Supporting Information

Computer-Aided Design of Chiral Ligands. Part II. Functionality Mapping as a Method to Identify Stereocontrol Elements for Asymmetric Reactions

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Table of Contents (8 pages)

Functionality Mapping Data	S2-S5
Table S1. CPU time for FUNMAP runs.	S2
Table S2. Effect of the MacroModel minimization gradient on clusters identified by FUNMAP.	S2
Table S3. Ranked interaction energies of the probe clusters from the FUNMAP searches of A(<i>si</i>) using 200 methane probes with several gradients.	S2
Corey Stein Reagent Transition States	S5-S6
Table S4. Parameters added to MM2* for calculations of S1 and S2 using MacroModel.	S6
MacMillan Iminium Diels Alder Transition States	S6-S8
Table S5. Boltzmann distribution at 298 K of the transition states (see Figure S3) and enantioselectivities for the iminium Diels Alder Reaction catalyzed by 7 , S3 and S4 (Figure S2) from MM2* calculations.	S7

Functionality Mapping Data:

Table S1. CPU time for FUNMAP runs.^a

target	probe	convergence criterion	CPU time
A	methane	0.01 RMSD	< 1 min
D	methyl formate	0.01 RMSD	4.2 min
C	benzene	0.01 RMSD	6.9 min
D	methyl formate	0.001 RMSD	35 min
C	benzene	0.001 RMSD	2 h

^aRuns were performed on an SGI Octane (R10,000) with 100 probes with a TNCG gradient. CPU times are for the entire FUNMAP process which includes minimization and clustering of probes.

Table S2. Effect of the MacroModel minimization gradient on clusters identified by FUNMAP.^a

gradient	# clusters	energy range of clusters (kJ/mol)	# clusters with interaction E stronger than -5.18 kJ/mol	#clusters in first 9 different from TNCG	cluster# identical to the first TNCG cluster	cluster# closest to stereodiscriminating methyl (energy in kJ/mol)
TNCG	9	-7.84 to -5.19	--	--	--	5 ^b (-7.05)
PRCG	10	-7.84 to -5.05	9	0	1	5 ^b (-7.05)
OSVM	10	-7.84 to -5.19	10	1	1	5 ^b (-7.05)
SD	101	-7.76 to -2.55	47	7	2 (-7.75, 0.22 Å) ^c	6 (-6.86, 0.36 Å) ^c
FMNR	113	-6.30 to -0.80	8	9	1 (-6.17, 0.09 Å) ^c	3 (-5.93, 0.17 Å) ^c

^aAll the mappings were done with A(*si*) using 200 methane probes and a convergence criterion of 0.001 RMSD. See Table 1 of the main text. ^bSame as closest cluster from TNCG. ^cClose in space to the first TNCG cluster. The interaction energy (kJ/mol) of the cluster is given in parantheses along with the distance between the methane carbon atom of the indicated cluster and that of the corresponding TNCG cluster.

Table S3. Ranked interaction energies of the probe clusters from the FUNMAP searches of A(*si*) using 200 methane probes with several gradients.

Cluster #	Interaction Energies in kJ/mol				
	TNCG	PRCG	OSVM	SD	FMNR
1	-7.843000	-7.843000	-7.843000	-7.762000	-6.175000
2.	-7.777000	-7.777000	-7.777000	-7.749000	-6.141000
3.	-7.255000	-7.255000	-7.255000	-7.717000	-5.926000
4.	-7.088000	-7.088000	-7.088000	-7.505000	-5.880000
5.	-7.051000	-7.051000	-7.051000	-7.072000	-5.561000
6.	-6.134000	-6.134000	-6.134000	-6.858000	-5.486000
7.	-5.942000	-5.943000	-6.108000	-6.841000	-5.439000

8.	-5.795000	-5.794000	-5.943000	-6.596000	-5.260000
9.	-5.190000	-5.189000	-5.796000	-6.518000	-5.167000
10.	0.000000	-5.047000	-5.190000	-6.504000	-5.160000
11.		0.000000	0.000000	-6.486000	-5.097000
12.				-6.455000	-5.005000
13.				-6.431000	-4.991000
14.				-6.424000	-4.795000
15.				-6.404000	-4.762000
16.				-6.390000	-4.527000
17.				-6.380000	-4.402000
18.				-6.329000	-4.389000
19.				-6.323000	-4.380000
20.				-6.172000	-4.366000
21.				-6.097000	-4.322000
22.				-6.031000	-4.271000
23.				-6.028000	-4.251000
24.				-5.951000	-4.240000
25.				-5.936000	-4.206000
26.				-5.895000	-4.145000
27.				-5.861000	-4.063000
28.				-5.771000	-4.051000
29.				-5.753000	-3.912000
30.				-5.716000	-3.911000
31.				-5.712000	-3.907000
32.				-5.683000	-3.877000
33.				-5.666000	-3.864000
34.				-5.650000	-3.755000
35.				-5.649000	-3.734000
36.				-5.595000	-3.724000
37.				-5.556000	-3.685000
38.				-5.540000	-3.674000
39.				-5.533000	-3.609000
40.				-5.471000	-3.608000
41.				-5.448000	-3.534000
42.				-5.395000	-3.510000
43.				-5.333000	-3.499000
44.				-5.323000	-3.438000
45.				-5.288000	-3.429000

46.	-5.252000	-3.422000
47.	-5.208000	-3.403000
48.	-5.162000	-3.373000
49.	-5.144000	-3.309000
50.	-5.057000	-3.272000
51.	-5.011000	-3.192000
52.	-4.979000	-3.135000
53.	-4.891000	-3.062000
54.	-4.872000	-3.051000
55.	-4.826000	-3.040000
56.	-4.808000	-3.035000
57.	-4.778000	-3.032000
58.	-4.758000	-3.000000
59.	-4.756000	-2.914000
60.	-4.678000	-2.906000
61.	-4.581000	-2.898000
62.	-4.526000	-2.885000
63.	-4.510000	-2.863000
64.	-4.429000	-2.852000
65.	-4.379000	-2.850000
66.	-4.361000	-2.845000
67.	-4.257000	-2.816000
68.	-4.204000	-2.771000
69.	-4.181000	-2.676000
70.	-4.156000	-2.649000
71.	-4.068000	-2.535000
72.	-4.055000	-2.379000
73.	-4.027000	-2.368000
74.	-4.016000	-2.292000
75.	-3.990000	-2.259000
76.	-3.958000	-2.231000
77.	-3.911000	-2.229000
78.	-3.861000	-2.172000
79.	-3.796000	-2.126000
80.	-3.731000	-2.108000
81.	-3.704000	-2.087000
82.	-3.700000	-2.049000
83.	-3.699000	-1.998000

84.	-3.697000	-1.997000
85.	-3.693000	-1.978000
86.	-3.691000	-1.968000
87.	-3.670000	-1.945000
88.	-3.667000	-1.907000
89.	-3.555000	-1.900000
90.	-3.436000	-1.883000
91.	-3.410000	-1.880000
92.	-3.307000	-1.879000
93.	-3.299000	-1.801000
94.	-3.061000	-1.721000
95.	-3.001000	-1.711000
96.	-2.962000	-1.682000
97.	-2.921000	-1.681000
98.	-2.801000	-1.473000
99.	-2.786000	-1.459000
100.	-2.758000	-1.450000
101.	-2.553000	-1.438000
102.	0.000000	-1.431000
103.		-1.414000
104.		-1.408000
105.		-1.397000
106.		-1.390000
107.		-0.823000
108.		-0.744000
109.		-0.495000
110.		0.000000

Corey Stein Reagent Transition States:

The two simplified diastereomeric chair transition states, **S1** and **S2** (Figure S1), for the aldol reactions of the Corey stein reagent were examined using molecular mechanics calculations. The geometries of **S1** and **S2** were optimized using an MM2* derived force field in MacroModel with the additional parameters listed in Table S4. The transition state **S1** which leads to the major product was found to be 2.6 kJ/mol lower in energy than the transition state **S2** which leads to the minor product. This energy difference corresponds to an 83:17 product ratio as calculated using a Boltzmann distribution. These results compare favorably to the closely related aldol reaction with propionaldehyde ($\text{CH}_3\text{CH}_2\text{CHO}$) and diethyl ketone examined experimentally by Corey where a 99:1 ratio was observed (see reference 27 of the main text).

Figure S1. Corey stein reagent transition states. **Table S4.** Parameters added to MM2* for calculations of S1 and S2 using MacroModel.

1	B3-N3	1.4200	4.0000	0.0000	0000	0000	A 3
1	B3-N2	1.6500	2.0000	0.0000	0000	0000	A 3
2	00-B3-00	120.0000	0.4000	0000	0000	0000	A 3
4	00-N3-B3-00	0.0000	0.0000	0.3500	0000	0000	0000 0000 A 3
4	00-N2-B3-00	0.0000	0.0000	0.4000	0000	0000	0000 0000 A 3

MacMillan Iminium Diels Alder Transition States:

MacMillan *et al.* (reference 35, main text) reported novel chiral secondary amines (**7**, **S3** and **S4**) as catalysts for enantioselective Diels Alder reactions (Figure S2). The amines form iminium ions that are in equilibrium with the α,β -unsaturated aldehydes. These iminiums act as dienophiles with reactivity similar to Lewis acid coordinated α,β -unsaturated aldehydes. We generated all the possible transition states for these reactions in MacroModel using a Monte Carlo conformational search with an MM2* force field. For each reaction/ligand combination, conformational searches were performed from four starting transition states: *exo si*, *exo re*, *endo si* and *endo re*. Although the force field employed is not fully parameterized to deal with this type of asynchronous Diels Alder reaction, a qualitative evaluation of the stability of the different diastereomeric transition structures based on van der Waals and electrostatic interactions is possible.

Figure S2. MacMillan iminium Diels-Alder reaction.

A Boltzmann distribution of the energies from all the transition states for the addition of cinnamaldehyde-7 iminium to cyclopentadiene reproduced the experimental results fairly well (Table S5). The stabilization of the *exo si* and *endo si* transition structures compared to their *re* counterparts can be identified by examination of the transition structures (Figure S3). The benzyl group attached to the ligand is parallel to the π -bond of the dienophile in the lowest energy transition state (*exo si*). As such, this phenyl group blocks the *re*-face of the olefin which indicates that the cyclopentadiene approaching from the *si* face would be the most favorable pathway. Based on these structures, catalyst **7** does not impart a large differentiation between *endo/exo* approaches but does impart a large facial bias (*si* vs *re*).

For the ligands **S3** and **S4**, the experimental enantioselectivities drop to 57% *exo R* and 48% *exo R*, respectively. The results of MM2* minimization of the transition structures for these two ligands are consistent with this trend although the calculated results do underestimate the selectivities.

Table S5. Boltzmann distribution at 298 K of the transition states (see Figure S3) and enantioselectivities for the iminium Diels Alder Reaction catalyzed by **7**, **S3** and **S4** (Figure S2) from MM2* calculations.

R	Ligand	Boltzmann distribution				Calculated		Experimental	
		<i>exo S</i>	<i>exo R</i>	<i>endo S</i>	<i>endo R</i>	%ee	<i>exo:endo</i>	%ee	<i>exo:endo</i>
H	7	36.1	6.6	50.5	6.6	69 <i>exo S</i> 77 <i>endo S</i>	0.7:1		
Ph	7	59	4	35.6	1.4	87 <i>exo S</i> 92 <i>endo S</i>	1.7:1	93 <i>exo S</i> 93 <i>endo S</i>	1.3:1
Ph	S3	22.3	37.8	9.6	30.3	25.8 <i>exo R</i> 51.9 <i>endo R</i>	1.5:1	57 <i>exo R</i>	2.6:1
Ph	S4	27.0	33.8	17.6	21.6	11.2 <i>exo R</i> 10.2 <i>endo R</i>	1.6:1	48 <i>exo R</i>	2.7:1
Me	7	44.7	5.3	46.9	3.1	78.8 <i>exo R</i> 87.6 <i>endo S</i>	1:1	86 <i>exo S</i> 93 <i>endo S</i>	1:1

Figure S3. Transitions states for MacMillan iminium Diels-Alder reaction. Cinnamaldehyde + cyclopentadiene with catalyst 7 (Figure S2). Relative energies are in kJ/mol.