A Data Intensive Approach to Mechanistic Elucidation Applied to Chiral Anion Catalysis

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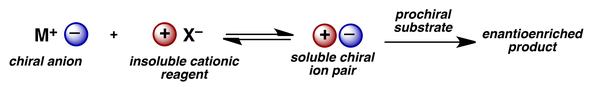
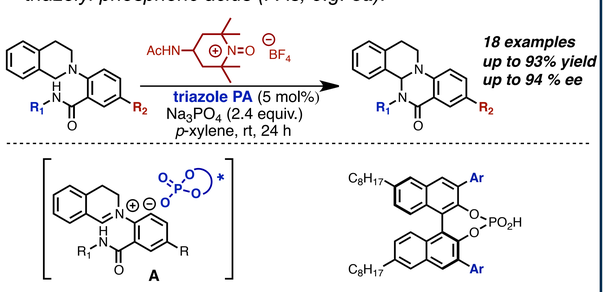
Summary: An understanding of the catalyst-substrate interactions that underlie selectivity (e.g. enantio-, diasterio-, or regioselectivity) in a given reaction is essential for the rational design of superior catalytic systems. Frequently however, it is difficult to discern how molecular features work in concert to achieve a desired outcome. We reasoned that in such instances, the outcome of *every* catalyst-substrate combination contains valuable information regarding their transition state interaction. Herein we describe a methodology for extracting this information in a meaningful way. This technique involves correlating various molecular descriptors with experimental enantioselectivity outcomes using linear regression techniques, and subsequently using the resulting predictive models to develop a mechanistic proposal that can be evaluated experimentally. Two case studies are presented from the field of chiral anion catalysis in which catalyst-substrate association is particularly challenging to discern. In each case, this data-intensive approach has yielded non-intuitive insights that have led to a deeper mechanistic understanding, enabling in one instance the rational design of a catalyst that displays the highest enantioselectivity observed for its system.

Background

- *The Toste group has a long standing interest in the use of chiral anions for asymmetric catalysis.[1] Recently, this strategy has been applied in the realm of phase transfer catalysis.[2]*



- *In 2013, Toste and coworkers reported an enantioselective oxidative coupling reaction enabled by a novel class of triazolyl phosphoric acids (PAs, e.g. **3a**).[3]*

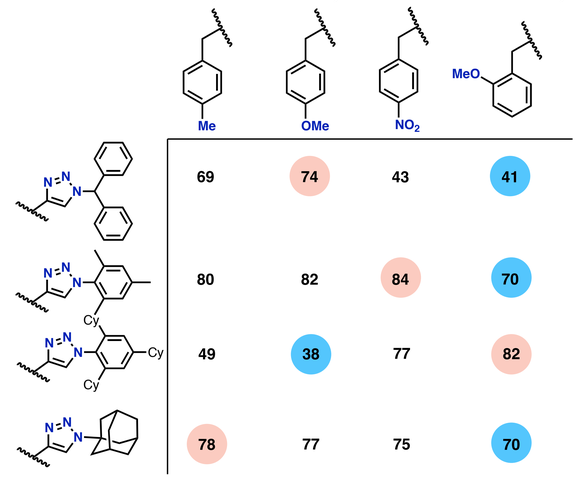


R_1 = Bn R_2 = H Ar = 1: R^2 = ^{i}Pr, 2: R^2 = Cy

entry	catalyst	conversion (%)	ee (%)
1	1	86	8
2	2	95	16
3	3a	91	-84
4	pyr-3a	88	-41
5	imid-3a	93	-45

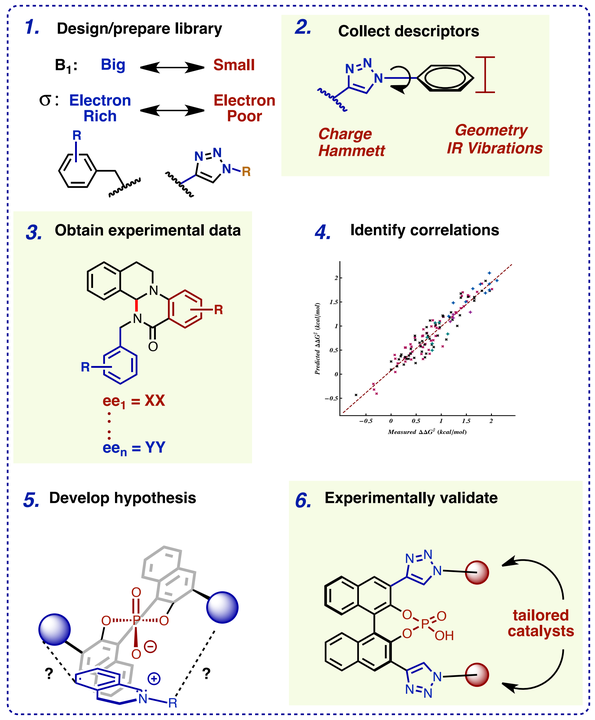
3a: X=N, Y=N; pyr-3a: X=CH, Y=N; imid-3a: X=N, Y=CH

- *Enantioselectivity trends not intuitive, even small modification to substrates or catalysts drastically affects enantioselectivity*

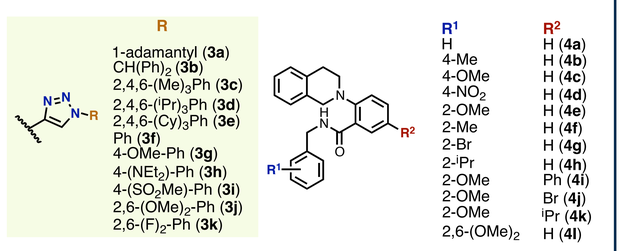


Data-Intensive Approach: Outline

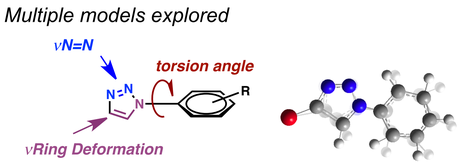
- *Hypothesis:* ***Every data point is meaningful****: even low selectivity values contain valuable information regarding substrate-catalyst interaction in the transition state*
- *Goal: Develop method to extract this information*



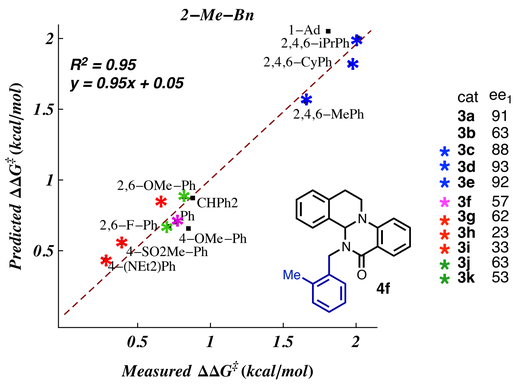
1. Asymmetric CDC



- *Ee determined for every catalyst-substrate combination (132 total)*
- *Ee of each substrate with all catalysts modeled using only catalyst descriptors[4] and vice versa (23 small models total)*
- *Multiple models explored*

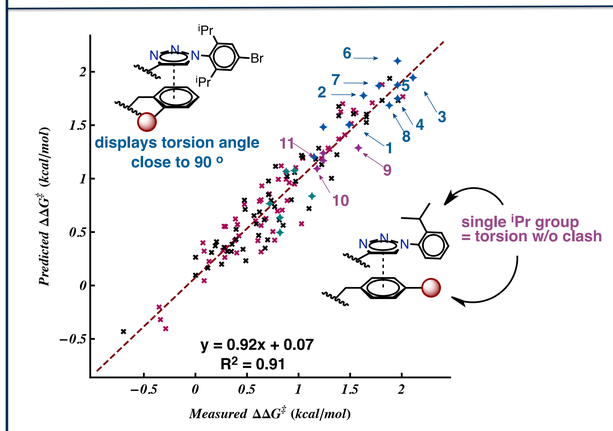


$$\Delta\Delta G^{\ddagger} = 1.18 + 0.67\,\nu N{=}N - 0.61\,\nu RingD - 0.18\,\nu RingD{:}\nu N{=}N$$



$$\text{Torsion Angle} = -0.14 - 0.18\,\nu N{=}N + 1.39\,\nu RingD + 0.33\,\nu N{=}N{:}\nu RingD \qquad R^2 = 0.91$$

$$\Delta\Delta G^{\ddagger} = 1.06 + 0.36\,\nu N{=}N - 0.42\,tor \qquad R^2 = 0.96$$

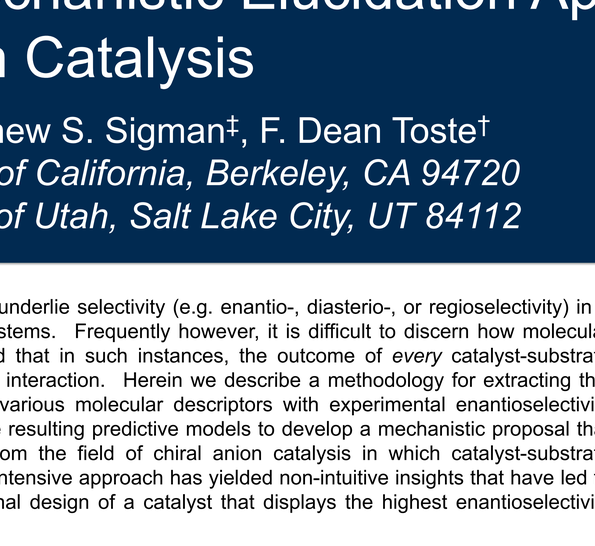


entry	substrate R1	substrate R2	% ee
1	H	H	85 (85)
2	2-OMe	H	88 (90)
3	2-Me	H	95 (93)
4	2-Br	H	93 (94)
5	2- iPr	H	93 (92)
6	2-OMe	Br	93 (90)
7	2-OMe	iPr	91 (92)
8	2-OMe	Ph	92 (89)
9	4-Me	H	78 (77)
10	4-OMe	H	78 (75)
11	4-NO2	H	87 (79)

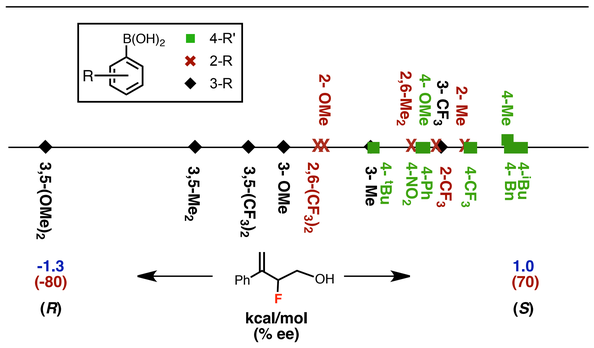
- *Conclusion: Succeeded in rationally modifying noncovalent interactions to improve an enantioselective reaction[5]*

2. Asymmetric Fluorination

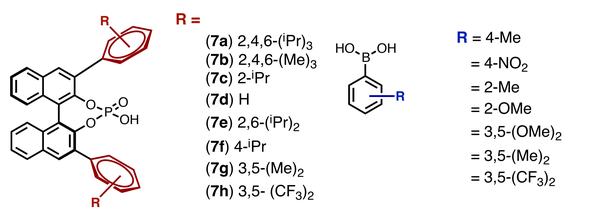
- *In 2014, Toste and coworkers disclosed a method for the enantioselective fluorination of allylic alcohols via chiral anion phase-transfer catalysis, using aryl boronic acids (BA) as transient directing groups (e.g. **B**).[6]*
- *Degree of asymmetric induction heavily dependent on BA and PA structure- better understanding of their interaction may facilitate improvement of scope.*



- *Preliminary survey reveals ability to tune ee over 2.5 kcal/mol range (–78 - 65 % ee) by changing only BA*



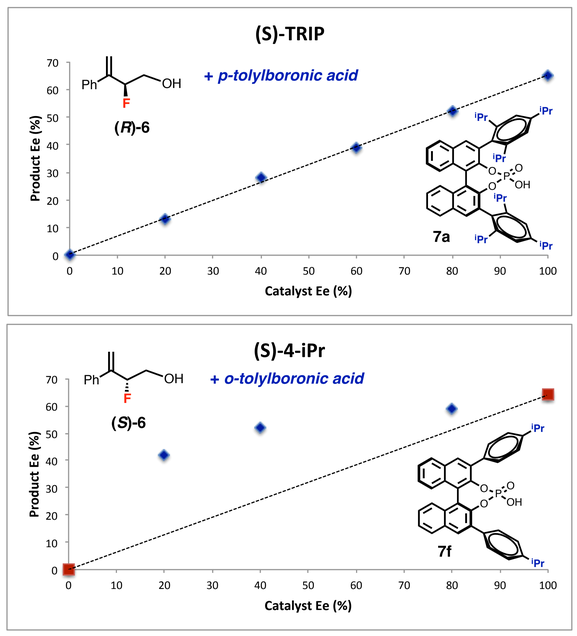
- *Library of PAs and BAs prepared to cover large structural space then ee's obtained for each combination*



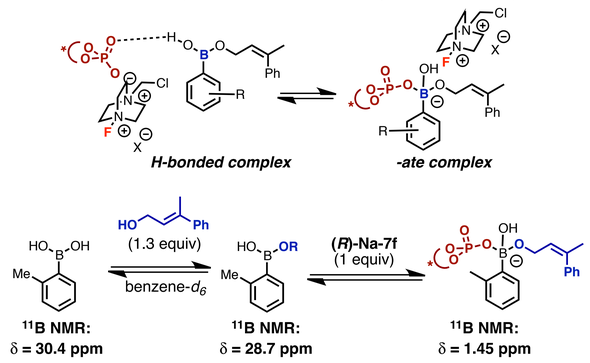
cat	Me	NO2	Me	MeO	MeO, OMe	Me, Me
7a	66	55	47	7	-77	-31
7b	91	70	72	28	20	63
7c	41	33	11	2	22	37
7d	29	19	24	4	23	42
7e	36	38	18	13	-12	10
7f	-57	-8	-61	-48	-23	-16
7g	-2	-2	-15	-15	12	34
7h	8	0	-8	-6	21	31

Asymmetric Fluorination (cont'd)

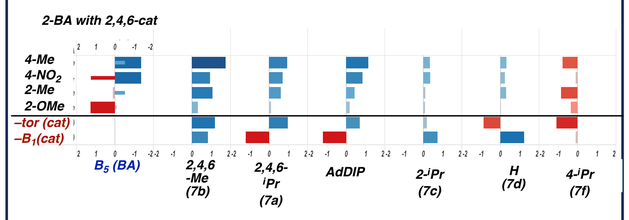
- *Dataset trends and model complexity suggest that different mechanisms may be operative depending on PA/BA structure.*
- *Catalyst-dependent nonlinear effect supports this notion.*



- *Catalyst speciation affected by PA/BA structure. Given propensity of phosphate anion to form –ate complex with boronic acids[7], a plausible scenario may involve this species.*



- *Current efforts focused on modeling subsets of the data to identify structural features controlling selectivity within a given regime.*
- *Specific goals: accurately predict new PA/BA outcomes via understanding of underlying mechanism.*



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