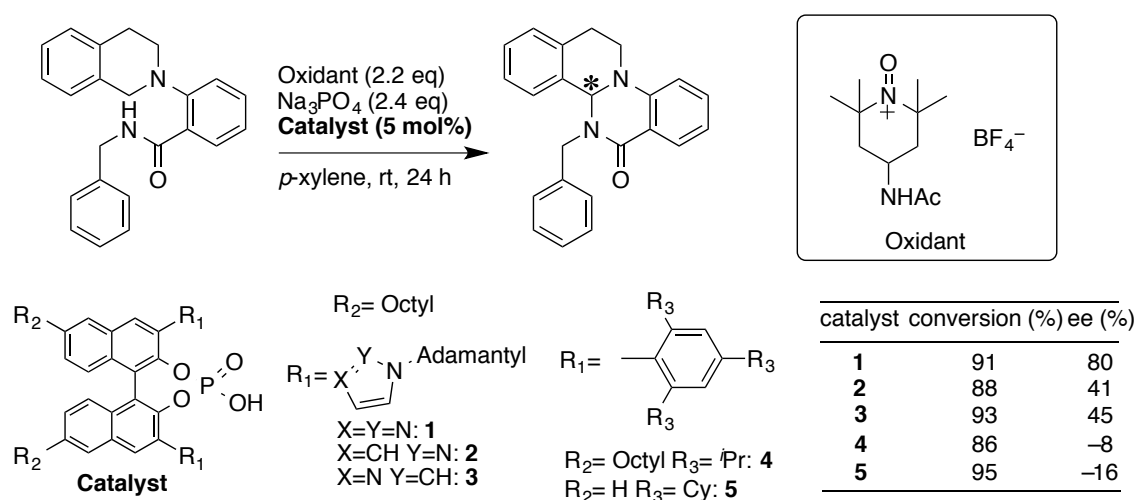
Figure 1. Target reaction[3]

✓ Substrate and catalyst affect the enantioselectivity

✓ Enantioselectivity is governed by noncovalent interaction

2. Results and Discussion

2-1. Experimental data

- Consider both electric and steric effect, the 12 substrate and 11 triazol catalyst were prepared. For every catalyst and substrate, identification of the correlation between molecular structure and enantioselectivity is determined by linear regression algorithm from the experimental results.
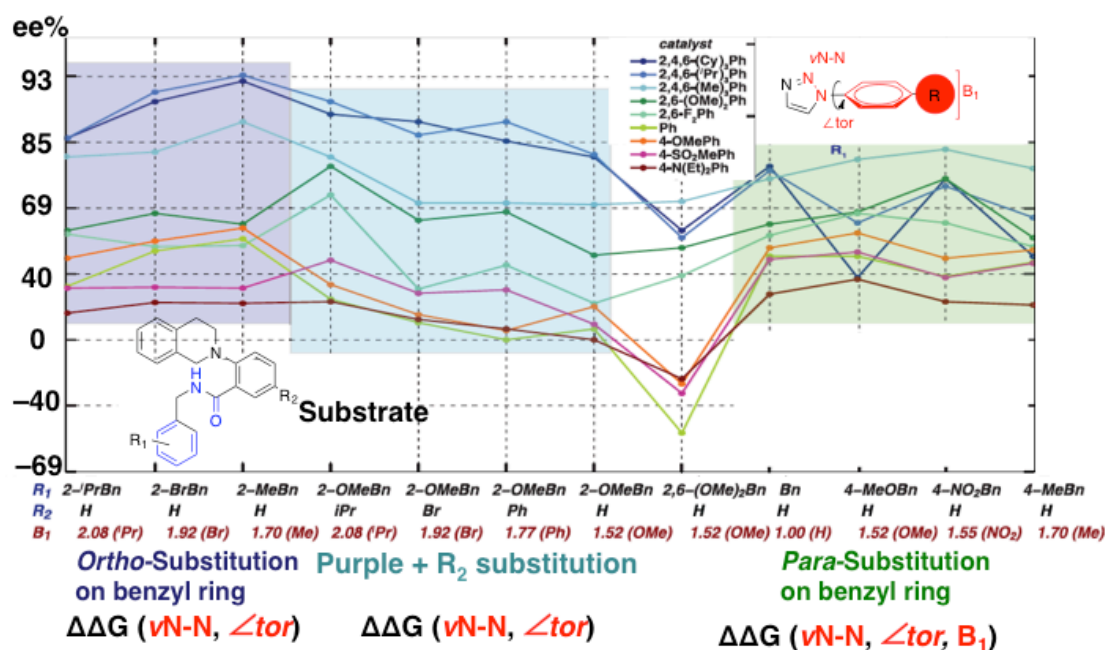

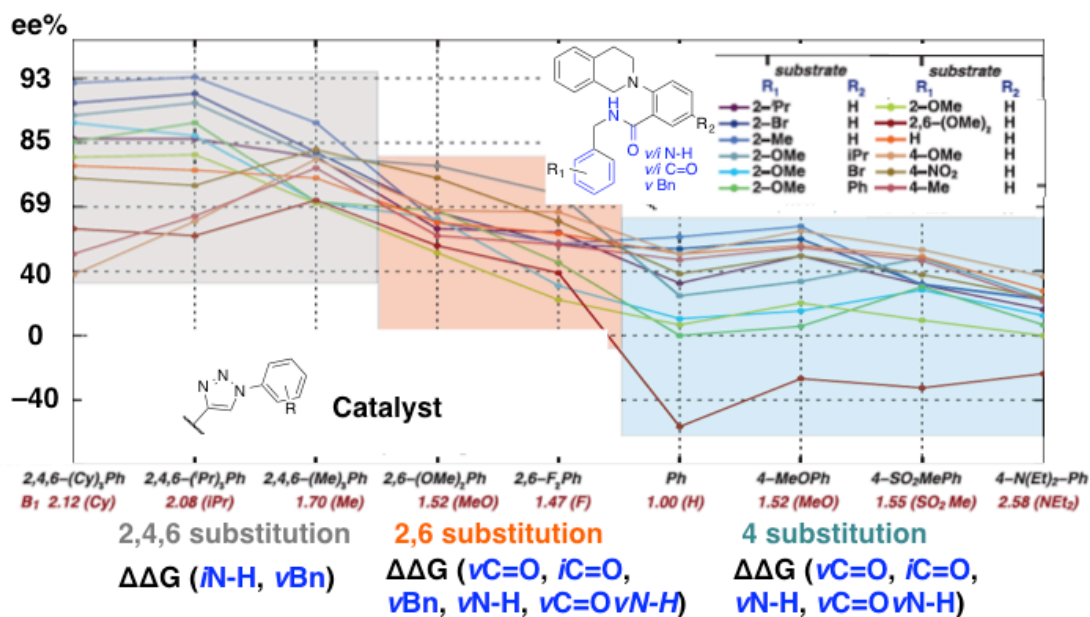**Figure 2. Catalyst structure-selectivity as a function of substrate**

Figure 3. Substrate structure-selectivity as a function of catalyst

2-2. Trend analysis

- *Fig 4*

a) In the case of *ortho*-substituted benzyl group (purple and blue), enantioselectivity can be modeled by torsion angle ($\angle$tor) and vibration frequency of N-N (νN-N).

b) In the case of *para*-substituted benzyl group (green), additional steric parameter B_1 (aryl ring width) is needed to model.

- *Fig 5*

A) Generally, enantioselectivity is preferred in the order 2,4,6 > 2,6 > 4 substitution.

B) In total, the model is composed of intensity and frequency of the vibration of N-H (i/νN-H) and C=O (i/νC=O) and frequency of the vibration of benzyl ring (νBn).

2-3. Trend interpretation

- These trends suggest that π-interaction between triazole and benzyl ring is governed the enantioselectivity. (*a* and *B*) This is also supported by heteroatom substitution (Fig. 1).

- The energy stabilization gained from π-interaction is affected by the geometry of each ring. And according to *A*, π-elongation is disfavor to the stabilization.

Unfavorable   Favorable
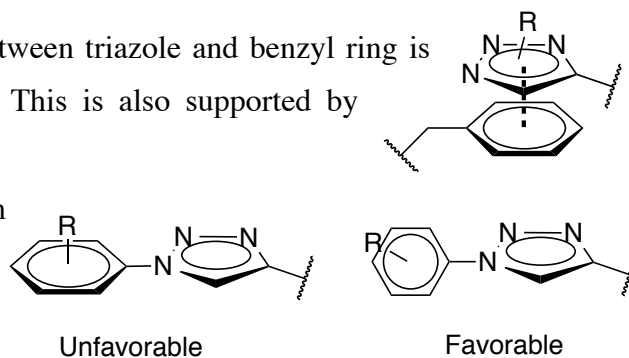
- Only substrates with elongated 4-substituents, lead to lower enantio selectivity with large substituents at the 2,6-position of the catalyst.
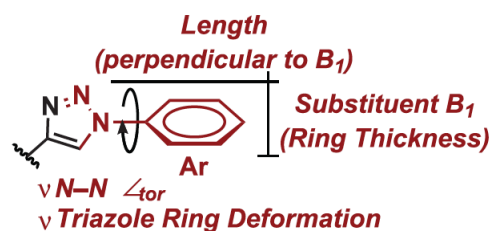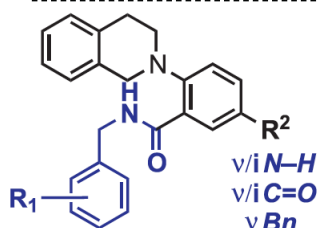
⇒ Steric repulsion between the *para*-position of the substrate benzyl and *ortho*-position of the catalyst (*b*).
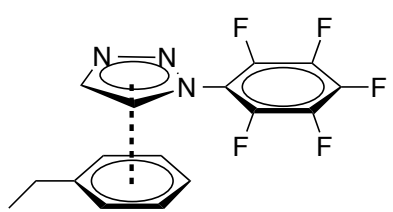
Steric repulsion
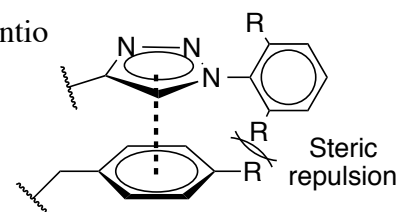
2-4. Probe of mechanistic hypothesis

- To probe this hypothesis, they set the model and predicted the enantioselectivity.

$$\Delta\Delta G^{\ddagger} = 1.01 + 0.30\,\nu N\text{–}N - 0.42\,\nu RingD + 0.11\,L - 0.19\,B_1 - 0.33\,\angle_{tor}$$
$$- 0.09\,iC\text{=}O - 0.23\,\nu N\text{–}H - 0.15\,\nu N\text{–}N \times \nu\,RingD - 0.09\,\nu N\text{–}N \times \nu N\text{–}H$$
$$- 0.09\,\angle_{tor} \times iC\text{=}O - 0.11\,B_1 \times \nu Bn + 0.20\,B_1 \times (\nu N\text{–}H + iN\text{–}H)$$

$\nu/i\,N\text{–}H$
$\nu/i\,C\text{=}O$
$\nu\,Bn$

Length (perpendicular to B_1)

Substituent B_1 (Ring Thickness)
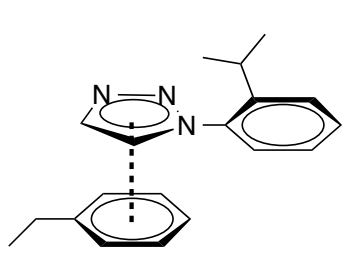
Ar

$\nu\,N\text{–}N$ $\angle_{tor}$
ν *Triazole Ring Deformation*

① Do not the aryl (catalyst) really π-interact with benzyl (substrate)?

catalyst	substrate	predicted %ee	measured %ee
F$_5$Ph	R$_1$ = 4-Me	72	67
2,6-F$_2$PH	R$_1$ = 4-Me	66	54
2,6-OMePh	R$_1$ = 4-Me	73	58
F$_5$Ph	R$_1$= 2-OMe	56	54
2,6-F$_2$PH	R$_1$= 2-OMe	50	44
2,6-OMePh	R$_1$= 2-OMe	67	67

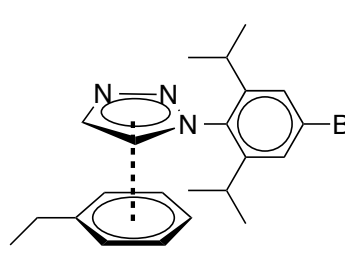No deference among the F or OMe ⇒ main function of aryl is steric

② Do the steric repulsion between the *ortho*-position of the aryl and *para*-position of benzyl inhibit the π-interaction?

catalyst	substrate	predicted %ee	measured %ee
2-^{i}Pr	R$_1$ = 4-Me	77	78
2,4,6-^{i}Pr	R$_1$ = 4-Me	58	66
2-^{i}Pr	R$_1$ = 4-OMe	75	78
2,4,6-^{i}Pr	R$_1$ = 4-OMe	58	63
2-^{i}Pr	R$_1$ = 4-NO$_2$	79	87
2,4,6-^{i}Pr	R$_1$ = 4-NO$_2$	76	76

Even the substrate have the substituent at 4-position, high enantio selectivity appeared

③ Is the perpendicular geometry favorable to enantio selectivity?

substrate	predicted %ee	measured %ee
R$_1$ = 4-H, R$_2$ = H	85	85
R$_1$ = 2-OMe, R$_2$ = H	90	88
R$_1$ = 2-Me, R$_2$ = H	93	95
R$_1$ = 2-Br, R$_2$ = H	94	93
R$_1$ = 2-^{i}Pr, R$_2$ = H	92	93
R$_1$ = 2-OMe, R$_2$ = Br	90	93
R$_1$ = 2-OMe, R$_2$ = ^{i}Pr	92	91
R$_1$ = 2-OMe, R$_2$ = Ph	89	92

Completely 90º geometry shows the highest enantioselectivity

3. Conclusion

- The author revealed that how do the catalyst interacted with the substrate by using the data-intensive analysis

- The author designed rational catalyst structure and show high enantioselectivity by considering the modeling

- This disclosed data-intensive approach is suited to addressing such intricacies and holds potential for the analysis of increasingly complicated catalytic systems streamlining both reaction and catalyst development.

4. Reference

(1) A. Milo, E. N. Bess, M. S. Sigman, *Nature*, **2014**, *507*, 210

(2) K. C. Harper, E. N. Bess, M. S. Sigman, *Nat. Chem.*, **2012**, *4*, 336

(3) A. J. Neel, J. P. Hehn, P. F. Tripet, F. D. Toste, *J. Am. Chem. Soc.*, **2013**, *135*, 14044