Predicting and Optimizing Asymmetric Catalyst Performance Using the Principles of Experimental Design and Steric and Electronic Parameters

XU Liping

Dec 27th, 2013

Introduction

- A centerpiece of modern organic chemistry is the development of new catalytic enantioselective methods.

- Screening numbers of chiral ligands experimentally is highly empirical and the results can be unsatisfactory for a given reaction.

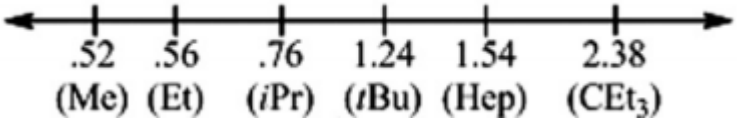
- How does one design a ligand for a given reaction type without engaging in a long term, empirical investigation of multiple ligand classes?

Introduction

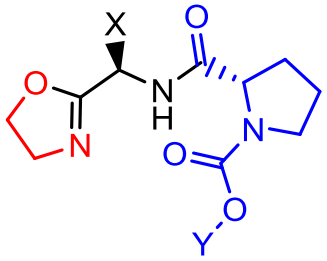
- The use of steric parameters develop by Taft and Charton can quantitatively evaluate ligand effects on enantioselectivity.

- Because the product distribution of enantiomers (R vs S) is directly related to the differences in free energy arising in the diastereomeric transition states, we were able to correlate er with the corresponding Charton steric parameter.

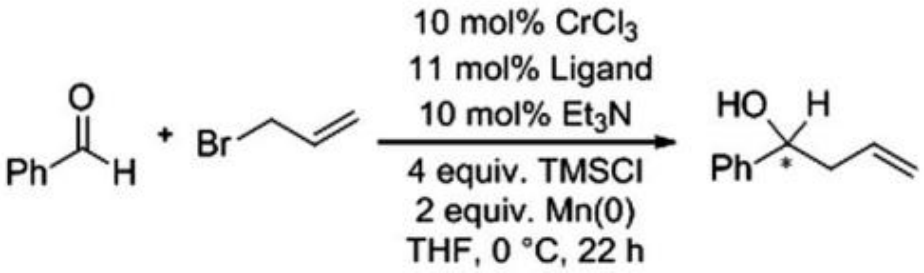
- Charton steric parameter: a parameter that describe the steric effect of a group (H, Me, ^{t}Bu…)



NHK Allylation of Benzaldehyde



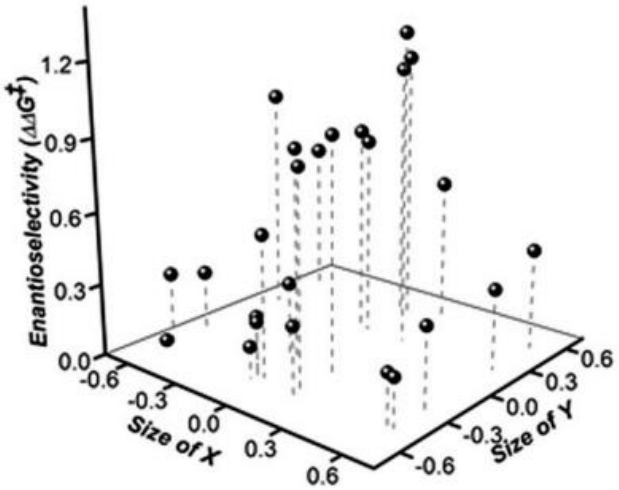
Ligand scaffold
Both X and Y contribute to the selectivity



Nozaki-Hiyama-Kishi (NHK) carbonyl allylation

X=	Y=
H	Me
Me	Et
Et	*i*Pr
*i*Pr	*t*Bu
*t*Bu	Hep =

Ligand library

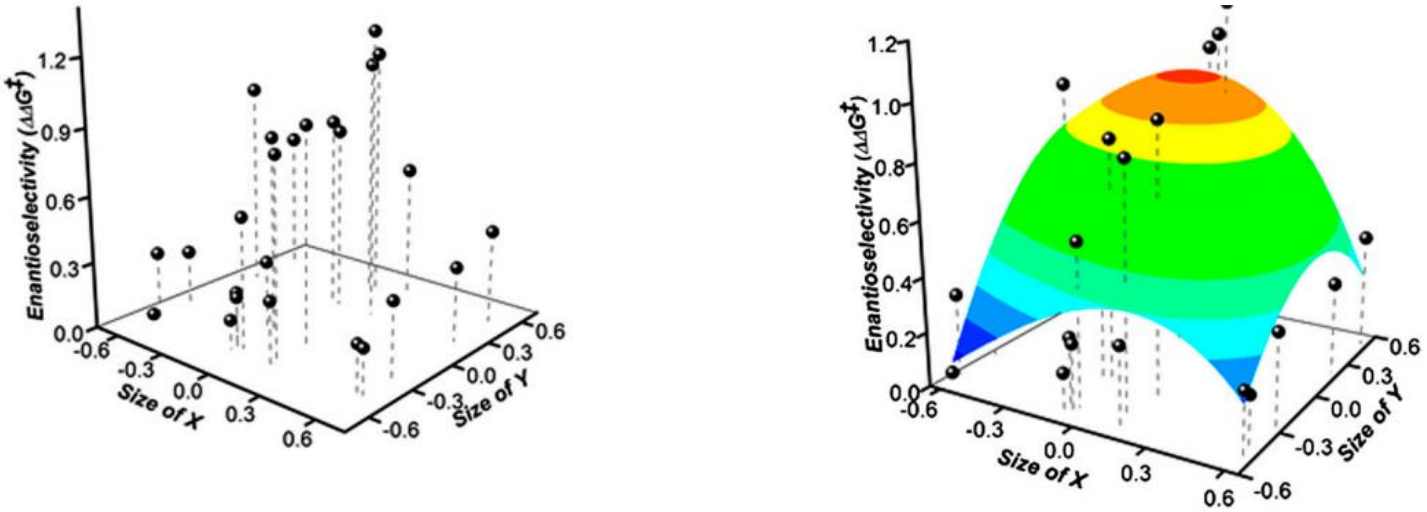


X, Y Charton parameter; Z enantioselectivity

- The relationship between X and Y is unclear;
  Thus we cannot predict the er with new substitute group combination.

3D Plot (A Surface) Can Show Relationships between X and Y

Dot to line (1D to 2D), got the relationship!



Dot to surface (1D to 3D), got the relationship!

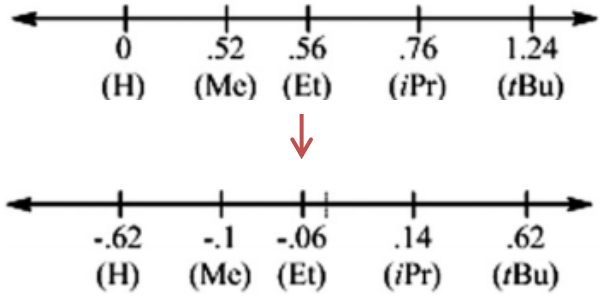
How to Get the 3D Plot (surface)?

- X, Y: Charton parameter; $\Delta\Delta G^{\ddagger}$: enantioselectivity

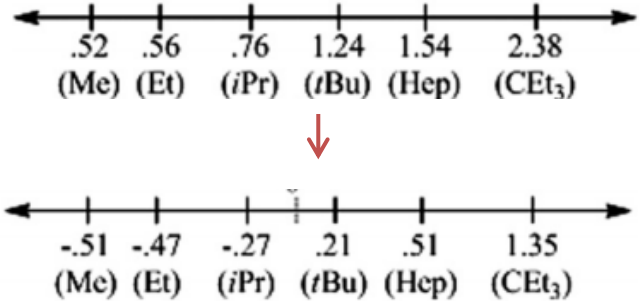
- Polynomial (多项式) models were attractive due to their simplicity wherein the functions would contain steric parameters for X and Y as the independent variables and enantioselectivity (expressed in terms of the free energy, $\Delta\Delta G^{\ddagger}$) as the dependent variable.

- Charton steric parameter translation for accuracy and simplicity (put the ceter at zero).

X



Y



Polynomial (多项式) Model

- Third order polynomials

$$\Delta\Delta G^{\ddagger} = z0 + aX + bY + cX^2 + dY^2 + fXY + gX^3 + hY^3 + iXY^2 + jYX^2$$

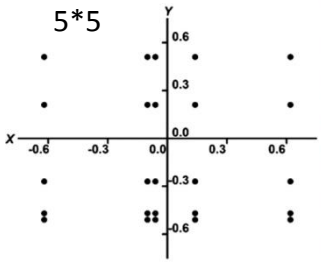
- The coefficient values (z0,a,b,c,d,f,g,h,i,j) were solved using multivariable linear least squares regression analysis (线性最小二乘回归分析).

C = $(M^TM)^{-1}(M^TN)$ *M: design matrix N: response matrix C: coefficient matrix*

M

Charton parameter

5*5



z0	X	Y	X^2	Y^2	XY	X^3	Y^3	YX^2	XY^2
1	-0.62	-1.45	0.3844	2.1025	0.899	-0.23833	-3.04863	-0.55738	-1.30355
1	-0.62	-0.21	0.3844	0.0441	0.1302	-0.23833	-0.00926	-0.08072	-0.02734
1	-0.62	1.45	0.3844	2.1025	-0.899	-0.23833	3.048625	0.55738	-1.30355
1	-0.1	-1.45	0.01	2.1025	0.145	-0.001	-3.04863	-0.0145	-0.21025
1	-0.1	-0.21	0.01	0.0441	0.021	-0.001	-0.00926	-0.0021	-0.00441
1	-0.1	1.45	0.01	2.1025	-0.145	-0.001	3.048625	0.0145	-0.21025
1	0.62	-1.45	0.3844	2.1025	-0.899	0.238328	-3.04863	-0.55738	1.30355
1	0.62	-0.21	0.3844	0.0441	-0.1302	0.238328	-0.00926	-0.08072	0.027342
1	0.14	1.45	0.0196	2.1025	0.203	0.002744	3.048625	0.02842	0.29435
1	-0.62	-1.45	0.3844	2.1025	0.899	-0.23833	-3.04863	-0.55738	-1.30355
1	-0.62	-0.21	0.3844	0.0441	0.1302	-0.23833	-0.00926	-0.08072	-0.02734
1	-0.62	1.45	0.3844	2.1025	-0.899	-0.23833	3.048625	0.55738	-1.30355
1	-0.1	-1.45	0.01	2.1025	0.145	-0.001	-3.04863	-0.0145	-0.21025
1	-0.1	-0.21	0.01	0.0441	0.021	-0.001	-0.00926	-0.0021	-0.00441
1	-0.1	1.45	0.01	2.1025	-0.145	-0.001	3.048625	0.0145	-0.21025
1	0.62	-1.45	0.3844	2.1025	-0.899	0.238328	-3.04863	-0.55738	1.30355
1	0.62	-0.21	0.3844	0.0441	-0.1302	0.238328	-0.00926	-0.08072	0.027342
1	0.14	1.45	0.0196	2.1025	0.203	0.002744	3.048625	0.02842	0.29435

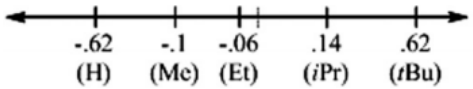
N

($\Delta\Delta G^{\ddagger}$)

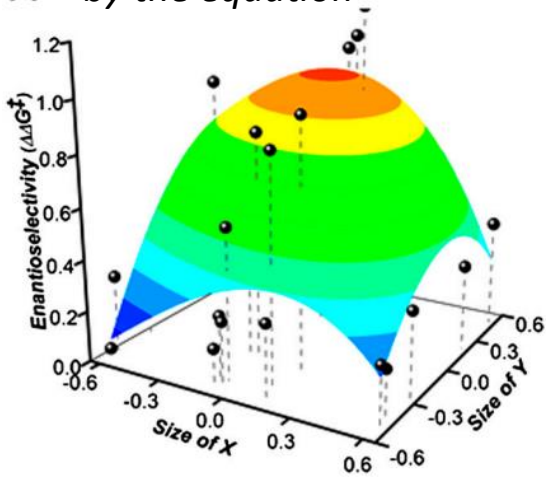
0.021702
0.984751
0.152897
0.130825
0.899549
0.219955
0.229012
0.359821
0.021702
0.021702
0.899549
0.175097
0.130825
0.822582
0.197442
0.242656
0.312121
0.021702

3D Model Give Accurate Fit

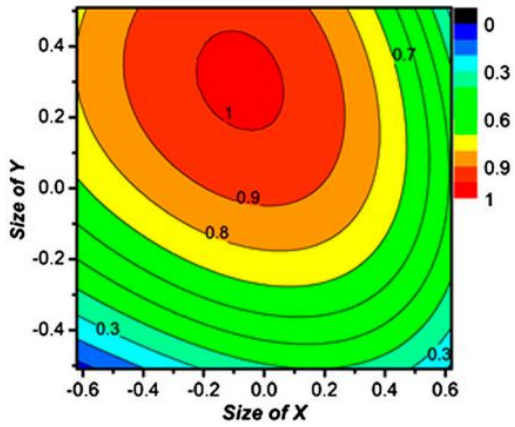
$$\Delta\Delta G^{\ddagger} = 0.931 + 0.576Y - 0.905X^2 - 1.005Y^2 - 0.502XY - 0.407X^3 - 0.475YX^2.$$



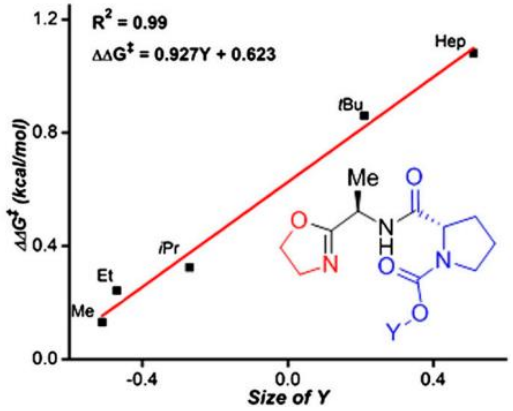
A *3D surface model given by the equation*



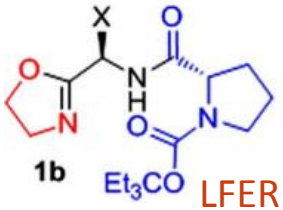
B *Contour plot of the surface model*



C *Linear free energy Correlation with X = Me*



Comparison of LFER and the 3D model on X substituent effect of three new catalysts



X	Predicted er Linear	3D	Error	Measured er
H	NA	40.8:59.2	±3	42.5:57.5
Me	3:97	46.7:53.3	±4	36:64
*i*Pr	NA	38.6:61.3	±3	40:60

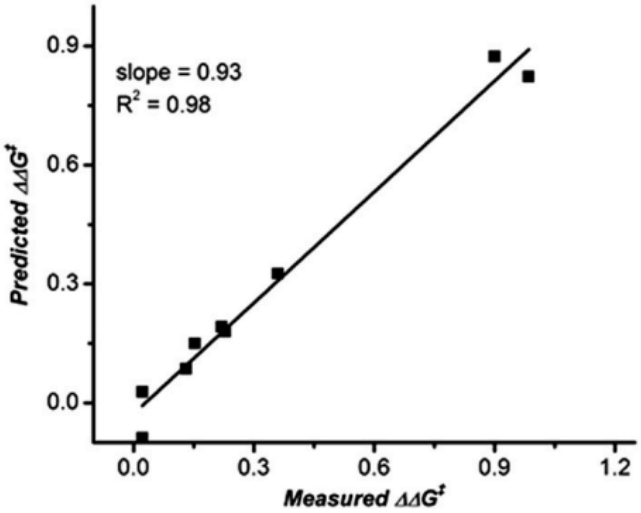
LFER: not accruate 3D model: accurate

The model relies on crossterms of X and Y providing evidence of the hypothesized synergistic effect (协同作用).

3*3 Simpler 3D Model

- In the realm of asymmetric catalysis, synthesis of 25 or even 16 ligands to determine optimal structure may be impractical.
- A 3*3 simpler dataset model was propsed.

Substituent		Measured		Predicted	
X =	Y =	er	ΔΔG‡	er	ΔΔG‡
H	Me	49:51	0.022	49:51	0.028
H	Me	14:86	0.985	18:82	0.823
H	Me	43:57	0.153	43:57	0.150
Me	^{t}Bu	44:56	0.131	46:54	0.086
Me	^{t}Bu	16:84	0.900	17:83	0.874
Me	^{t}Bu	40:60	0.220	41:59	0.192
^{t}Bu	CEt_3	40:60	0.229	42:58	0.180
^{t}Bu	CEt_3	34:66	0.360	35:65	0.326
^{i}Pr	CEt_3	49:51	0.022	54:46	-0.088

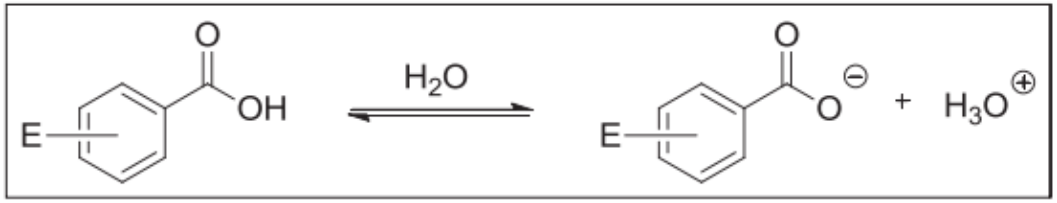


- This excellent correlation confirms the reliability of the model.

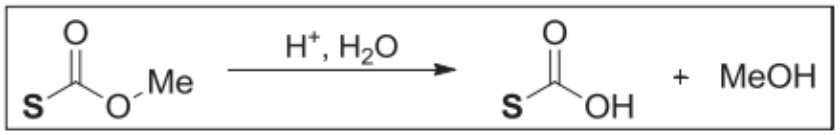
Take Electronic Effect into Consideration

- Classical electronic and steric parameters in organic chemistry

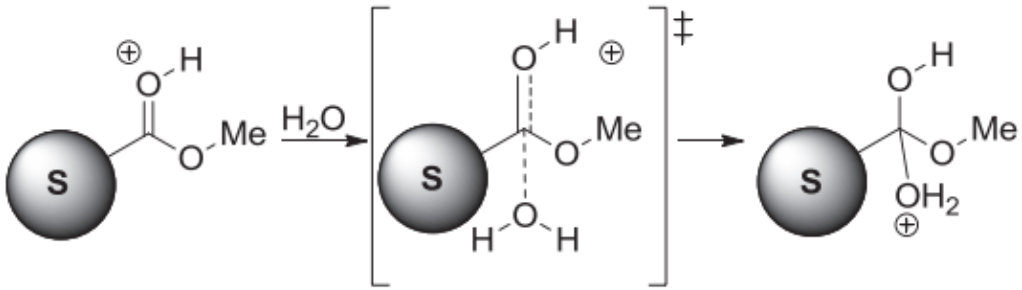
Hammett Electronic Effects



Taft Steric Effects



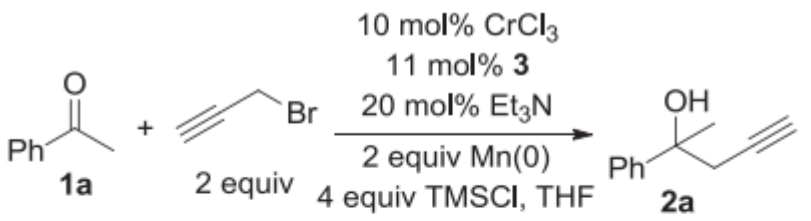
Rate Determining Step

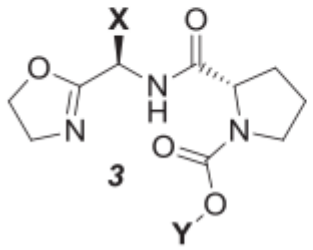


- Not only steric but also electronic effect play important roles in asymmetric synthesis.

Ligand Evaluation of Ketone Propargylation

Ligand library based evaluation of ketone propargylation





X	υ	Y	υ
H	0	Me	0.52
Me	0.52	*t*Bu	1.24
*t*Bu	1.24	CEt_3	2.38

υ = Charton Value

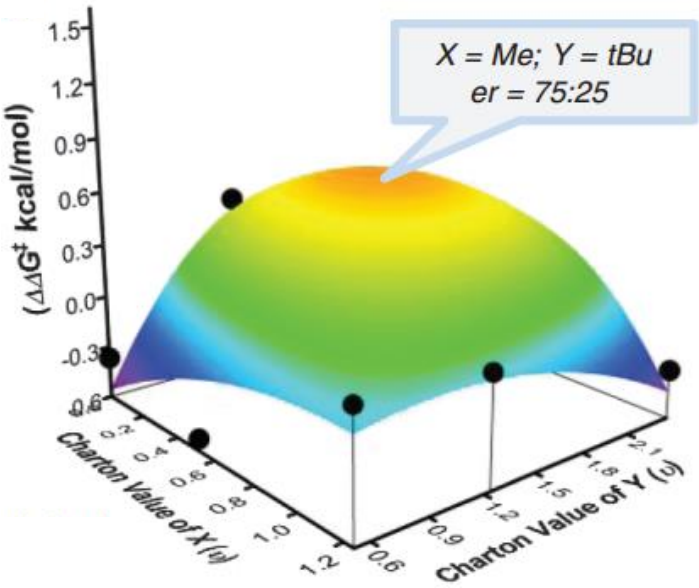
Me = CH_3; Et = CH_2CH_3

tBu = $C(CH_3)_3$

Polynomial equation

$$\Delta\Delta G^{\ddagger} = -1.87 + 1.34X + 3.03Y - 0.99Y^2 - 1.19XY + 0.62XY^2 - 0.73YX^2$$

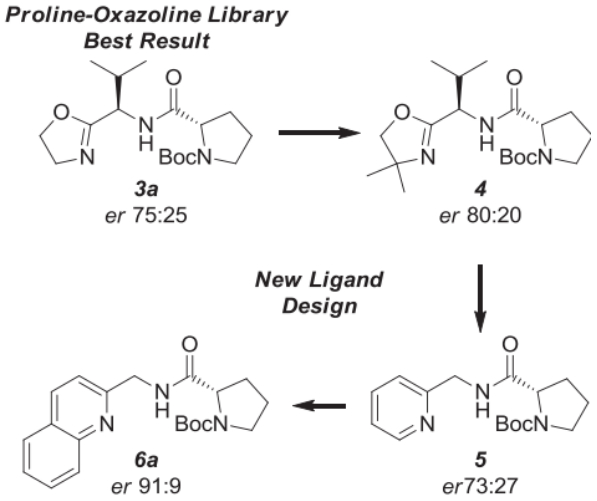
3D surface derived from ligand library evaluation. Relate the Charton value of groups X and Y to the measured enantioselectivity.



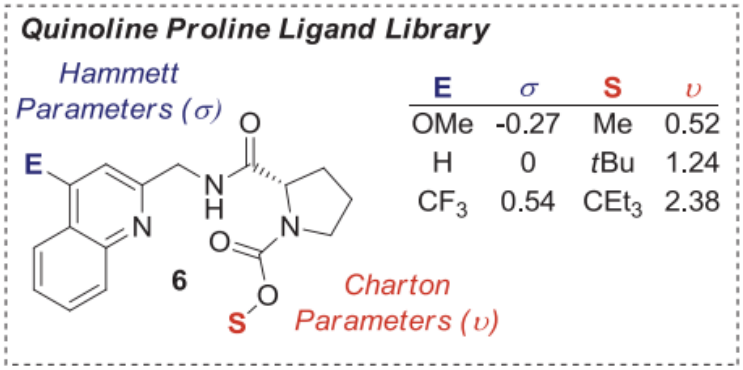
The best er gotten from this ligand scaffold is 75:25; Other ligand scaffolds may be worth looking for.

Ligand Evaluation of Ketone Propargylation

- Experimental evaluation to get the quinoline proline scaffold



- Take electronic and steric effects into consideration of the 3D model

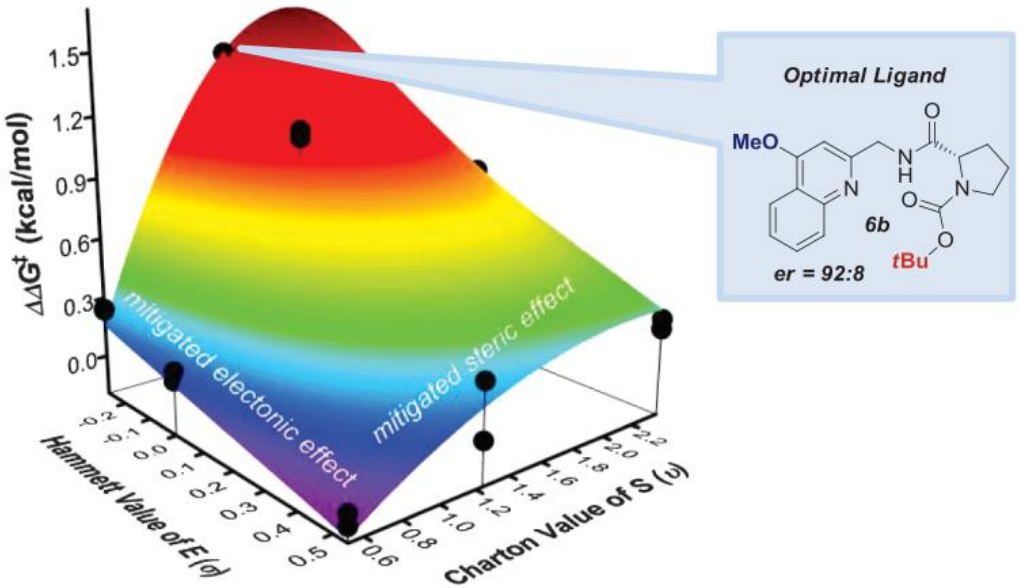


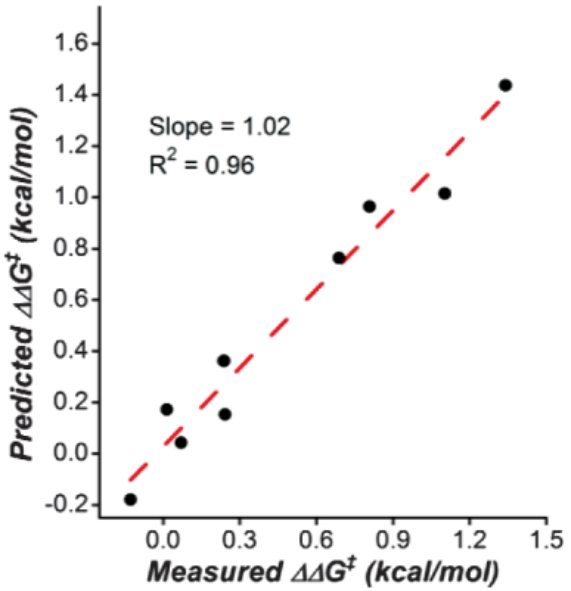
Optimal Ligand Derived from the 3D Model

- Polynomial equation

$$\Delta\Delta G^{\ddagger} = -1.20 + 1.22E + 2.84S - 0.85S^2 - 3.79ES + 1.25ES^2$$

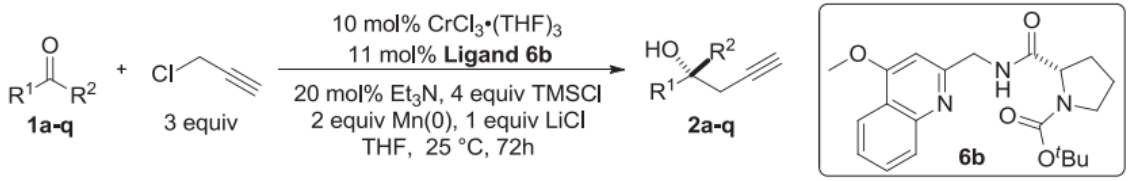
- 3D surface plot shows the optimal ligand
- Predict ΔΔG‡ VS measured ΔΔG‡

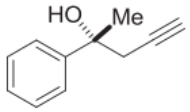




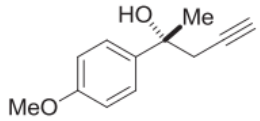
Experimental Validation

- Substrate scope of the enantioselective ketone propargylation reaction

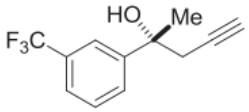




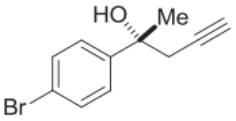
***2a**; 75% yield**
96:4 er†



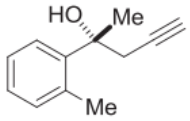
***2b**; 74% yield*
96:4 er



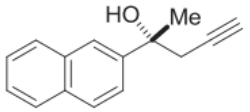
***2c**; 60% yield*
92:8 er



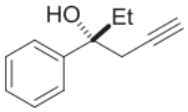
***2d**; 74% yield*
94:6 er



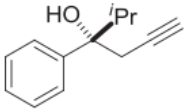
***2e**; 62% yield*
96:4 er



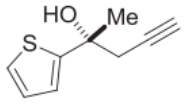
***2f**; 72% yield*
95:5 er



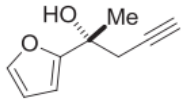
***2g**; 76% yield*
86:14 er



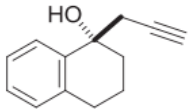
***2h**; 80% yield*
96:4 er



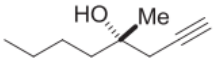
***2i**; 68% yield*
95:5 er



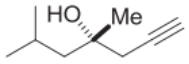
***2j**; 68% yield*
95:5 er



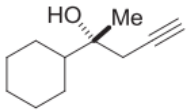
***2k**; 61% yield*
93:7 er



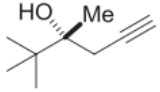
***2l**; 70% yield*
85:15 er



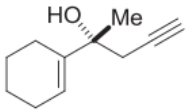
***2m**; 70% yield*
85:15 er



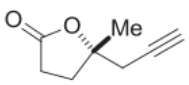
***2n**; 62% yield*
96:4 er



***2o**; 86% yield*
98:2 er



***2p**; 72% yield*
95:5 er



***2q**; 72% yield*
92:8 er

Me = CH_3; Et = CH_2CH_3; ^{i}Pr = $CH(CH_3)_2$

- High er and good yield were observed.
- The steric-electronic correlations provide a means for efficient optimization of the catalytic system.

Take-Home Message

- The 3D mathematical surface model which is based on the steric and electronic parameters of the ligand can describe the interplay of substituent effects on enantioselectivity accurately.

- Accurate predictions made by this 3D model lead to successful ligand evaluation of several important asymmetric reactions.

- This approach is attractive for optimizing reactions with limited detailed mechanistic and structural understanding as it is tied to basic physical organic precepts.

- Reference:

[1] Harper, K. C.; Sigman, M. S. *PNAS*, **2011**, *108*, 2179
[2] Harper, K. C.; Sigman, M. S. *Science*, **2011**, *333*, 1875