QSAR Study of Catalytic Asymmetric Reactions with Topological Indices

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The relationships between the e.e.% of product in catalytic asymmetry reaction and the structures of the catalyst and reagents in several asymmetric reactions were studied by using topological indices and their chiral expansions. The general regression method used can be applied to designing or screening a new asymmetric catalyst, predicting catalytic effects, and proving or improving the reaction mechanism supposed.

INTRODUCTION

Chirality or asymmetry is a common and important phenomenon in nature. Many researchers have shown that the biology activity and many other important properties are often much different between a pair of enantiomers. Thus, there is a great need to synthesize enantiomeric pure chiral compounds. More and more scientists have focused on the asymmetric synthesis and its applications in chemistry, biomedicine, and agriculture.[1,2]

An asymmetric synthesis is a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in an unequal amount. In the early ages, chiral products were inducted by a large amount of chiral reagent or auxiliaries.[3,4] Soon the catalytic asymmetric reactions were developed, in which one chiral catalyst molecule can create millions of chiral product molecules.[5,6] As the tiny request of the asymmetric catalyst and the high efficiency of synthesizing new chiral molecules, the catalytic asymmetric reaction becomes one of the most important topics of synthetic organic chemistry. Dozens of catalytic asymmetric reactions are developed such as the hydrogenation reaction, the oxidation reaction, the cyclopropanation reaction, the pinacol coupling reaction, the cross-coupling reaction, and the Diels−Alder reaction,[7,8] and plenty of asymmetric catalysts have been synthesized, including hundreds of excellent ones which lead to a high enantiomer excess (e.e.%) over 90%.

However, the design pattern of an asymmetric catalyst still remains a blur. In most cases, the mechanism of the catalysis is unclear, and the intermediate of the reaction is intangible. Researchers are often unable to pursue explicit instructions to design a new catalyst, while the stanchions of such tasks are few but experience and inspiration. It is necessary to find a method to discover the relations between the structure and the selectivity of the catalyst. Through those relations, a new and effective catalyst can be designed and screened much more easily. As concealing the mechanism of an asymmetric catalyzed reaction is always a hard task for researchers, a method was suggested here which is based on multiple regression and topological indices to model those relations without the explicit mechanism of reactions.

Our method can be applied to a variety of catalytic asymmetric reactions. Different substituents on the fixed frame of catalyst or reagents were used to identify those compounds as most QSAR methods do. To one certain type of catalyst and reaction, an equation between e.e.% and the structure of catalyst and reagents was generated. Those equations may imply the principle for designing a catalyst, predict the effect of new catalyst, and even awake clues of the reaction mechanism.

METHOD OF CALCULATION AND EXPERIMENTAL DATA

1. Topological Molecular Descriptor. Topological descriptors A_{x1}, A_{x2}, and A_{x3} suggested by Yao et al.[9] are used in our study. Those three descriptors are deprived from the path matrix of a hydrogen-suppressed graph of a molecule:

$$G_1 = (g_{ij}^{\,1}) = \begin{cases} \begin{cases} \text{square root of vertex degrees} & (i = 1) \\ \text{square root of van der Waals radii of atoms} & (i = 2) \end{cases} & (1 \le i \le 2) \\ \begin{cases} 1 & \text{if there is a path of length 1 between vertices } i-2 \text{ and } j \\ 0 & \text{if there is no path of length 1 between vertices } i-2 \text{ and } j \end{cases} & (i > 2) \end{cases}$$

$$G_2 = (g_{ij}^{\,2}) = \begin{cases} \begin{cases} \text{square root of vertex degrees} & (i = 1) \\ \text{square root of van der Waals radii of atoms} & (i = 2) \end{cases} & (1 \le i \le 2) \\ \begin{cases} 2 & \text{if there is a path of length 2 between vertices } i-2 \text{ and } j \\ 0 & \text{if there is no path of length 2 between vertices } i-2 \text{ and } j \end{cases} & (i > 2) \end{cases}$$

$$G_3 = (g_{ij}^{\,3}) = \begin{cases} \begin{cases} \text{square root of vertex degrees} & (i = 1) \\ \text{square root of van der Waals radii of atoms} & (i = 2) \end{cases} & (1 \le i \le 2) \\ \begin{cases} 3 & \text{if there is a path of length 3 between vertices } i-2 \text{ and } j \\ 0 & \text{if there is no path of length 3 between vertices } i-2 \text{ and } j \end{cases} & (i > 2) \end{cases}$$

$$\mathbf{Z}_1 = G_1' \times G_1, \mathbf{Z}_2 = G_2' \times G_2, \mathbf{Z}_3 = G_3' \times G_3$$

The three topological indices A_{x1}, A_{x2}, and A_{x3} are defined as

$$A_{x1} = \lambda_{\max 1}/2, A_{x2} = \lambda_{\max 2}/2, A_{x3} = \lambda_{\max 3}/2$$

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where $\lambda_{max1}-\lambda_{max3}$ are the largest eigenvalues of matrices $\mathbf{Z}_1-\mathbf{Z}_3$.

Generally, the larger substituents have the larger $A_{x1}-A_{x3}$ descriptors. As for the isomers, the one which has the less branched chains has the larger A_{x3} and the smaller A_{x1}.

Those topological descriptors are easy to calculate and can fit the needs of describing an atom group with heteroatoms. They have been applied to several applications of physical properties forecast, medicine logP calculation, and so on.

2. Asymmetric Expansion of Descriptors A_{x1}, A_{x2}, and A_{x3}. Most topological indices are not fitted for asymmetric compounds. Some of them have been expanded for asymmetric situations.[10−12]

The original descriptors A_{x1}, A_{x2}, and A_{x3} cannot adapt to the molecule with chiral atoms. They cannot distinguish a pair of enantiomers. Those descriptors were expanded by us to accommodate the molecule with chiral atoms.

The path matrices were expanded as

$G_1 = (g_{ij}^{1}) =$

$$\begin{cases} \begin{cases} \text{square root of vertex degrees} & (i=1) \\ \text{square root of van der Waals radii of atoms} & (i=2) \end{cases} & (1 \le i \le 2) \\ \begin{cases} 1 & \text{if there is a path of length 1 between vertices } i-2 \text{ and } j \text{ the atoms } i, j \text{ are nonchiral} \\ 1 \pm \delta & \text{if there is a path of length 1 between vertices } i-2 \text{ and } ij \text{ the atom is in } S \text{ or } R \text{ conformation} \quad (i>2) \\ 0 & \text{if there is no path of length 1 between vertices } i-2 \text{ and } j \end{cases} \end{cases}$$

$G_2 = (g_{ij}^{2}) =$

$$\begin{cases} \begin{cases} \text{square root of vertex degrees} & (i=1) \\ \text{square root of van der Waals radii of atoms} & (i=2) \end{cases} & (1 \le i \le 2) \\ \begin{cases} 2 & \text{if there is a path of length 1 between vertices } i-2 \text{ and } j \text{ the atoms } i, j \text{ are nonchiral} \\ 2 \pm 2\delta & \text{if there is a path of length 1 between vertices } i-2 \text{ and } j \text{ the atom is in } S \text{ or } R \text{ conformation} \quad (i>2) \\ 0 & \text{if there is no path of length 1 between vertices } i-2 \text{ and } j \end{cases} \end{cases}$$

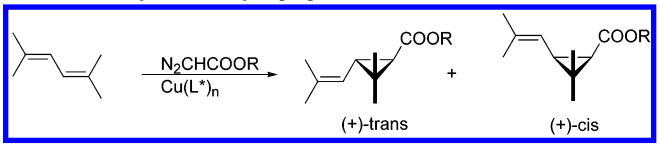
$G_3 = (g_{ij}^{3}) =$

$$\begin{cases} \begin{cases} \text{square root of vertex degrees} & (i=1) \\ \text{square root of van der Waals radii of atoms} & (i=2) \end{cases} & (1 \le i \le 2) \\ \begin{cases} 3 & \text{if there is a path of length 1 between vertices } i-2 \text{ and } j \text{ the atoms } i, j \text{ are nonchiral} \\ 3 \pm 3\delta & \text{if there is a path of length 1 between vertices } i-2 \text{ and } j \text{ the atom is in } S \text{ or } R \text{ conformation} \quad (i>2) \\ 0 & \text{if there is no path of length 1 between vertices } i-2 \text{ and } j \end{cases} \end{cases}$$

δ is the adjust parameter between 0 and 1 to identify a pair of enantiomers. From those matrices, we can achieve a set of chiral descriptors A^*_{x1-3} similar to A_{x1-3}. Those new descriptors can be applied to distinguish enantiomers.

3. Indicator Variable.[13,14] The indicator variable was also used to identify simple asymmetric substituents in some molecules. A variable representing chirality was introduced to the regression equation. If the substituent is a chiral one, this variable is set to +1 or −1, otherwise, the value is 0. For example, in molecule l-menthyl-OOCCHN$_2$ and d-menthyl-OOCCHN$_2$, a value of +1 was assigned to the former one, and −1 was assigned to the latter one.

Scheme 1. Asymmetric Cyclopropanation Reaction 1[a]



[a] The catalyst ligands (L*) are shown in Scheme 2.

4. QSAR Calculation. Multiple regression analysis was used to generate the QSAR model equation. In all regression equations, n is the number of cases used in analysis, r^2 is the squared correlation coefficient, R^2 is the adjusted squared correlation coefficient, s is the standard error of the estimates, and F is the Fisher significance radio. The standard errors of coefficients are shown in parentheses.

In each model, a case was selected randomly from the experimental data for an internal validation to examine the predictability of the QSAR model.

5. Experimental Data. All experimental data are obtained from papers published.

RESULTS AND DISCUSSION

1. Asymmetric Cyclopropanation Reaction. The first catalytic reaction we inspected is the famous work of cyclopropanation by Aratani[15] as shown in Scheme 1.The mainframe of the catalyst is actually fixed with three varied substituents (R_1, r_1, and r_2). So nine topological molecule descriptors (A_{x1}, A_{x2}, and A_{x3} for R_1, r_1, and r_2, respectively) may be used to identify a set of catalysts. The e.e.% of the (+)-trans product acts as the dependent variables in multiple regression. An equation was generated via multiple regression with four variables. The calculation results are shown in Table 1 and Figure 1. They were quite satisfying.

$$\text{e.e.\%} = 13.7(4.3) - 0.3(0.3)A_{x1}^{R1} + 11.1(4.3)A_{x2}^{r1} - 7.9(3.8)A_{x3}^{r1} + 1.2(0.8)A_{x1}^{r2}$$

$$r^2 = 0.870,\ R^2 = 0.823,\ F = 18.409,\ s = 8.255,\ n = 16$$

Another asymmetric cyclopropanation reaction of olefins with diazoacetates[16] was also investigated as shown in Scheme 3.

Four enantiomers ((1*S*,2*R*), (1*S*,2*S*), (1*R*,2*R*), (1*R*,2*S*)) of trans and cis products are observed from that reaction. The catalyst ligands of this reaction (L*) are shown in Scheme 4.

Nine topological molecule descriptors (A_{x1}, A_{x2}, and A_{x3} for R_1, R_2, and R_3, respectively) may be used to identify a set of reagent and catalyst, and four descriptors were finally chosen. e.e.(cis)% and e.e.(trans)% are dependent variables in multiple regression.

There was one problem of asymmetric groups in these reactions: R_2 may be l-menthyl or d-menthyl. Classic A_{x1-3} descriptors cannot distinguish between those two enantiomers. So an indicator variable was introduced into the

Scheme 2. Catalyst Ligand for Cyclopropanation Reaction 1

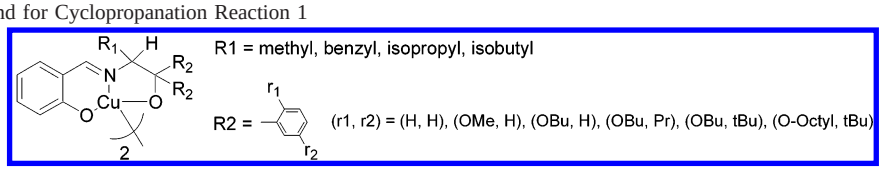


Table 1. Substituent Pattern and the Observed and Calculated e.e.% of the Asymmetric Cyclopropanation Reaction 1

				e.e.%	
entry	R_1	r_1	r_2	(expt)	(calc)
1	Me	H	H	4	13
2	Me	OMe	H	20	22
3	Me	OBu	H	50	45
4	Me	OBu	Me	48	46
5[a]	Me	OBu	Pr	56	52
6	Me	OBu	tBu	64	55
7	Me	O−Octyl	tBu	70	64
8	CH_2Ph	H	H	8	8
9	CH_2Ph	OBu	H	45	40
10	CH_2Ph	OBu	Pr	46	47
11	CH_2Ph	OBu	tBu	53	50
12	CH_2Ph	O−Octyl	tBu	53	59
13	$CHMe_2$	H	H	8	12
14	$CHMe_2$	OBu	H	31	44
15	$CHMe_2$	OBu	tBu	42	53
16	CHMeEt	H	H	18	12
17	CHMeEt	OMe	H	32	20

[a] Case for internal validation.

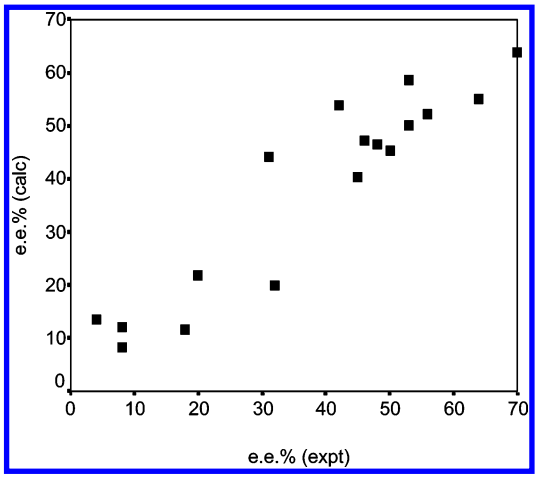
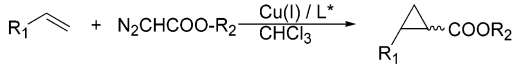
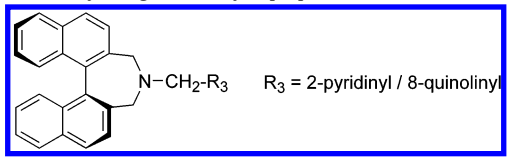


Figure 1. Plot of experimental vs calculated e.e.% of asymmetric cyclopropanation reaction 1.

Scheme 3. Asymmetric Cyclopropanation Reaction 2



Scheme 4. Catalyst Ligand for Cyclopropanation Reaction 2



calculation. The variable named C_{R2} indicates the chirality of group R_2, if R_2 is in L conformation, $C_{R2} = -1$, if R_2 is in D conformation, $C_{R2} = +1$, otherwise $C_{R2} = 0$. The results are shown in Table 2 and Figure 2. From the regression equations, the bulk of R_1 is the dominate factor to improve e.e.%; the L conformation of R_2 is preferred for both cis or trans e.e.%.

Table 2. Substituent Pattern and the Observed and Calculated e.e.% of the Asymmetric Cyclopropanation Reaction 2

				e.e.%(cis)		e.e.%(trans)	
entry	R_1	R_2	R_3	(expt)	(calc)	(expt)	(calc)
1	Ph	Et	pyridinyl	36	34	40	39
2	Ph	Et	quinolinyl	43	42	45	46
3	Ph	DCM[a]	pyridinyl	71	68	63	69
4	Ph	DCM	quinolinyl	80	77	83	76
5	Ph	L-menthyl	pyridinyl	77	77	74	76
6	Ph	L-menthyl	quinolinyl	83	85	87	83
7	Ph	D-menthyl	pyridinyl	39	41	46	45
8	Ph	D-menthyl	quinolinyl	47	49	51	52
9[b]	4-MePh	L-menthyl	pyridinyl	65	74	66	67
10	4-MePh	L-menthyl	quinolinyl	77	82	72	76
11	4-MeOPh	L-menthyl	pyridinyl	73	69	64	59
12	4-MeOPh	L-menthyl	quinolinyl	75	77	65	67
13	4Cl−Ph	L-menthyl	pyridinyl	42	49	46	44
14	4Cl−Ph	L-menthyl	quinolinyl	64	57	49	51

[a] Dicyclohexylmethyl diazoacetate. [b] Case for internal validation.

$$\text{e.e.\%(cis)} = -526.4(93.6) + 50.9(8.6)A_{x1}{}^{R1} - 14.6(2.4)A_{x3}{}^{R1} + 1.4(0.2)A_{x1}{}^{R2} + 0.7(0.3)A_{x1}{}^{R3} - 17.9(2.5)C_{R2}$$

$$r^2 = 0.953,\ R^2 = 0.919,\ F = 28.308,\ s = 5.045,\ n = 13$$

$$\text{e.e.\%(trans)} = -533.5(86.8) + 53.3(8.0)A_{x1}{}^{R1} - 15.9(2.2)A_{x3}{}^{R1} + 1.2(0.2)A_{x1}{}^{R2} + 0.6(0.2)A_{x1}{}^{R3} - 15.5(2.3)C_{R2}$$

$$r^2 = 0.947,\ R^2 = 0.908,\ F = 24.811,\ s = 4.676,\ n = 13$$

2. Asymmetric Pinacol Coupling Reaction. A type of asymmetric pinacol coupling reactions of aldehydes catalyzed by Titanium-schiff base complexes was also evaluated here[17] as shown in Scheme 5.

The value of dl/(dl+meso) % was used as the dependent variable in the regression.

The regression was launched as the above two, and something special was found. In the calculation, there were two exception points (entries 6 and 13 in Table 3).

After wiping off these two cases temporarily, the result of the regression was quite excellent as shown in Table 3 and Figure 3. From the regression equations, the bulkier and less branched R_1 in the catalyst ligand is preferred to lead to higher e.e.%.

$$\text{DL/(DL+meso) \%} = 93.9(4.2) + 1.6(0.5)A_{x1}{}^{R} - 1.0(0.2)A_{x3}{}^{R} - 46.7(9.1)A_{x1}{}^{R1} + 34.1(6.6)A_{x2}{}^{R1}$$

$$r^2 = 0.926,\ R^2 = 0.866,\ F = 15.532,\ s = 3.002,\ n = 10$$

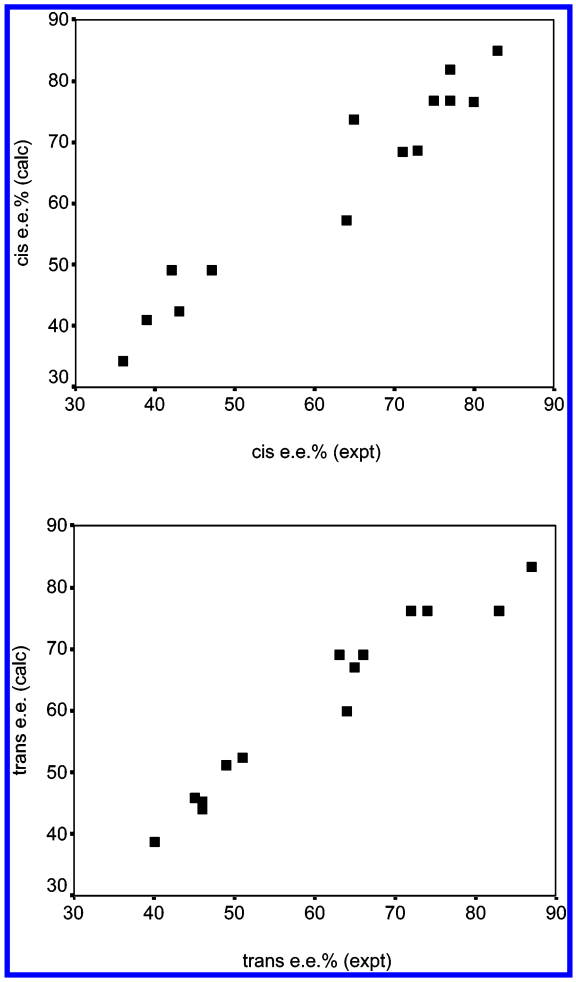
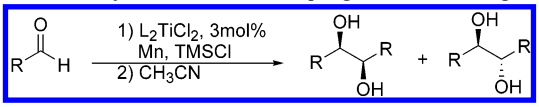


Figure 2. Plot of experimental vs calculated e.e.%(cis) and e.e.%-(trans) of asymmetric cyclopropanation reaction 2.

Scheme 5. The Asymmetric Pinacol Coupling Reaction Investigated[a]

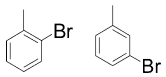


[a] The catalyst ligands are shown in Scheme 6.

Then why are those two points far away from the regression line? One exception occurred when R =

and R_1 = Ph. Note that we also have a case in which R =

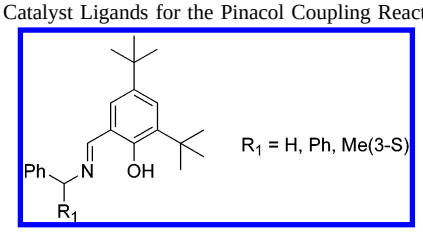
and R_1 = Ph. To the topological indices we used, substituents



are all regarded as

Therefore, though the steric extrusions are quite different, our method cannot distinguish them. This is one of the shortcomings in our regression due to the limitation of the topological indices used.

Scheme 6. Catalyst Ligands for the Pinacol Coupling Reaction[a]



[a] Three substituent groups, R, R_1, and R_2, were used to identify the reagent and the catalyst.

Table 3. Substituent Pattern and the Observed and Calculated dl/(dl+meso) % Values of the Asymmetric Pinacol Coupling Reaction 1

Entry	R	R_1	dl/(dl+meso) % (expt)	dl/(dl+meso) % (calc)
1	Ph	H	99	100
2	Ph	Ph	97	97
3	Ph	Me	92	90
4		Me	70	74
5		H	92	93
6		Ph	58	93
7[a]		H	96	97
8		H	95	97
9		H	88	86
10		H	91	88
11		Ph	91	91
12	PhCH=CH	Me	84	82
13	$PhCH_2CH_2$	Me	66	82

[a] Case for internal validation.

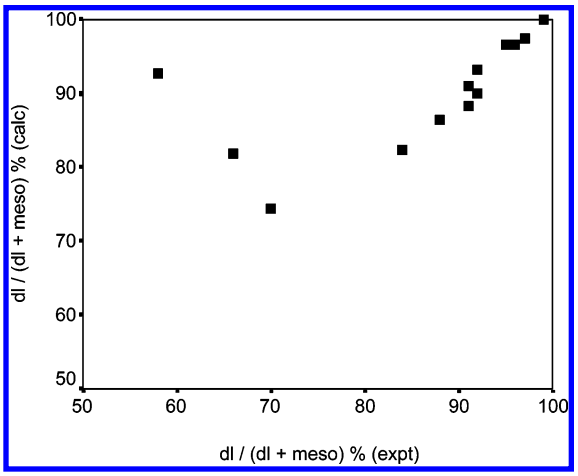
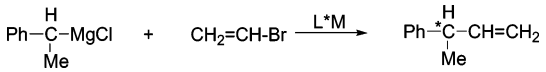


Figure 3. Plot of experimental vs calculated DL/(DL+meso) value of asymmetric pinacol coupling reaction.

The other exception case lies in the situation when R = $PhCH_2CH_2$ and R_1 = Me. Compared with the case in which R = PhCH=CH, the topological indices for $PhCH_2CH_2$ and PhCH=CH are close while the experimental value of dl/(dl+meso) % are quite different. So a conclusion may be drawn that the tiny structure difference between the single

Scheme 7. Asymmetric Grignard Cross-Coupling Reaction Inspected Catalyst Ligands Are the Ferrocene Ramifications in Scheme 8



Scheme 8. Catalyst Ligands for the Asymmetric Grignard Cross-Coupling Reaction

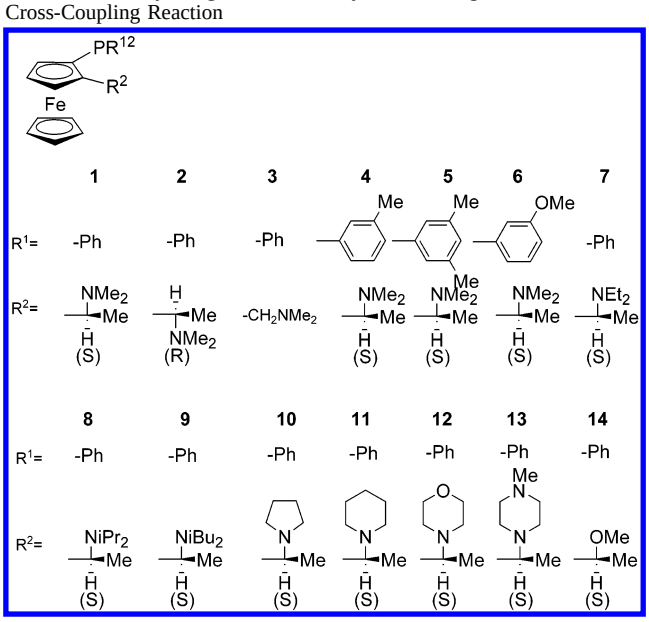
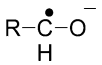


Table 4. Substituent Pattern and the Observed and Calculated e.e.% of the Asymmetric Grignard Cross-Coupling Reaction

entry	R^1	R^2	planar chirality	e.e.% (expt)	e.e.% (calc)
1	Ph	**1**	R	63	57
2	Ph	**2**	R	54	57
3	Ph	**3**	S	-65	-65[a]
4	PhMe	**4**	R	65	65
5[b]	$PhMe_2$	**5**	R	65	73
6	PhOMe	**6**	R	57	57
7	Ph	**7**	R	35	40
8	Ph	**8**	R	-7	9
9	Ph	**9**	R	-15	-27
10	Ph	**10**	R	62	54
11	Ph	**11**	R	-42	20
12	Ph	**12**	R	17	22
13	Ph	**13**	R	65	10
14	Ph	**14**	R	57	53

[a] Negative e.e.% means enantiomer excess of *S* confirmation product. [b] Case for internal validation.

and the double bond leads to the huge difference in stereoselectivity. From the mechanism supposed by Marco Bandini, the intermediate of



must be formed first, and the double bond together with the benzene ring of PhCH═CHCHO may provide a large conjuge system to enhance the stability of the intermediate. That complex situation is also out of the ability of the molecule descriptor we used. On the other hand, the exception cases in regression may bring the careful check of reactions, suggest a new mechanism, or prove existed ones.

3. Asymmetric Grignard Cross-Coupling Reaction. At last, we inspected a classic work of asymmetric Grignard cross-coupling reaction by Tamio Hayashi et al.[18] shown in Scheme 7.As the set of substituents of R^2 in the catalyst has two steric configurations, the expansion of topological descriptor A^*_{x1-3} must be used. Here, the adjust parameters used were $\delta = +0.5$ for (*S*) conformation and $\delta = -0.5$ for (*R*) conformation. The planar chirality of the ferrocene was also considered as an indicator variable C_{planar}. $C_{planar} = +1$ for the *R* conformation and -1 for the *S* conformation. The e.e.% of the product of *R* conformation was used as the dependent variable. There were also two exception points in regression (entry 11 and 13 in Table 4). After wiping them off temporarily, the following equation was calculated. Results based on this equation are shown in Table 4 and Figure 4.

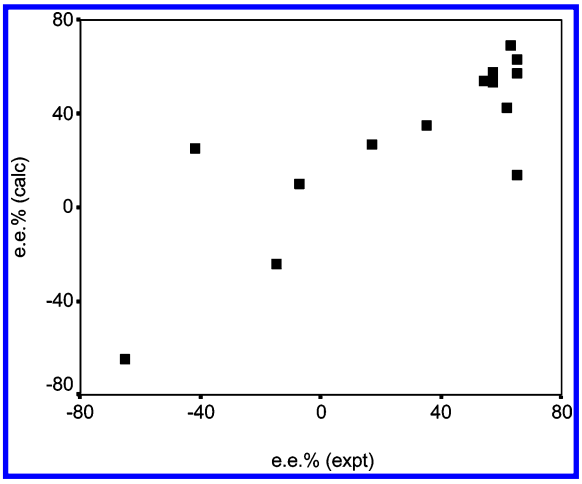
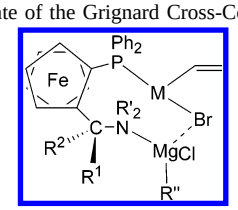


Figure 4. Plot of experimental vs calculated e.e.% of asymmetric Grignard cross-coupling reaction.

Scheme 9. Intermediate of the Grignard Cross-Coupling Reaction



$$\text{e.e.\%} = 101.077(68.8) - 3.0(3.8)A_{x1}{}^{R1} - 12.7(2.7)A^*_{x1}{}^{R2} + 4.162(1.5)A^*_{x2}{}^{R2} + 71.9(7.4)C_{planar}$$

$$r^2 = 0.949,\ R^2 = 0.915,\ F = 27.988,\ s = 12.347,\ n = 11$$

From the results, we can observe that most of the points are fitted well except two cases of entries 11 and 13. A mechanism has been suggested by Hayashi in which the intermediate shown in Scheme 9 must be formed first. The hexatomic ring in entry 11 prevents the formation of that chelate. As for entry 13, the other N atom on the hexatomic ring acts as the donor instead of the original one, and the chelate can still be formed but with some difference. So those two cases cannot be fitted well to the calculation result.

The large coefficient of C_{planar} also accords with the conclusion drawn by Hayashi that the ferrocene planar chirality plays a dominant role in the high stereoselectivity.

CONCLUSION

Some models may be developed for varieties of asymmetric catalytic reactions by using molecule topological

indices and a multiple regression method. Our method can instruct the designing and screening of catalysts, predict the stereoselectivity of new catalysts, and help to testify or improve the mechanism existed.

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