Tetrahedron 70 (2014) 1289–1297

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

QSAR analysis of the catalytic asymmetric ethylation of ketone using physical steric parameters of chiral ligand substituents

Huayin Huang, Hua Zong, Bin Shen, Huifeng Yue, Guangling Bian, Ling Song *

The State Key Lab of Structural Chemistry, The Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences, 155 Yangqiao Road West, Fuzhou, Fujian 350002, China

ARTICLE INFO

Article history:
Received 21 September 2013
Received in revised form 10 December 2013
Accepted 20 December 2013
Available online 31 December 2013

Keywords:
Sterimol parameters
Asymmetric catalysis
Ketones
Molar refraction

ABSTRACT

We have demonstrated that a validated QSAR (quantitative structure–activity relationship) model can be constructed between sterimol steric parameters of the *N*-substituents of chiral 1,2-amino-phosphoramide ligands and the enantiomeric ratios of alcohol products produced in the asymmetric additions of diethylzinc to acetophenone, which is powerful for predicting the steric effects of ligand substituents on enantioselectivities and instructive for ligand optimization.

1. Introduction

Exploring the relationship between structures and catalytic properties of chiral ligands is instructive for the reasonable prediction and modification of ligand structure. However, for a long time, optimizing chiral ligands in asymmetric reactions has been mainly based on qualitative correlation between the steric and electronic effects of ligands and enantioselectivities, which is not practically useful for instructing ligand modification due to the lack of accurate information. In this decade, investigating quantitative correlation between the structures of chiral ligands and the enantioselectivities of asymmetric reactions by using computer methods based on transition state models has achieved significant progress.[1–15] Recently, Sigman and his co-workers have also shown that QSARs (quantitative structure–activity relationships) between structures and enantioselectivities can be established by using varied physical reference parameters, such as sterimol parameters, Hammett electronic parameters, pK_a values, and Charton values, etc.[16–27]

Several computer assisted studies on the quantitative correlations of chiral ligand structures with enantioselectivities of the asymmetric addition reactions of organozinc reagents to aldehydes have been reported using the enantioselective ethylation of benzylaldehyde as a model reaction.[6,7,9,28–32] With this model reaction, our group has also shown that excellent QSARs between ligand substituent sizes and enantiomeric ratios of products can be constructed by appropriately combining the sets of substituents and steric reference parameters.[33] As one of the most common used strategies to generate a quaternary stereogenic carbon center, the asymmetric addition of organozinc reagents to ketones is a hot topic.[34–37] However, in sharp contrast with aldehydes, simple ketones such as acetophenone have much more steric and electronic constraints. On the other hand, dialkylzinc reagents have lower reactivities compared with diphenylzinc and dialkynylzinc reagents. Moreover, many side reactions can be caused by the basicity of dialkyzinc reagents. Therefore, as far as we known, only a few excellent chiral ligands have been reported for the catalytic asymmetric addition of dialkylzinc reagent to simple ketone.[38–54] In 2007, Ishihara and co-workers reported their pioneering work on the efficient catalytic enantioselective additions of diorganozinc reagents to ketones using L-valine-derived phosphoramide ligand with up to 98% ee.[49] However, no QSAR studies based on systematic modification of chiral ligand structures have been reported for this reaction system.

Herein, we report our investigation on the quantitative correlations of the substituent sizes of chiral ligands and the enantiomeric ratios of alcohol products in the asymmetric addition reactions of diethylzinc to ketones with the uses of steric parameters. Our results show that an excellent QSAR model between sterimol steric parameters of ligand substituents and enantioselectivities can be constructed, which is powerfully useful for

* Corresponding author. Tel.: +86 591 83720913; fax: +86 591 83722697; e-mail address: songling@fjirsm.ac.cn (L. Song).

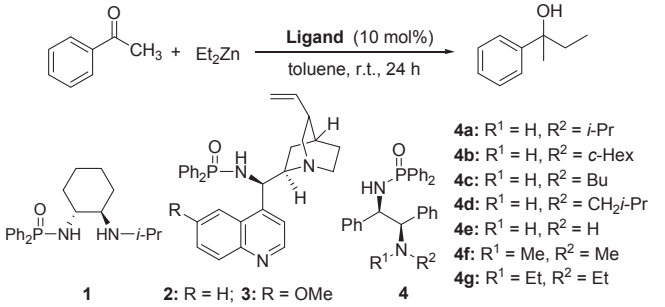
0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.12.054

predicting the steric effects of chiral ligand substituents on enantioselectivities of the asymmetric reactions.

2. Results and discussion

Investigation on the catalytic properties of several *N*-substituted ligands (**1**–**3** and **4a** in Table 1, entries 1–4) derived from (1*R*,2*R*)-cyclohexanediamine, cinchona alkaloids, and (1*R*,2*R*)-diphenylethylenediamine showed that chiral phosphoramide ligand **4a** derived from chiral (1*R*,2*R*)-diphenylethylenediamine was most active for the asymmetric addition reaction of diethylzinc to acetophenone with 52% of yield and 81% of ee value (Table 1, entry 4). It was noteworthy that chiral ligand **1**, which was highly efficient for the asymmetric addition of diethylzinc to benzylaldehyde,[33] was very poor for this addition reaction and only 3% of yield and 58% of ee value of the tertiary alcohol product were obtained (Table 1, entry 1). Therefore, chiral ligand **1** was not suitable for QSAR study. For cinchona alkaloids based chiral ligand **2** and **3**, which showed good to excellent activities in the ethylation of a variety of aldehydes,[55] were also less active for acetophenone as the substrate. In addition, the *N*-alkyl groups on the skeletons of chiral ligand **2** and **3** could not be modified systematically. Therefore, we chose (1*R*,2*R*)-diphenylethylenediamine as the chiral pool to synthesize a series of chiral ligands **4a**–**4g** (Table 1, entries 4–10) with varied *N*-substituents as the training set for the development of a QSAR model. Each chiral ligand was used three times and the ee values were averaged.

Table 1
Evaluation of chiral phosphoramide ligands in the enantioselective ethylation reactions of acetophenone with diethylzinc



Entry	Ligand	Yield[a] (%)	Averaged ee[b] (%)
1	**1**	3	58.1
2	**2**	19	60.2
3	**3**	33	62.2
4	**4a**	52	80.5
5	**4b**	41	84.2
6	**4c**	55	84.8
7	**4d**	50	81.7
8	**4e**	15	63.8
9	**4f**	25	62.6
10	**4g**	19	50.7

[a] Isolated yields.
[b] Determined by chiral GC analysis.

Sterimol parameters (*L*, B_1, B_5), which were proposed by Verloop,[56–58] are dimensions of a substituent. *L* is defined as the length of the substituent measured along the axis of the primary bond that joins the substituent to the parent molecule. B_1 and B_5 are the minimum and maximum distances from the axis of the primary bond (Fig. 1).

Since sterimol reference parameters had shown their advantages on constructing QSAR in the enantioselective ethylation of benzylaldehyde in our previous study,[33] they were chosen firstly to investigate the quantitative correlation of ligand *N*-substituent sizes and enantioselectivities in the asymmetric additions of diethylzinc to acetophenone. The sterimol parameters used in our investigation are listed in Table 2.

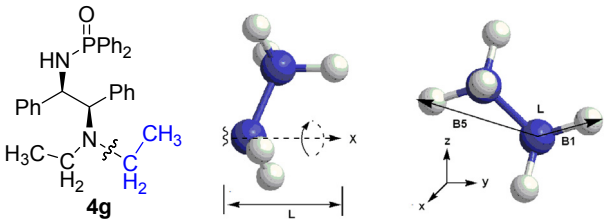


Fig. 1. Sterimol parameters using ethyl group of chiral ligand **4g** as an example.

Table 2
Sterimol parameters[a] (B_1, B_5, *L*) of R groups

Entry	R group	B_1	B_5	*L*
1	H	1	1	2.06
2	Me	1.52	2.04	2.87
3	Et	1.52	3.17	4.11
4	Bu	1.52	4.54	6.17
5	CH_2i-Pr	1.52	4.45	4.92
6	CH_2Bu	1.52	4.94	6.97
7	*i*-Pr	1.90	3.17	4.11
8	*s*-Bu	1.90	3.49	4.92
9	*c*-C_6H_{11}	1.91	3.49	6.17

[a] See Refs. 56–58.

We evaluated two sets of three-dimensional sterimol parameters simultaneously. The base model included all sterimol sub-parameters of *N*-substituents (R^1, R^2) of chiral phosphoramide **4** and cross-terms relating each R^1-sterimol subparameter to the R^2-sterimol subparameter. A backward stepwise regression analysis was performed on the system by removing terms and optimizing the model based on *f*-tests of statistical significance for the model and *p*-tests for the individual coefficients, to generate the correlation represented by Eq. 1, in which X and Y represent the respective R^1 and R^2 substituents.

$$\Delta\Delta G^{\ddagger} = 2.260 - 0.837 \times X_L + 0.162 \times X_{B_1} \times Y_{B_1} + 0.059 \times X_{B_5} \times Y_{B_5} + 0.067 \times X_{B_5} \times Y_L \quad (1)$$

Analysis of the sterimol-based model shows that $\Delta\Delta G^{\ddagger}$ is related to both substituents (see Supplementary data for details). The relatively large negative coefficient value relating the X_L term indicates that a R^1 substituent with increased length along the primary bond will lead to a decrease in the level of enantioselectivity dramatically. In contrast, the X_{B_1} and X_{B_5} terms of a R^1 substituent and all sub-parameters of a R^2 substituent make positive contributions to $\Delta\Delta G^{\ddagger}$. Fig. 2 shows that a plot of the predicted $\Delta\Delta G^{\ddagger}$ values from Eq. 1 and experimentally determined $\Delta\Delta G^{\ddagger}$ values is linear with slope=0.999 and R^2=0.999.

To examine the predictive power of the model Eq. 1, additional four ligands **4h**–**4k** with varied *N*-substituents were synthesized as test set. By using these four chiral ligands in the model reaction of asymmetric addition of diethylzinc to acetopheneone, 12 experimental enantioselectivities were obtained. The predicted and observed values for these four ligands are listed in Table 3 and depicted in Fig. 3 as a linear plot with slope=0.879 and R^2=0.960. Since a linear model with the slope in the range of 0.6–1.4 for test set is considered predictive,[26] the slope of 0.879 indicates that Eq. 1 is a validated QSAR model and highly predictive.

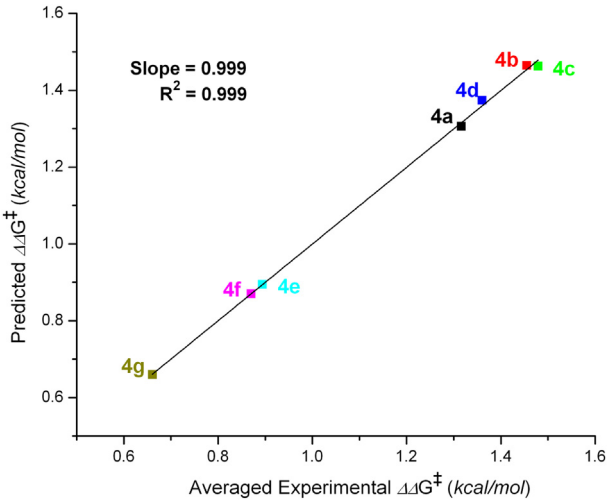
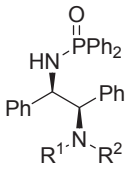


Fig. 2. Plot of averaged experimental $\Delta\Delta G^{\ddagger}$ values versus predicted $\Delta\Delta G^{\ddagger}$ values from Eq. 1 for ligands **4a**–**4g** using acetophenone as the substrate.

Table 3
Experimental and predicted ee values of the asymmetric additions of Et_2Zn to acetophenone catalyzed by chiral phosphoramides **4h**–**4k**



4h: R^1 = H, R^2 = Et
4i: R^1 = H, R^2 = CH_2Bu
4j: R^1 = H, R^2 = *s*-Bu
4k: R^1 = Me, R^2 = Et

Entry	Ligand	Yield[a] (%)	Averaged experimental ee[b] (%)	Averaged experimental $\Delta\Delta G^{\ddagger}$[c]	Averaged predicted $\Delta\Delta G^{\ddagger}$[d]
1	**4h**	51	79.6	1.288	1.244
2	**4i**	58	86.8	1.570	1.540
3	**4j**	56	83.6	1.429	1.379
4	**4k**	41	74.9	1.150	1.175

[a] Isolated yields.
[b] Determined by using chiral GC analysis.
[c] Estimated at 298 K (25 °C), $\Delta\Delta G^{\ddagger}=-RT\ln(S/R)$, R=0.001986 kcal K^{-1} mol^{-1}.
[d] Predicted $\Delta\Delta G^{\ddagger}$ was calculated by Eq. 1.

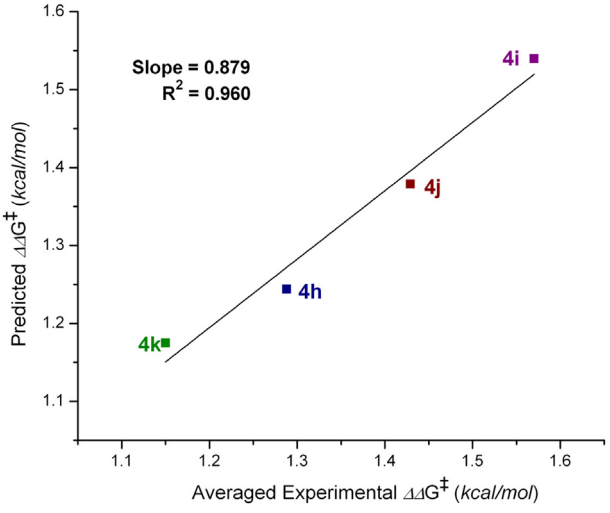


Fig. 3. Plot of averaged experimental $\Delta\Delta G^{\ddagger}$ values versus predicted $\Delta\Delta G^{\ddagger}$ values from Eq. 1 for ligand **4h**–**4k** using acetophenone as the substrate.

Since a better model could be constructed with more experimental data points, we combined the ligands of training and test sets to investigate the quantitative correlation between sterimol parameters and enantioselectivities. Using the same analysis methodology as above, we obtained Eq. 2, in which X and Y represent the respective R^1 and R^2 substituents.

$$\Delta\Delta G^{\ddagger} = 2.727 - 1.067 \times X_L + 0.184 \times X_{B_5} \times Y_{B_1} + 0.060 \times X_{B_5} \times Y_{B_5} + 0.064 \times X_{B_5} \times Y_L \quad (2)$$

Analysis of Eqs. 1 and 2 shows that they are different but similar. In Eq. 2, X_L of a R^1 group makes large negative contribution to $\Delta\Delta G^{\ddagger}$, and all sub-parameters of a R^2 group make positive contributions to $\Delta\Delta G^{\ddagger}$, which are similar as in Eq. 1 constructed with training set only. Fig. 4 shows that a plot of the predicted $\Delta\Delta G^{\ddagger}$ values from Eq. 2 and experimentally determined $\Delta\Delta G^{\ddagger}$ values is linear with slope=0.994 and R^2=0.995. The results indicate that X_L, X_{B_5}, Y_{B_1}, Y_{B_5} and Y_L are the key steric factors in our investigated system and a high enantioselectivity is favored by a chiral ligand, which has a R^1 group with short length along the primary bond and a large R^2 group.

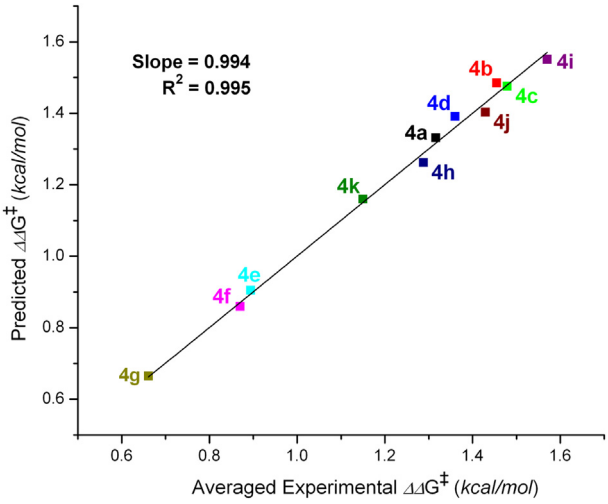


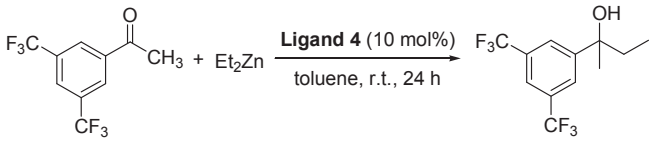
Fig. 4. Plot of averaged experimental $\Delta\Delta G^{\ddagger}$ values versus predicted $\Delta\Delta G^{\ddagger}$ values from Eq. 2 for ligand **4a**–**4k** using acetophenone as the substrate.

In order to investigate the effect of changing substrate on the construction of QSAR model, we also run the asymmetric addition reactions of diethylzinc with 3,5-bis(trifluoromethyl)-acetophenone catalyzed by these 11 chiral ligands. Compared with acetophenone, 3,5-bis(trifluoromethyl)-acetophenone gave higher yields and ee values as shown in Table 4. With sterimol values, Eq. 3 was given as follow in which X and Y represent the respective R^1 and R^2 substituents.

$$\Delta\Delta G^{\ddagger} = 3.225 - 1.366 \times X_L + 0.184 \times X_{B_1} \times Y_{B_5} + 0.331 \times X_L \times Y_{B_1} + 0.033 \times X_L \times Y_L \quad (3)$$

In Eq. 3, similar as in Eq. 2, X_L of a R^1 group still has large negative coefficient value, and all sub-parameters of a R^2 group still make positive contributions to $\Delta\Delta G^{\ddagger}$. Fig. 5 presents an excellent linear relationship with R^2=0.997 between the predicted $\Delta\Delta G^{\ddagger}$ values from Eq. 3 and experimentally determined $\Delta\Delta G^{\ddagger}$ values shown in Table 4. These results indicate that similar QSAR models could be established with different ketones despite the differences of catalytic properties of these chiral ligands for the substrates.

Table 4
Evaluation of chiral phosphoramides in the enantioselective ethylation of 3,5-bis(trifluoromethyl)-acetophenone with diethylzinc



Entry	Ligand	Yield[a] (%)	Averaged ee[b] (%)
1	**4a**	56	97.4
2	**4b**	86	98.0
3	**4c**	84	97.8
4	**4d**	58	97.5
5	**4e**	10	83.0
6	**4f**	84	86.9
7	**4g**	12	74.4
8	**4h**	57	96.3
9	**4i**	86	98.4
10	**4j**	83	97.9
11	**4k**	45	93.2

[a] Isolated yields.
[b] Determined by chiral GC analysis.

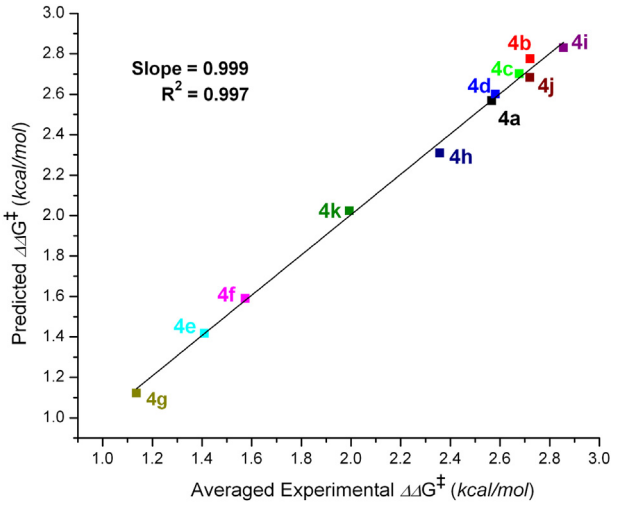


Fig. 5. Plot of averaged experimental $\Delta\Delta G^{\ddagger}$ values versus predicted $\Delta\Delta G^{\ddagger}$ values from Eq. 3 for ligand **4a**–**4k** using 3,5-bis(trifluoromethyl)-acetophenone as the substrate.

Next, we also examined the quantitative correlations between other kinds of steric parameters and enantioselectivities in this reaction system. Molar refraction (MR) is a particularly useful physical parameter in chemistry, pharmaceutical science, and biological chemistry because it is closely related to the bulkiness and polarizability of a molecule. It is usually defined by Lorenz–Lorentz equation: $MR=((n^2-1)^*M)/((n^2+2)^*\rho)$, where n is the relative index, M is the molecular weight, and ρ is the density.[59] They have been widely used as steric parameters in QSAR analysis of drug design,[57,60] but have not been applied in QSAR analysis of asymmetric reactions. With MR parameters (Table 5), Eqs. 4 and 5 were obtained using acetophenone and 3,5-bis(trifluoromethyl)-acetophenone as the substrates, respectively, in which X and Y represent the respective R^1 and R^2 substituents.

Table 5
MR parameters[a] of R groups

Entry	Substituent	MR	Entry	Substituent	MR
1	H	0.10	6	CH_2*i*-Pr	1.96
2	Me	0.56	7	*s*-Bu	1.96
3	Et	1.03	8	CH_2Bu	2.42
4	*i*-Pr	1.50	9	*c*-C_6H_{11}	2.67
5	Bu	1.96	10	—	—

[a] See Refs. 57,58.

$$\Delta\Delta G^{\ddagger} = 1.034 - 0.503 \times X_{MR} + 0.221 \times Y_{MR} \quad (4)$$

$$\Delta\Delta G^{\ddagger} = 1.776 - 0.956 \times X_{MR} + 0.485 \times Y_{MR} \quad (5)$$

Eqs. 4 and 5 are similar with different coefficient values. Both equations have negative coefficients of X_{MR} and positive coefficients of Y_{MR}, indicating that decreasing R^1 size and increasing R^2 size lead to higher enantioselectivity. The plots of the predicted via experimentally determined $\Delta\Delta G^{\ddagger}$ values with R^2=0.900 for acetophenone and R^2=0.901 for 3,5-bis(trifluoromethyl)-acetophenone as shown in Fig. 6 demonstrate that MR parameters can also be used to construct QSAR, but are less accurate as sterimol parameters do. The advantages of sterimol over MR parameters may be that sterimol parameters are three-dimensional parameters of substituents and MR parameters are only one-dimensional parameters. However, poor quantitative relationships were observed for *N*-mono substituted ligands or all of the *N*-substituted ligands between substituent sizes and enantioselectivities in the asymmetric additions of diethylzinc to both ketones with the use of Charton values[61–65] as the steric parameters (for details please see Supplementary data), which give excellent linear relationship in the asymmetric addition of diethylzinc to benzylaldehyde for

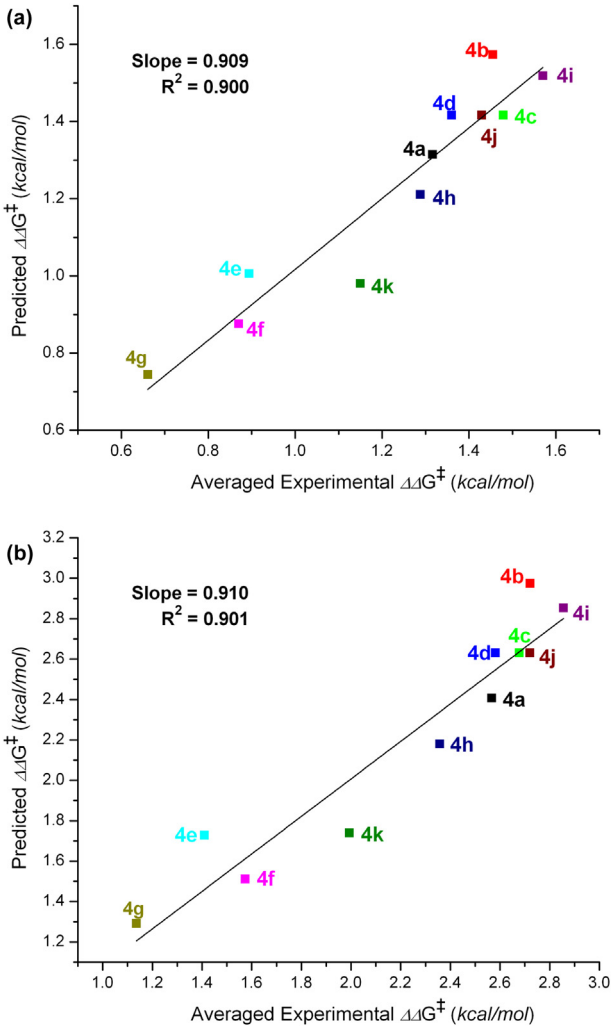


Fig. 6. Plots of averaged experimental $\Delta\Delta G^{\ddagger}$ values versus predicted $\Delta\Delta G^{\ddagger}$ values for ligands **4a**–**4k** with MR as the steric parameters using (a) acetophenone and (b) 3,5-bis(trifluoromethyl)-acetophenone as the substrates, respectively.

N-mono substituted ligands.[33] These results indicate the limitations of applying Charton parameters for sterically large groups in quantitative correlation analysis.[23,24]

In order to present how the R^1 and R^2 groups of the catalysts interact with the substrates, a working model is given in Fig. 7 on the basis of Ishihara's conjugate Lewis acid–Lewis base double activated transition state mode.[49] This model clearly shows that a *Re*-face attack, which leads to (*R*)-product should be favored without steric repulsion between the R^1 and R^2 groups of the chiral catalytic zinc complex and the benzyl group of acetophenone. In addition, for the *Re*-face attack, a catalyst with a small R^1 and a big R^2 would give higher enantioselectivity because of the less steric hindrance with the methyl group of acetophenone. Therefore,

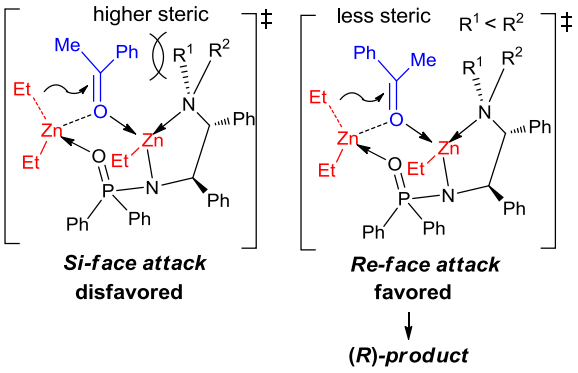


Fig. 7. The proposed working model.

among these 11 chiral ligands, **4i** is the most efficient catalyst in the asymmetric ethylation reaction and gives the highest enantioselectivity of the tertiary alcohol product.

3. Conclusion

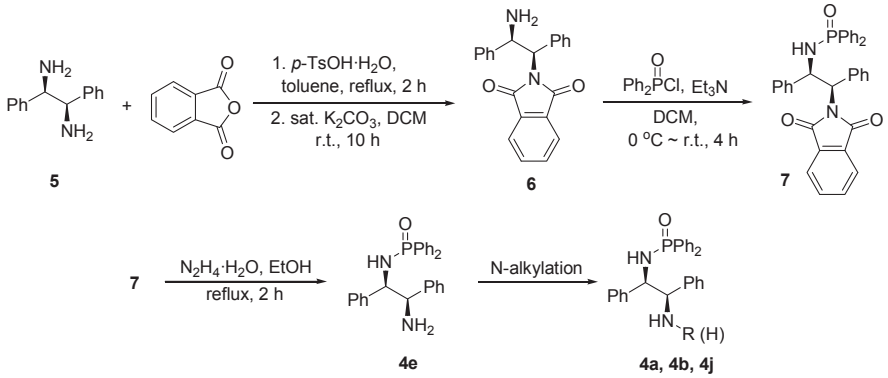
In summary, we have explored quantitative correlations between the *N*-substituent sizes of chiral phosphoramide ligands and enantioselectivities in the asymmetric addition reactions of diethylzinc to ketones using different steric parameters. Our results show that both sterimol and MR parameters can be used to construct QSAR models in this system. With different substrates, the catalytic properties of chiral ligands are different, but similar QASR models can be established. Using sterimol parameters, the developed QSAR model is highly predictive for ee values of tertiary alcohol products catalyzed by new synthesized chiral ligands. In addition, Charton values are not suitable for this system. Our studies on the effects of different steric parameters on QSAR construction demonstrate the importance of choosing appropriate sets of physical reference parameters and the power of an excellent QSAR model for instructing ligand optimization.

4. Experimental section

4.1. General methods

Unless stated otherwise, all experiments were carried out in dried glassware with magnetic stirring under an atmosphere of dry nitrogen. ^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz), and ^{31}P NMR (162 MHz) spectra were recorded in $CDCl_3$ solutions using a 400 MHz spectrometer. Chemical shifts were reported in parts per million (ppm, δ) relative to $CDCl_3$ (δ 7.26 for ^{1}H NMR), or $CDCl_3$ (δ 77.0 for ^{13}C NMR). Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Commercial reagents were used as received unless otherwise indicated. All solvents were purified and dried prior to use according to standard methods. Optical rotations were measured on a polarimeter and reported as follows: $[\alpha]_D^T$ (*c* g/100 mL, solvent). GC analysis was performed on a gas chromatograph with a FID detector on fused silica chiral capillary column (Chirasil Dex CB column, 25 m length×0.32 mm ID×0.25 mm film thickness). High-resolution mass spectra (HRMS) were obtained by the ESI ionization sources. Chiral ligands **1** were prepared according to literature,[33] **2** and **3** were prepared according to literature.[55]

4.2. Representative procedure for preparing chiral ligands 4a, 4b, 4e, 4j



*4.2.1. 2-[(1R,2R)-2-Amino-1,2-diphenylethyl]-2,3-dihydro-1H-isoindole-1,3-dione (**6**).* A solution of *p*-TsOH·H_2O (5.70 g, 30 mmol) in toluene (30 mL) was dehydrated by azeotropic distillation (oil bath 120 °C). After being cooled to room temperature, (1*R*,2*R*)-1,2-diphenylethane-1,2-diamine (6.36 g, 30 mmol) was added to the solution, followed by phthalic anhydride (4.44 g, 30 mmol). The mixture was stirred at reflux for 12 h, then cooled to room temperature. The solid crude product was collected by filtration, washed with toluene–hexane and air-dried. The solid crude product was then added to a solution of saturated K_2CO_3 solution (150 mL) and CH_2Cl_2 (150 mL), and stirred overnight. After that, the organic solution was separated and extracted with CH_2Cl_2 (150 mL) to give combined organic layers, which were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give 7.39 g (72%) of **6** as a white solid. Compound **6** was directly used in the following step without further purification. Mp 133–134 °C; $[\alpha]_D^{24.7}$ 79.8 (*c* 1.00, CH_2Cl_2); R_f=0.35 (petroleum ether/EtOAc=1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67–1.70 (br, 2H), 5.40 (dd, *J*=11.0, 36.0 Hz, 2H), 7.13–7.31 (m, 8H), 7.39–7.45 (m, 2H), 7.70–7.76 (m, 2H), 7.83–7.91 (m, 2H). ^{13}C

NMR (100 MHz, $CDCl_3$): δ 56.0, 62.9, 123.3, 127.3, 127.4, 127.7, 128.3, 128.5, 129.1, 131.9, 134.0, 137.9, 143.0, 168.9. HRMS (ESI): (*m*/*z*) calcd for $C_{22}H_{18}N_2O_2$ $[M+H]^+$: 343.1447, found: 343.1444.

*4.2.2. 2-[(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenylethyl]-2,3-dihydro-1H-isoindole-1,3-dione (**7**).* To a solution of **6** (6.84 g, 20 mmol) in dry CH_2Cl_2 (60 mL), Et_3N (6.06 g, 60 mmol) was added at room temperature. After being stirred for 10 min,diphenylphosphinic chloride (9.46 g, 40 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise to the solution at 0 °C. The mixture was stirred for 4 h at room temperature, cooled in ice bath, and diluted with water (20 mL). Extraction with CH_2Cl_2 gave combined organic layers, which were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a residue. This residue was subjected to silica gel column chromatography (EtOAc/hexane=1:2) to afford 7.37 g (68%) of **7** as a white solid. Mp 103–104 °C; $[\alpha]_D^{27.7}$ −76.4 (*c* 1.00, CH_2Cl_2); R_f=0.45 (petroleum ether/EtOAc=1:1). ^1H NMR (400 MHz, $CDCl_3$): δ 4.47 (t, *J*=10.1 Hz, 1H), 5.40 (q, *J*=20.3 Hz, 1H), 5.79 (d, *J*=9.2 Hz, 1H), 7.05–7.25 (m, 10H), 7.28–7.49 (m, 8H), 7.57–7.71 (m, 4H), 7.73–7.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.6, 61.3, 123.2, 126.9, 127.2, 127.7, 128.00, 128.04, 128.1, 128.2, 128.3, 129.1, 131.40, 131.43, 131.56, 131.6, 131.7, 131.8, 132.2, 132.3, 132.7, 133.1, 133.8, 136.5, 140.6, 168.8. ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.5. HRMS (ESI): (*m*/*z*) calcd for $C_{34}H_{27}N_2O_3P$ $[M+H]^+$: 543.1833, found: 543.1832.

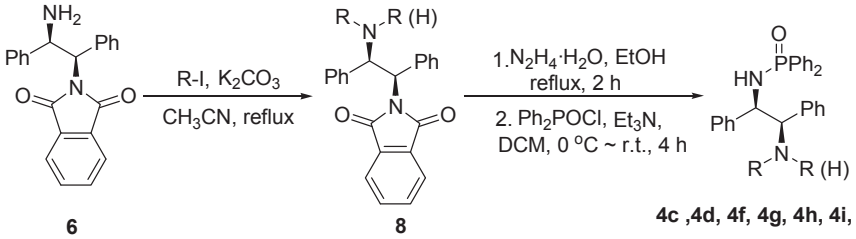
*4.2.3. [(1R,2R)-2-Amino-1,2-diphenylethyl](diphenylphosphoroso) amine (**4e**).* A solution of **7** (7.37 g, 13.6 mmol) in ethanol (50 mL) containing hydrazine monohydrate (13.6 mL) was stirred at reflux for 1 h. The mixture was then cooled to room temperature and diluted with diethyl ether, forming a precipitate that was removed by filtration. The filtrate was dried over $MgSO_4$ and concentrated in vacuo to afford 5.32 g (95%) **4e** as a white solid, which was used in the following step without further purification. Mp 217–218 °C; $[\alpha]_D^{26.8}$ −78.0 (*c* 1.00, CH_2Cl_2); R_f=0.30 ($MeOH/CH_2Cl_2$=1:20). ^1H NMR (400 MHz, $CDCl_3$): δ 1.67 (br, 2H), 4.21–4.30 (m, 1H), 4.30–4.35 (m, 1H), 4.45 (t, *J*=9.2 Hz, 1H), 7.15–7.27 (m, 7H), 7.27–7.39 (m, 10H), 7.39–7.45 (m, 1H), 7.65–7.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.3, 61.4, 126.9, 127.1, 127.2, 127.5, 128.09, 128.10, 128.18, 128.21, 128.23, 131.31, 131.33, 131.48, 131.5, 132.0, 132.10, 132.12, 132.2, 132.4, 132.6, 133.6, 141.50, 141.52, 142.4. ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.3. HRMS (ESI): (*m*/*z*) calcd for $C_{26}H_{25}N_2OP$ $[M+H]^+$: 413.1775, found: 413.1774.

*4.2.4. [(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenylethyl](propan-2-yl)amine (**4a**).* To the solution of **4e** (412 mg, 1.0 mmol) in CH_3CN (5 mL), K_2CO_3 (414 mg, 3.0 mmol) and *iso*-propyl iodide (540 mg, 3.0 mmol) were added at room temperature. The resulting mixture was stirred at reflux overnight, cooled to room temperature, and concentrated in vacuo to give an oily residue. The residue was diluted with CH_2Cl_2 (20 mL) and water (20 mL). Then, the organic layer was separated and the aqueous layer (pH ~10) was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo, to give a residue that was subjected to silica gel column chromatography ($MeOH/CH_2Cl_2$=1:40) to afford 254 mg (56%) of **4a** as a white solid. Mp 206–207 °C; $[\alpha]_D^{20.5}$ −18.4 (*c* 1.00, CH_2Cl_2); R_f=0.30 ($MeOH/CH_2Cl_2$=1:30). ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (d, *J*=6.1 Hz, 3H), 0.97 (d, *J*=6.4 Hz, 3H), 2.51–2.65 (m, 1H), 4.00 (d, *J*=6.1 Hz, 1H), 4.29–4.37 (m, 1H), 4.45–4.65 (br, 1H), 7.05–7.16 (m, 5H), 7.17–7.22 (m, 2H), 7.23–7.33 (m, 7H), 7.34–7.44 (m, 2H), 7.51–7.61 (m, 2H), 7.65–7.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.6, 24.1, 45.3, 60.9, 66.0 (d, *J*=6.8 Hz), 126.9, 127.1, 127.3, 127.7, 127.9, 128.0, 128.04, 128.1, 128.3, 131.24, 131.28, 131.36, 131.4, 131.7, 131.8, 132.1, 132.2, 133.1, 133.14, 140.67, 140.69, 140.8. ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.4. HRMS (ESI): (*m*/*z*) calcd for $C_{29}H_{31}N_2OP$ $[M+H]^+$: 455.2244, found: 455.2244.

*4.2.5. [(1R,2R)-2-[(Cyclohexylamino)-1,2-diphenyl] (diphenylphosphoroso)amine (**4b**).* Cyclohexanone (108 mg, 1.1 mmol) was added to a stirred solution of **4e** (412 mg, 1.0 mmol) in dried methanol (10 mL) with molecular sieves (2 g), followed by three drops of glacial acetic acid. After being stirred for 2 h, sodium cyanoborohydride (158 mg, 2.5 mmol) was added to the solution, and the resulting mixture was stirred overnight at room temperature. The molecular sieves were filtered through filter paper and the solution was concentrated in vacuo to remove the methanol. The residue was dissolved in CH_2Cl_2 (60 mL) and washed with saturated K_2CO_3 solution (50 mL). Then the organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc/hexane=1:1) to afford 351 mg (71%) of **4b** as a white solid. Mp 204–205 °C; $[\alpha]_D^{26.9}$ 57.2 (*c* 1.00, CH_2Cl_2); R_f=0.20 (EtOAc/hexane=1:2). ^1H NMR (400 MHz, $CDCl_3$): δ 0.76–0.88 (m, 1H), 0.97–1.17 (m, 4H), 1.40–1.70 (m, 5H), 1.74–1.82 (m, 1H), 2.18–2.30 (m, 1H), 4.06 (d, *J*=6.0 Hz, 1H), 4.30 (m, 1H), 4.54 (t, *J*=6.7 Hz, 1H), 7.07–7.19 (m, 5H), 7.19–7.25 (m, 2H), 7.26–7.34 (m, 7H), 7.35–7.45 (m, 2H), 7.45–7.55 (m, 2H), 7.63–7.75 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 24.9, 26.0, 32.2, 34.6, 52.8, 61.1, 65.4 (d, *J*=7.1 Hz), 127.0, 127.2, 127.3, 127.9, 128.0, 128.10, 128.12, 128.14, 128.3, 128.4, 131.4 (d, *J*=2.8 Hz), 131.5 (d, *J*=2.6 Hz), 131.8, 131.9, 132.0, 132.1, 132.2, 132.3, 133.1, 133.4, 140.9, 141.2. ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.1. HRMS (ESI): (*m*/*z*) calcd for $C_{32}H_{35}N_2OP$ $[M+H]^+$: 495.2564, found: 495.2560.

*4.2.6. (Butan-2-yl)[(1R,2R)-2-[(diphenylphosphoroso)amino]-1,2-diphenyethyl]amine (**4j**).* The title compound was prepared following the general procedure described for **4a** on the same scale and was obtained as a white solid with the yield of 314 mg (67%). Mp 203–204 °C; $[\alpha]_D^{26.0}$ −51.9 (*c* 1.00, CH_2Cl_2); R_f=0.25 (EtOAc/hexane=1:1). ^1H NMR (400 MHz, $CDCl_3$): δ 0.52 (t, *J*=7.5 Hz, 1H), 0.65–0.87 (m, 5H), 1.00–1.38 (m, 3H), 2.20–2.41 (m, 1H), 3.80–4.00 (m, 1H), 4.15–4.30 (m, 1H), 4.49 (br, 1H), 6.87–7.50 (m, 18H), 7.55–7.65 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.7, 9.4, 17.9, 19.7, 26.3, 28.6, 29.8, 49.7, 49.8, 60.1, 64.7 (d, *J*=7.0 Hz), 65.2 (d, *J*=7.3 Hz), 126.0, 126.2, 126.3, 126.4, 126.8, 126.9, 127.0, 127.02, 127.07, 127.1, 127.2, 127.3, 130.3, 130.35, 130.4, 130.43, 130.7, 130.77, 130.83, 130.87, 130.9, 131.07, 131.15, 131.18, 131.24, 131.3, 132.0, 132.1, 132.3, 132.4, 139.7, 139.82, 139.84, 140.2. ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.2. HRMS (ESI): (*m*/*z*) calcd for $C_{30}H_{33}N_2OP$ $[M+H]^+$: 469.2402, found: 469.2403.

4.3. Representative procedure for preparing chiral ligands 4c, 4d, 4f, 4g, 4h, 4i, 4k



6 **8** **4c ,4d, 4f, 4g, 4h, 4i, 4k**

*4.3.1. 2-[(1R,2R)-2-(Butylamino)-1,2-diphenylethyl]-2,3-dihydro-1H-isoindole-1,3-dione (**8c**).* To the solution of **6** (342 mg, 1.0 mmol) in CH_3CN (5 mL) at room temperature, K_2CO_3 (276 mg, 2.0 mmol) and 1-butyl iodide (368 mg, 2 mmol) were added. The resulting mixture was stirred at reflux overnight, cooled to room temperature, and concentrated in vacuo to give an oily residue. The residue was diluted with CH_2Cl_2 (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer (pH ~10) was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo, to give a residue that was subjected to silica gel column chromatography (EtOAc/hexane=1:40) to afford 259 mg (65%) of **8c** as a white solid. Mp 131–133 °C; $[\alpha]_D^{26.1}$ 69.5 (*c* 1.00, CH_2Cl_2); R_f=0.25 (EtOAc/hexane=1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.75 (t, *J*=7.3 Hz, 3H), 1.07–1.21 (m, 2H), 1.22–1.36 (m, 2H), 2.31–2.53 (m, 2H), 5.07 (d, *J*=11.0 Hz, 1H), 5.48 (d, *J*=11.0 Hz, 1H), 7.08–7.32 (m, 8H), 7.41–7.51 (m, 2H), 7.63–7.76 (m, 2H), 7.82–7.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 21.2, 32.2, 46.6, 61.2, 62.0, 123.2, 127.2, 127.6, 128.0, 128.2, 128.3, 129.4, 132.1, 133.8, 137.8, 168.8. HRMS (ESI): (*m*/*z*) calcd for $C_{26}H_{26}N_2O_2$ $[M+H]^+$: 399.2067, found: 399.2067.

*4.3.2. 2-[(1R,2R)-2-[(2-Methylpropyl)amino]-1,2-diphenylethyl]-2,3-dihydro-1H-isoindole-1,3-dione (**8d**).* The title compound was prepared following the general procedure described for **8c** on the same scale and was obtained as a white solid with the yield of 239 mg (60%). Mp 116–117 °C; $[\alpha]_D^{25.9}$ 8.9 (*c* 1.00, CH_2Cl_2); R_f=0.25 (EtOAc/hexane=1:8). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.68 (d, *J*=6.7 Hz, 3H), 0.71 (d, *J*=6.7 Hz, 3H), 1.30–1.60 (m, 2H), 2.13–2.35 (m, 2H), 5.01 (d, *J*=11.5 Hz, 1H), 5.48 (d, *J*=11.5 Hz, 1H), 7.06–7.32 (m, 8H), 7.43–7.51 (m, 2H), 7.64–7.74 (m, 2H), 7.83–7.89 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 28.5, 55.2, 61.2, 62.3, 123.2, 127.2, 127.6, 127.9, 128.2, 128.3, 129.4, 132.1, 133.9, 137.7, 141.3, 168.9. HRMS (ESI): (*m*/*z*) calcd for $C_{26}H_{26}N_2O_2$ $[M+H]^+$: 399.2065, found: 399.2070.

*4.3.3. 2-[(1R,2R)-2-(Dimethylamino)-1,2-diphenylethyl]-2,3-dihydro-1H-isoindole-1,3-dione (**8f**).* A mixture of **6** (342 mg, 1.0 mmol), 80% formic acid (1.0 mL), and 36% formaldehyde solution (0.6 mL, 6.0 mmol) was stirred at reflux (oil bath 85 °C) for 8 h. Then, the solvent was removed in vacuo, followed by the addition of saturated Na_2CO_3 solution (10 mL) and extraction with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc/hexane=1:30) to afford 311 mg (84%) of **8f** as a white solid. Mp 211–212 °C; $[\alpha]_D^{26.8}$ −88.6 (*c* 1.00, CH_2Cl_2); R_f=0.25 (EtOAc/hexane=1:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 6H), 5.22 (d, *J*=12.4 Hz, 1H), 5.98 (d, *J*=12.3 Hz, 1H), 7.03–7.26 (m, 8H), 7.50–7.56 (m, 2H), 7.65–7.71 (m, 2H), 7.79–7.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.8, 54.9, 66.0, 123.1, 123.5, 127.2, 127.6, 127.7, 128.2, 128.5, 129.2, 129.6, 132.7, 133.7, 133.9, 137.5, 168.6. HRMS (ESI): (*m*/*z*) calcd for $C_{24}H_{22}N_2O_2$ $[M+H]^+$: 371.1758, found: 371.1757.

*4.3.4. 2-[(1R,2R)-2-(Diethylamino)-1,2-diphenylethyl]-2,3-dihydro-1H-isoindole-1,3-dione (**8g**).* To the solution of **6** (342 mg, 1.0 mmol) in CH_3CN (5 mL) at room temperature, K_2CO_3 (276 mg, 2.0 mmol) and ethyl iodide (624 mg, 4 mmol) were added. The resulting mixture was stirred at reflux overnight, cooled to room temperature, and concentrated in vacuo to give an oily residue. The residue was diluted with CH_2Cl_2 (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer (pH ~10) was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo, to give a residue that was subjected to silica gel column chromatography (EtOAc/hexane=1:40) to afford 295 mg (74%) of **8g** as a white solid. Mp 152–153 °C; $[\alpha]_D^{27.8}$ −212.5 (*c* 1.00, CH_2Cl_2); R_f=0.30 (EtOAc/hexane=1:20). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J*=7.2 Hz, 6H), 1.97–2.15 (m, 2H), 2.50–2.86 (m, 2H), 5.32 (d, *J*=12.1 Hz, 1H), 6.01 (d, *J*=12.1 Hz, 1H), 7.03–7.26 (m, 8H), 7.51–7.59 (m, 2H), 7.65–7.74 (m, 2H), 7.76–7.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 43.6, 55.1, 61.8, 122.9, 123.1, 127.1, 127.6, 127.8, 128.2, 129.3, 129.9, 131.7, 132.5, 133.7, 133.8, 135.3, 137.2, 168.3, 168.7. HRMS (ESI): (*m*/*z*) calcd for $C_{26}H_{26}N_2O_2$ $[M+H]^+$: 399.2068, found: 399.2067.

*4.3.5. 2-[(1R,2R)-2-(Ethylamino)-1,2-diphenylethyl]-2,3-dihydro-1H-isoindole-1,3-dione (**8h**).* To the solution of **6** (342 mg, 1.0 mmol) in CH_3CN (5 mL) at room temperature, K_2CO_3 (276 mg, 2.0 mmol) and ethyl iodide (312 mg, 2 mmol) were added. The resulting mixture was stirred at reflux overnight, cooled to room temperature, and concentrated in vacuo to give an oily residue. The residue was diluted with CH_2Cl_2 (20 mL) and water (20 mL). The organic layer was separated and the aqueous layer (pH ~10) was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo, to give a residue that was subjected to silica gel column chromatography (EtOAc/hexane=1:20) to afford 274 mg (74%) of **8h** as a white solid. Mp 102–103 °C; $[\alpha]_D^{27.8}$ 31.4 (*c* 1.00, CH_2Cl_2); R_f=0.30 (EtOAc/hexane=1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, *J*=7.1 Hz, 3H), 1.45 (br, 1H), 2.36–2.52 (m, 2H), 5.06 (d, *J*=11.3 Hz, 1H), 5.42 (d, *J*=11.3 Hz, 1H), 7.04–7.28 (m, 8H), 7.32–7.46 (m, 2H), 7.65–7.74 (m, 2H), 7.80–7.89 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.3, 41.2, 61.2, 61.7, 123.2, 127.2, 127.5. 127.9, 128.1, 128.2, 129.3, 132.0, 133.8, 137.8, 141.1, 168.8. HRMS (ESI): (*m*/*z*) calcd for $C_{24}H_{22}N_2O_2$ $[M+H]^+$: 371.1752, found: 371.1754.

*4.3.6. 2-[(1R,2R)-2-(Pentylamino)-1,2-diphenylethyl]-2,3-dihydro-1H-isoindole-1,3-dione (**8i**).* The title compound was prepared following the general procedure described for **8g** on the same scale and was obtained as a white solid with the yield of 280 mg (68%). Mp 104–105 °C; $[\alpha]_D^{25.9}$ 17.3 (*c* 1.00, CH_2Cl_2); R_f=0.25 (EtOAc/hexane=1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.72 (d, *J*=7.2 Hz, 3H), 1.03–1.21 (m, 4H), 1.24–1.49 (m, 3H), 2.32–2.54 (m, 2H), 5.05 (d, *J*=11.3 Hz, 1H), 5.48 (d, *J*=11.3 Hz, 1H), 7.08–7.31 (m, 8H), 7.42–7.50 (m, 2H), 7.67–7.75 (m, 2H), 7.81–7.92 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.4, 29.3, 29.7, 61.1, 62.0, 123.2, 127.2, 127.6, 127.9, 128.2, 128.3, 129.4, 132.1, 133.8, 137.2, 168.8. HRMS (ESI): (*m*/*z*) calcd for $C_{27}H_{28}N_2O_2$ $[M+H]^+$: 413.2220, found: 413.2223.

*4.3.7. 2-[(1R,2R)-2-[Ethyl(methyl)amino]-1,2-diphenylethyl]-2,3-dihydro-1H-isoindole-1,3-dione (**8k**).* A mixture of **8h** (370 mg, 1.0 mmol), 80% formic acid (1.0 mL), and 36% formaldehyde solution (0.3 mL, 5.0 mmol) was stirred at reflux (oil bath 85 °C) for 8 h. The solvents were removed in vacuo, followed by the addition of saturated Na_2CO_3 solution (10 mL) and extraction with CH_2Cl_2 (10 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (EtOAc/hexane=1:30) to afford 322.5 mg (84%) of **8k** as a white solid. Mp 157–158 °C; $[\alpha]_D^{26.8}$ −134.8 (*c* 1.00, CH_2Cl_2); R_f=0.25 (EtOAc/hexane=1:15). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.85 (t, *J*=7.0 Hz, 3H), 2.1 (s, 3H), 2.13–2.23 (m, 1H), 2.38–2.49 (m, 1H), 5.27 (d, *J*=12.3 Hz, 1H), 6.02 (d, *J*=12.2 Hz, 1H), 7.04–7.11 (m, 1H), 7.12–7.18 (m, 3H), 7.19–7.25 (m, 4H), 7.50–7.59 (m, 2H), 7.64–7.71 (m, 2H), 7.77–7.91 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 29.6, 36.8, 47.5, 54.9, 65.3, 122.9, 127.0, 127.2, 127.5, 127.7, 128.1, 129.3, 129.6, 131.6, 132.4, 133.6, 133.7, 137.3, 168.5. HRMS (ESI): (*m*/*z*) calcd for $C_{25}H_{24}N_2O_2$ $[M+H]^+$: 385.1913, found: 385.1914.

*4.3.8. Butyl[(1R,2R)-2-[(diphenylphosphoroso)amino]-1,2-diphenyethyl]amine (**4c**).* A solution of **8c** (796 mg, 2.0 mmol) in ethanol (5 mL) containing hydrazine monohydrate (2.0 mL) was stirred at reflux for 1 h. The mixture was then cooled to room temperature and diluted with diethyl ether, forming a precipitate

that was removed by filtration. The filtrate was dried over $MgSO_4$ and concentrated in vacuo to give 480 mg of colorless oil, which was used in the following step without further purification. To a solution of this oil in dry CH_2Cl_2 (4 mL), Et_3N (606 mg, 6 mmol) was added at room temperature. After being stirred for 10 min, diphenylphosphinic chloride (710 mg, 3 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise to the solution at 0 °C. The mixture was stirred for 4 h at room temperature, cooled in ice bath, and diluted with water (20 mL). Extraction with CH_2Cl_2 gave combined organic layers that were washed with brine, dried over $MgSO_4$ and concentrated in vacuo to give a residue. This residue was subjected to silica gel column chromatography (EtOAc/hexane=1:2) to afford 721 mg (77%) of **4c** as a white solid. Mp 201–202 °C; $[\alpha]_D^{21.6}$ −42.1 (*c* 1.00, CH_2Cl_2); R_f=0.20 (EtOAc/hexane=1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (t, *J*=7.3 Hz, 3H), 1.13–1.39 (m, 5H), 2.22–2.34 (m, 1H), 2.40–2.52 (m, 1H), 3.91 (d, *J*=5.7 Hz, 1H), 4.29–4.37 (m, 1H), 4.37–4.44 (m, 1H), 7.11–7.21 (m, 5H), 7.22–7.25 (m, 2H), 7.26–7.35 (m, 7H), 7.37–7.53 (m, 4H), 7.67–7.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.8, 20.2, 30.0, 47.0, 61.0, 68.8 (d, *J*=6.7 Hz), 127.0, 127.2, 127.3, 128.0, 128.1, 128.2, 128.3, 131.4, 131.7, 131.9, 132.0, 132.1, 132.3, 133.0, 133.4, 140.6, 140.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.9. HRMS (ESI): (*m*/*z*) calcd for $C_{30}H_{33}N_2OP$ $[M+H]^+$: 469.2403, found: 469.2403.

*4.3.9. [(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenyethyl](2-methylpropyl)amine (**4d**).* The title compound was prepared following the general procedure described for **4c** on the same scale and was obtained as a white solid with the yield of 749 mg (80%). Mp 214–215 °C; $[\alpha]_D^{23.3}$ −58.8 (*c* 1.00, CH_2Cl_2); R_f=0.20 (EtOAc/hexane=1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78 (d, *J*=6.7 Hz, 6H), 1.51–1.70 (m, 2H), 2.08–2.17 (m, 1H), 2.21–2.30 (m, 1H), 3.88 (d, *J*=5.8 Hz, 1H), 4.27–4.51 (m, 2H), 7.12–7.26 (m, 7H), 7.27–7.36 (m, 7H), 7.38–7.51 (m, 4H), 7.65–7.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 20.6, 28.3, 55.3, 61.1, 68.9 (d, *J*=7.0 Hz), 127.1, 127.26, 127.3, 128.0, 128.1, 128.2, 128.3, 131.4, 131.9, 132.0, 132.2, 132.3, 140.7, 140.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.9. HRMS (ESI): (*m*/*z*) calcd for $C_{30}H_{33}N_2OP$ $[M+H]^+$: 469.2397, found: 469.2400.

*4.3.10. [(1R,2R)-2-(Dimethylamino)-1,2-diphenylethyl](diphenylphosphoroso)amine (**4f**).* The title compound was prepared following the general procedure described for **4c** on the same scale and was obtained as a white solid with the yield of 660 mg (75%). Mp 197–198 °C; $[\alpha]_D^{27.1}$ 82.9 (*c* 1.00, CH_2Cl_2); R_f=0.20 (EtOAc/hexane=1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 6H), 3.72 (d, *J*=10.7 Hz, 1H), 4.83 (t, *J*=11.0 Hz, 1H), 5.37 (s, 1H), 6.78–6.87 (m, 3H), 6.90–6.98 (m, 2H), 6.99–7.09 (m, 4H), 7.11–7.23 (m, 4H), 7.40–7.60 (m, 5H), 7.82–7.97 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.5, 54.7 (d, *J*=2.0 Hz), 74.5, 74.6, 126.5, 127.31, 127.37, 127.4, 127.5, 127.52, 128.3, 128.5, 128.6, 129.9, 130.7, 130.72, 131.2, 131.3, 131.4, 131.47, 131.5, 132.36, 132.42, 132.46, 132.5, 133.5, 134.8, 140.8. ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.8. HRMS (ESI): (*m*/*z*) calcd for $C_{28}H_{29}N_2OP$ $[M+H]^+$: 441.2090, found: 441.2090.

*4.3.11. [(1R,2R)-2-(Diethylamino)-1,2-diphenylethyl](diphenylphosphoroso)amine (**4g**).* The title compound was prepared following the general procedure described for **4c** on the same scale and was obtained as a white solid with the yield of 749 mg (80%). Mp 167–168 °C; $[\alpha]_D^{23.0}$ 43.7 (*c* 1.00, CH_2Cl_2); R_f=0.20 (EtOAc/hexane=1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, *J*=7.1 Hz, 6H), 2.06–2.24 (m, 2H), 2.77–2.94 (m, 2H), 3.93 (d, *J*=10.7 Hz, 1H), 4.88 (t, *J*=10.6 Hz, 1H), 5.62 (s, 1H), 6.78–6.88 (m, 3H), 6.91–6.99 (m, 2H), 7.00–7.20 (m, 8H), 7.37–7.62 (m, 5H), 7.82–7.95 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 42.7, 54.5, 69.7, 69.8, 126.6, 127.2, 127.4, 127.5, 127.6, 128.1, 128.3, 128.4, 128.6, 129.8, 130.6, 130.7, 131.1, 131.2, 131.3, 131.4, 131.7, 132.2, 132.4, 133.0, 133.6, 134.6, 134.9, 140.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.1. HRMS (ESI): (*m*/*z*) calcd for $C_{30}H_{33}N_2OP$ $[M+H]^+$: 469.2407, found: 469.2403.

*4.3.12. [(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenyethyl](ethyl)amine (**4h**).* The title compound was prepared following the general procedure described for **4c** on the same scale and was obtained as a white solid with the yield of 598 mg (68%). Mp 202–203 °C; $[\alpha]_D^{22.1}$ −58.9 (*c* 1.00, CH_2Cl_2); R_f=0.20 (EtOAc/hexane=1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, *J*=6.9 Hz, 3H), 1.45–1.80 (br, 1H), 2.26–2.41 (m, 1H), 2.46–2.57 (m, 1H), 3.91–4.00 (m, 1H), 4.27–4.42 (m, 2H), 7.10–7.26 (m, 7H), 7.26–7.36 (m, 7H), 7.38–7.52 (m, 4H), 7.66–7.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.2, 41.6, 60.9, 68.7 (d, *J*=6.5 Hz), 127.1, 127.28, 127.33, 128.01, 128.04, 128.12, 128.17, 128.24, 128.4, 131.5 (d, *J*=2.5 Hz), 131.8, 132.0, 132.1, 132.2, 132.4, 133.0, 133.3, 140.6, 140.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.1. HRMS (ESI): (*m*/*z*) calcd for $C_{28}H_{29}N_2OP$ $[M+H]^+$: 441.2095, found: 441.2090.

*4.3.13. [(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenyethyl](pentyl)amine (**4i**).* The title compound was prepared following the general procedure described for **4c** on the same scale and was obtained as a white solid with the yield of 704 mg (73%). Mp 176–177 °C; $[\alpha]_D^{20.9}$ −74.8 (*c* 1.00, CH_2Cl_2); R_f=0.25 (EtOAc/hexane=1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, *J*=7.2 Hz, 3H), 1.07–1.25 (m, 4H), 1.31–1.41 (m, 2H), 1.51–1.77 (br, 1H), 2.22–2.35 (m, 1H), 2.38–2.53 (m, 1H), 3.91 (d, *J*=5.4 Hz, 1H), 4.29–4.37 (m, 1H), 4.37–4.48 (m, 1H), 7.09–7.36 (m, 14H), 7.38–7.52 (m, 4H), 7.64–7.76 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 29.3, 29.5, 47.2, 61.0, 68.8 (d, *J*=6.7 Hz), 127.1, 127.30, 127.34, 128.01, 128.03, 128.14, 128.16, 128.22, 128.4, 131.5, 131.7, 131.9, 132.0, 132.1, 132.25, 132.35, 133.0, 133.4, 140.6, 140.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.0. HRMS (ESI): (*m*/*z*) calcd for $C_{31}H_{35}N_2OP$ $[M+H]^+$: 483.2552, found: 483.2557.

*4.3.14. (Diphenylphosphoroso)[(1R,2R)-2-[ethyl(methyl)amino]-1,2-diphenyl]amine (**4k**).* The title compound was prepared following the general procedure described for **4c** on the same scale and was obtained as a white solid with the yield of 699 mg (77%). Mp 177–178 °C; $[\alpha]_D^{22.5}$ 46.4 (*c* 1.00, CH_2Cl_2); R_f=0.25 (EtOAc/hexane=1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, *J*=7.1 Hz, 3H), 2.24 (s, 3H), 2.25–2.35 (m, 1H), 2.49–2.61 (m, 1H), 3.82 (d, *J*=10.8 Hz, 1H), 4.87 (t, *J*=10.9 Hz, 1H), 5.52 (s, 1H), 6.78–6.86 (m, 3H), 6.91–6.98 (m, 2H), 7.00–7.09 (m, 4H), 7.10–7.22 (m, 4H), 7.39–7.60 (m, 5H), 7.82–7.93 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 36.1, 47.3, 54.5, 73.6, 73.7, 126.6, 127.3, 127.4, 127.5, 127.6, 128.3, 128.5, 128.6, 129.8, 130.7, 130.73, 131.2, 131.3, 131.36, 131.44, 131.5, 132.4, 132.5, 132.7, 133.3, 133.6, 134.9, 140.8. ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.7. HRMS (ESI): (*m*/*z*) calcd for $C_{29}H_{31}N_2OP$ $[M+H]^+$: 455.2245, found: 455.2244.

4.4. General procedure for the enantioselective additions of diethylzinc to ketones

A well-dried Pyrex Schlenk tube was charged with chiral ligand **4** (0.10 mmol). Then, diethylzinc (2.0 mL of 1.5 M solution in toluene, 3.0 mmol) was slowly added at 0 °C under nitrogen atmosphere and the mixture was stirred for 30 min, followed by the addition of acetophenone (1.0 mmol) dropwise. The resulting mixture was stirred for 24 h at room temperature, cooled in ice bath, and quenched with aqueous HCl (10%, 10 mL). Extraction with EtOAc (10 mL×3) gave combined organic layers, which were washed with brine (10 mL), dried over $MgSO_4$, and concentrated in vacuo to give a residue. This residue was subjected to silica gel column chromatography (EtOAc/hexane=1:10) to afford the desired tertiary alcohol product. The enantiomeric purity was determined by GC on chiral column.

4.4.1. 2-Phenylbutan-2-ol.[40] Colorless oil, $[\alpha]_D^{28.3}$ +16.5 (*c* 1.0, acetone) for 87% ee (*R*) [lit.[40] $[\alpha]_D^{20.0}$ −16.7 (*c* 0.72, acetone) for 96% ee (*S*)]; R_f=0.30 (EtOAc/hexane=1:8). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.4 Hz, 3H), 1.58 (s, 3H), 1.77 (s, 1H), 1.87 (m, 2H), 7.24–7.47 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 8.3, 29.6, 36.7, 74.9, 124.9, 126.5, 128.1, 147.8. The ee value was determined by Chiral GC Chirasil Dex CB [column temperature: 130 °C, t_R=9.9 min (minor, *S*), t_R=10.3 min (major, *R*)].

4.4.2. 2-[3,5-Bis(trifluoromethyl)]butan-2-ol.[66] Colorless oil, $[\alpha]_D^{29.0}$ +9.9 (*c* 1.80, $CHCl_3$) for 98.4% ee (*R*) [lit.[66] $[\alpha]_D^{20.0}$ −1.1 (*c* 1.0, $CHCl_3$) for 22% ee (*S*)]; R_f=0.30 (EtOAc/hexane=1:10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, *J*=7.5 Hz, 3H), 1.59 (s, 3H), 1.80–1.93 (m, 2H), 1.94–1.99 (m, 1H), 7.76 (s, 1H), 7.90 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.9, 29.7, 36.7, 74.7, 120.6 (m), 122.2, 124.9, 125.4 (d, *J*=3.2 Hz), 131.3, 131.6, 150.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.9. The ee value was determined by Chiral GC Chirasil Dex CB [column temperature: 110 °C, t_R=12.4 min (minor, *S*), t_R=13.6 min (major, *R*)].

Acknowledgements

The authors would like to thank State Key Lab of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences for financial support.

Supplementary data

Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.12.054. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Oslob, J. D.; Akermark, B.; Helquist, P.; Norrby, P. O. *Organometallics* **1997**, *16*, 3015–3021.
2. Lipkowitz, K. B.; D'Hue, C. A.; Sakamoto, T.; Stack, J. N. *J. Am. Chem. Soc.* **2002**, *124*, 14255–14267.
3. Lipkowitz, K. B.; Kozlowski, M. C. *Synlett* **2003**, 1547–1565.
4. Kozlowski, M. C.; Panda, M. *J. Org. Chem.* **2003**, *68*, 2061–2076.
5. Alvarez, S.; Schefzick, S.; Lipkowitz, K.; Avnir, D. *Chem.—Eur. J.* **2003**, *9*, 5832–5837.
6. Kozlowski, M. C.; Dixon, S. L.; Panda, M.; Lauri, G. *J. Am. Chem. Soc.* **2003**, *125*, 6614–6615.
7. Ianni, J. C.; Annamalai, V.; Phuan, P. W.; Panda, M.; Kozlowski, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 5502–5505.
8. Chen, J.; Wen, J. W.; Li, M. Z.; Tianpa, Y. P. *J. Mol. Catal. A: Chem.* **2006**, *258*, 191–197.
9. Urbano-Cuadrado, M.; Carbo, J. J.; Maldonado, A. G.; Bo, C. *J. Chem. Inf. Model.* **2007**, *47*, 2228–2234.
10. Houk, K. N.; Cheong, P. H. Y. *Nature* **2008**, *455*, 309–313.
11. Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358–15374.
12. Donoghue, P. J.; Helquist, P.; Norrby, P. O.; Wiest, O. *J. Am. Chem. Soc.* **2009**, *131*, 410–411.
13. Maldonado, A. G.; Rothenberg, G. *Chem. Soc. Rev.* **2010**, *39*, 1891–1902.
14. Denmark, S. E.; Gould, N. D.; Wolf, L. M. *J. Org. Chem.* **2011**, *76*, 4260–4336.
15. Denmark, S. E.; Gould, N. D.; Wolf, L. M. *J. Org. Chem.* **2011**, *76*, 4337–4357.
16. Jensen, K. H.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4748–4750.
17. Miller, J. J.; Sigman, M. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 771–774.
18. Sigman, M. S.; Miller, J. J. *J. Org. Chem.* **2009**, *74*, 7633–7643.
19. Jensen, K. H.; Sigman, M. S. *J. Org. Chem.* **2010**, *75*, 7194–7201.
20. Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471–17482.
21. Harper, K. C.; Sigman, M. S. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 2179–2183.
22. Harper, K. C.; Sigman, M. S. *Science* **2011**, *333*, 1875–1878.
23. Gustafson, J. L.; Sigman, M. S.; Miller, S. J. *Org. Lett.* **2010**, *12*, 2794–2797.
24. Harper, K. C.; Bess, E. N.; Sigman, M. S. *Nat. Chem.* **2012**, *4*, 366–374.
25. Harper, K. C.; Sigman, M. S. *J. Org. Chem.* **2013**, *78*, 2813–2818.
26. Harper, K. C.; Vilardi, S. C.; Sigman, M. S. *J. Am. Chem. Soc.* **2013**, *135*, 2482–2485.
27. Miller, S. J. *Nat. Chem.* **2012**, *4*, 344–345.
28. Rudolph, J.; Bolm, C.; Norrby, P. O. *J. Am. Chem. Soc.* **2005**, *127*, 1548–1552.
29. Sciabola, S.; Alex, A.; Higginson, P. D.; Mitchelll, J. C.; Snowden, M. J.; Morao, I. *J. Org. Chem.* **2005**, *70*, 9025–9027.
30. Zhu, H. J.; Jiang, J. X.; Saebo, S.; Pittman, C. U. *J. Org. Chem.* **2005**, *70*, 261–267.
31. Huang, J.; Ianni, J. C.; Antoline, J. E.; Hsung, R. P.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 1565–1568.
32. Kozlowski, M. C.; Ianni, J. C. *J. Mol. Catal. A: Chem.* **2010**, *324*, 141–145.
33. Huang, H. Y.; Zong, H.; Bian, G. L.; Song, L. *J. Org. Chem.* **2012**, *77*, 10427–10434.
34. Fuji, K. *Chem. Rev.* **1993**, *93*, 2037–2066.
35. Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388–401.
36. Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886.
37. Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 284–287.
38. Ramon, D. J.; Yus, M. *Tetrahedron Lett.* **1998**, *39*, 1239–1242.
39. Ramon, D. J.; Yus, M. *Tetrahedron* **1998**, *54*, 5651–5666.
40. Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10970–10971.
41. Yus, M.; Ramon, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2002**, *13*, 2291–2293.
42. Yus, M.; Ramon, D. J.; Prieto, O. *Eur. J. Org. Chem.* **2003**, 2745–2748.
43. Yus, M.; Ramon, D. J.; Prieto, O. *Tetrahedron: Asymmetry* **2003**, *14*, 1103–1114.
44. de Parrodi, C. A.; Walsh, P. J. *Synlett* **2004**, 2417–2420.
45. Forrat, V. J.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2005**, *16*, 3341–3344.
46. Jeon, S. J.; Li, H. M.; Garcia, C.; LaRochelle, L. K.; Walsh, P. J. *J. Org. Chem.* **2005**, *70*, 448–455.
47. Jeon, S. J.; Li, H. M.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416–16425.
48. Cozzi, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 2951–2954.
49. Hatano, M.; Miyamoto, T.; Ishihara, K. *Org. Lett.* **2007**, *9*, 4535–4538.
50. Fernandez-lbanez, M. A.; Macia, B.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2008**, 2571–2573.
51. Forrat, V. J.; Ramon, D. J.; Yus, M. *Tetrahedron: Asymmetry* **2008**, *19*, 537–541.
52. Hanato, M.; Ishihara, K. *Chem. Rec.* **2008**, *8*, 143–155.
53. Hatano, M.; Mizuno, T.; Ishihara, K. *Tetrahedron* **2011**, *67*, 4417–4424.
54. Hatano, M.; Gouzu, R.; Mizuno, T.; Abe, H.; Yamada, T.; Ishihara, K. *Catal. Sci. Technol.* **2011**, *1*, 1149–1158.
55. Shen, B.; Huang, H. Y.; Bian, G. L.; Zong, H.; Song, L. *Chirality* **2013**, *25*, 561–566.
56. Verloop, A.; Tipker, J. In *QSAR in Drug Design and Toxicology*; Hadzi, D., Borka, J. B., Eds.; Elsevier: Amsterdam, 1987; pp 97–100.
57. Hansch, C.; Leo, A. *Exploring QSAR: Fundamentals and Applications in Chemistry and Biology*; American Chemical Society: Washington, DC, 1995.
58. Hansch, C.; Leo, A.; Hoekma, D. *Exploring QSAR: Hydrophobic, Electronic, and Steric Constants*; American Chemical Society: Washington, DC, 1995.
59. Consonni, V.; Todeschini, R. *Handbook of Molecular Descriptors*; Wiley-VCH: Weinheim, Germany/New York, NY, 2000; pp 297–298.
60. Kubinyi, H. *QSAR: Hansch Analysis and Related Approaches*; Wiley-VCH: Weinheim, Germany/New York, NY, 1993; pp 40–43.
61. Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552–1556.
62. Charton, M. *J. Org. Chem.* **1976**, *41*, 2217–2220.
63. Taft, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 2729–2732.
64. Taft, R. W. *J. Am. Chem. Soc.* **1953**, *75*, 4538–4539.
65. Charton, M. *J. Org. Chem.* **1977**, *42*, 3535–3538.
66. Madduri, A. V. R.; Harutyunyan, S. R.; Minnaard, A. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 3164–3167.