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Correlating the Effects of the N-Substituent Sizes of Chiral 1,2-Amino Phosphinamide Ligands on Enantioselectivities in Catalytic Asymmetric Henry Reaction Using Physical Steric Parameters

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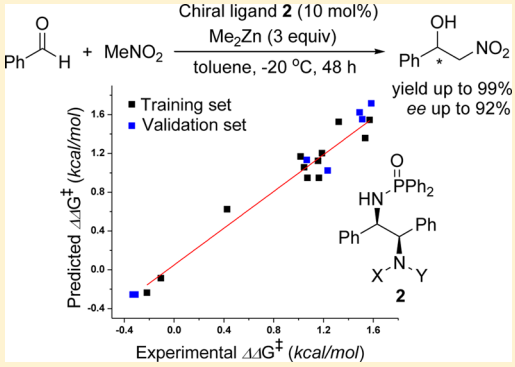
Supporting Information

ABSTRACT: In this study, a series of mono- and dialkylated chiral 1,2-amino phosphinamide ligands derived from modular (1*R*,2*R*)-diphenylethylenediamine were successfully applied in the chiral 1,2-amino phosphinamide-Zn(II) catalyzed asymmetric Henry reaction between benzaldehyde and nitromethane. Although the chiral N-monosubstituted and N,N-disubstituted 1,2-amino phosphinamide ligands gave the main alcohol products with opposite configurations, a validated quantitative structure−activity relationship (QSAR) mathematical model could be constructed between the physical Sterimol steric parameters of the N-substituents of the chiral ligands and the enantiomeric ratios of the alcohol products produced in the asymmetric Henry reaction. Since two sets of N-substituents are involved in the QSAR model construction, the key factor to succesfully construct a highly correlative and predictive model is to appropriately assign the N-substitutents. Ligand optimization based on the established QSAR model led to chiral 1,2-amino phosphinamide ligand **2r**, which produced (*R*)-*β*-nitroalcohol in excellent yield and enantioselectivity (99% yield and 92% *ee*). In addition, a quantitative correlation could also be established with the use of subtractive Sterimol parameters.



1. INTRODUCTION

The development of highly efficient transformations for catalytic asymmetric reactions relies on the identification and optimization of chiral catalysts. Therefore, over the past three decades, great effort was focused on the development of chiral catalysts;[1−4] however, most approaches are based on empirical and qualitative observations despite the fact that great progress has been made by computer methods.[5−19] Sigman and co-workers have made important advances in the design and optimization of chiral catalysts using quantitative methods.[20−28] They demonstrated that a quantitative structure−activity relationship (QSAR) model between steric parameters of chiral ligand substituents and enantiomeric ratios of the outcome products could be established, which could provide insight into the transition state and be used to optimize the structure of chiral catalysts. Inspired by their pioneer work, we quantitatively evaluated the ligand substituent effect on enantioselectivities in the asymmetric ethylation reactions of aldehydes and ketones using physical parameters such as Charton and Sterimol values.[29,30]

The asymmetric Henry reaction is a very useful carbon−carbon bond formation process in organic chemistry.[31−34] It could provide *β*-hydroxy nitroalkanes, which are useful intermediates for the syntheses of polyfunctionalized molecules and biologically active compounds.[35−39] Since the pioneer work on the first asymmetric Henry reaction disclosed by Shibasaki in 1992,[40] a variety of metal-catalyzed (Zn,[41−52] Cu,[53−61] Cr,[62] Mg,[63] or Co[64]) and organocatalyzed reaction systems[65−70] were developed. Some excellent results were obtained using metal-based bifunctional chiral catalysts to doubly activate the aldehyde and nitroalkane as reported by Shibasaki et al.[31,40−42,54] In our previous investigations, a series of chiral 1,2-diamino phosphinamide ligands based on (1*R*,2*R*)-1,2-diphenylethylenediamine and (1*R*,2*R*)-1,2-diaminocyclohexane were synthesized and applied in the ethylation reactions of adehydes and ketones as conjugated Lewis acid−base catalysts, which afforded excellent yields and enantioselectivities.[29,30] As part of a continuing effort to develop highly efficient asymmetric reactions, the purpose of this investigation is to explore the catalytic efficiency of (1*R*,2*R*)-1,2-diamino phosphinamide-Zn(II) complexes as bifunctional catalysts in the asymmetric Henry reaction and correlate the physical steric parameters of the N-substituents of these chiral ligands to the enantiomeric ratios of the outcome products. We found that N-monosubstituted ligands gave (*R*)-alcohols and N,N-disubstituted ligands gave (*S*)-alcohols as the main products in the Henry reaction despite that all of the chiral 1,2-diamino phosphinamide ligands gave (*R*)-alcohols as the main products in our previous studied ethylation reactions of aldehydes and ketones. Successfully, by appropriately assigning the N-substitutents of the ligands, a predictive QSAR model was

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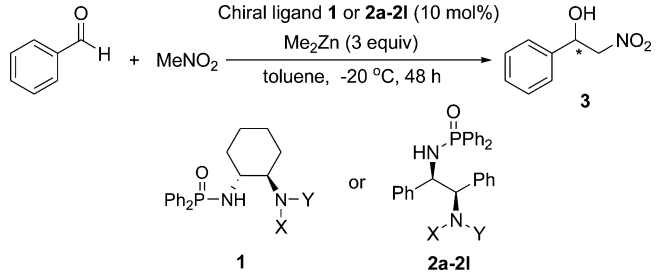
Table 1. Evaluation of (1*R*,2*R*)-1,2-Diamino Phosphinamide Chiral Ligands 1 and 2a−2l in the Asymmetric Henry Reaction between Benzaldehyde and Nitromethane



entry	ligand	X	Y	yield (%)[a]	average *er*[b] (%)	average $\Delta\Delta G^{\ddagger}$[c]	predicted $\Delta\Delta G^{\ddagger}$[d]	residual[e]
1	**1**	H	*i*-Pr	70	73.5:26.5	0.513		
2	**2a**	H	H	23	70:30	0.426	0.625	−0.199
3	**2b**	Me	Me	15	39.3:60.7	−0.218	−0.237	0.019
4	**2c**	Et	Et	39	44.7:55.3	−0.107	−0.087	−0.02
5	**2d**	H	Et	76	89.4:10.6	1.071	0.948	0.123
6	**2e**	H	*i*-Pr	81	91:9	1.163	0.948	0.215
7	**2f**	H	Bu	80	88.3:11.7	1.016	1.168	−0.152
8	**2g**	H	CH_2Bu	81	91.4:8.6	1.188	1.203	−0.015
9	**2h**	H	*c*-Hex	52	90.9:9.1	1.156	1.124	0.032
10	**2i**	H	$CHEt_2$	65	88.9:11.1	1.045	1.057	−0.012
11	**2j**	H	Bn	95	95.5:4.5	1.535	1.359	−0.176
12	**2k**	H	$CH_2(p\text{-}CH_3C_6H_4)$	98	95.8:4.2	1.571	1.546	0.025
13	**2l**	H	CH_2(1-Nap)	85	93.3:6.7	1.323	1.527	−0.204

[a]Isolated yields. [b]*er* is *R*/*S*, which was determined by a chiral high performance liquid chromatography (HPLC) analysis, and each *er* was performed twice and averaged. [c]Estimated at 253 K (−20 °C), $\Delta\Delta G^{\ddagger} = RT \ln(R/S)$, R = 0.001986 kcal K^{-1} mol^{-1}. [d]Calculated by eq 2. [e]Residual = experimental $\Delta\Delta G^{\ddagger}$ − predicted $\Delta\Delta G^{\ddagger}$.

established to instruct the design and optimization of the chiral ligands.

2. RESULTS AND DISCUSSION

With a variety of (1*R*,2*R*)-1,2-diamino phosphinamide ligands in hand, we first examined the catalytic efficiencies of chiral ligands **1** and **2e** in the catalytic asymmetric addition of nitromethane to benzaldehyde (Table 1, entries 1 and 6). Chiral ligand **1**, which was highly efficient in the asymmetric addition reactions between diethylzinc and aldehyde,[29,71] afforded only 70% yield and 47% enantiomeric excess (*ee*) of the alcohol product **3**; however, chiral ligand **2e** afforded **3** with 81% yield and 82% *ee*. Therefore, a series of chiral 1,2-diamino phosphinamide ligands **2a−2l** derived from (1*R*,2*R*)-1,2-diphenylethylenediamine with systematically modified *N*-alkyl groups were applied in the catalytic asymmetric Henry reaction, which provided 12 enantiomeric ratios (Table 1, entries 2−13). Then, Verloop's Sterimol parameters[72−74] (B_1, B_5, and L) were used to quantitatively correlate the steric effect of the N-substituent sizes of the chiral ligands on the enantioselectivities (Figure 1).

The Sterimol parameters used in our investigation are listed in Table 2. The Sterimol parameters of the X and Y substituents attached on the N atom of (1*R*,2*R*)-1,2-diamino phosphinamide ligands **2a−2l** were used, and two sets of three-dimensional Sterimol parameters were evaluated simultaneously using eq 1 as the pool of terms from which all models could be constructed:

$$\Delta\Delta G^{\ddagger} = z0 + aB_{1X} + bB_{5X} + cL_X + dB_{1Y} + eB_{5Y} + fL_Y \quad (1)$$

(z, a, b, c.....f are coefficients of the equation)

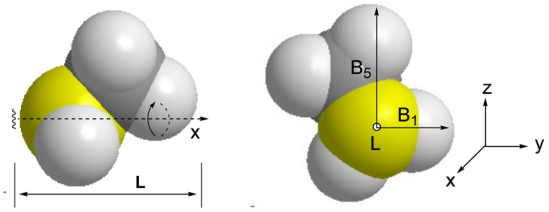


Figure 1. Verloop's Sterimol parameters using ethyl group as an example (L, length of the substituent measured along the axis of the primary bond that joins the substituent to the parent molecule; B_1, minimum width orthogonal to the primary bond; B_5, maximum width orthogonal to the primary bond).

Equation 1 included all of the Sterimol subparameters of the X substituent (B_{1X}, B_{5X}, and L_X) and Y substituent (B_{1Y}, B_{5Y}, and L_Y) of chiral ligands **2a−2l**.

As one of the most classical and commonly used statistical methods for the construction of QSAR models, a multiple linear regression was applied in our investigation. To avoid the chance correlations among terms, exclude the terms that destabilize regression models, and keep the significance of the models, a stepwise regression was introduced in the process of multiple linear regression. By performing a forward stepwise regression analysis on the system by adding one term in each step and optimizing the generated model based on *F*-tests of statistical significance for the model and *p*-tests for the individual coefficients, three models were generated with three steps. The corresponding statistical parameters of each model generated in each step, such as the correlation coefficient (R^2), cross-validated correlation coefficient (q^2), root−mean−square error (RMSE), and *F*-test value, which could be used to evaluate the robustness of a QSAR model, are listed in Table 3.

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Table 2. Calculated Sterimol Parameters[a] (B_1, B_5, L) of R-Groups

entry	R-group	B_1	B_5	L	entry	R-group	B_1	B_5	L
1	H	1.17	1.17	2.20	10	$CHEt_2$	2.26	4.13	5.41
2	Me	1.70	2.22	3.04	11	Bn	1.70	6.20	5.44
3	Et	1.71	3.38	4.33	12	CH_2(*p*-ClC_6H_4)	1.72	7.52	5.07
4	*i*-Pr	2.10	3.38	4.27	13	CH_2(*p*-$CF_3C_6H_4$)	1.71	8.01	5.74
5	Bu	1.71	4.89	6.39	14	CH_2(*p*-$CH_3C_6H_4$)	1.70	7.48	5.73
6	CH_2*i*-Pr	1.71	4.65	5.21	15	CH_2(*p*-$CH_3OC_6H_4$)	1.70	8.65	4.90
7	*s*-Bu	2.12	3.91	5.30	16	CH_2(1-Nap)	1.70	7.35	4.23
8	CH_2Bu	1.71	5.13	7.26	17	CH_2(*p*-FC_6H_4)	1.70	7.09	4.65
9	*c*-C_6H_{11}	2.08	4.59	5.46	18				

[a]Sterimol parameters of R-groups used in this investigation were calculated using Molecular Modeling Pro software available from ChemSW.

Table 3. Results of Forward Stepwise Regression Analysis

step	added term	R^2	RMSE	F	q^2
1	B_{1X}	0.756	0.304	30.957	0.692
2	B_{1X}, B_{5Y}	0.947	0.149	80.951	0.896
3	B_{1X}, B_{5Y}, B_{1Y}	0.960	0.137	64.212	0.890

In step one, B_{1X} was introduced and a model with $R^2 = 0.756$ and RMSE = 0.304 was generated. In step two, B_{1X} and B_{5Y} were used as the terms, the corresponding model was obtained with much better values of $R^2 = 0.947$ and RMSE = 0.149, which indicates the improvement of the model's fitting ability. The addition of B_{1Y} in step three only improved the R^2 and RMSE values slightly. Since the R^2 value is necessary but not sufficient to evaluate a QSAR model, the best model was also evaluated based on the q^2 value and the *F*-test value. In the process of a leave-one-out cross validation, the q^2 value with B_{1X} in step one increased from 0.692 to 0.896 with the addition of B_{5Y} in step two and then decreased to 0.890 with the further addition of B_{1Y} in step three, which indicates that the model with B_{1X} and B_{5Y} as terms has the best predictive ability. In addition, the model with B_{1X} and B_{5Y} as terms also has the largest *F* value. As a result, the corresponding eq 2, based on B_{1X} and B_{5Y}, was chosen as the best fitted model:

$$\Delta\Delta G^{\ddagger} = 2.696 - 1.916B_{1X} + 0.146B_{5Y} \quad (2)$$

$R^2 = 0.947$, $q^2 = 0.896$, $F = 80.951$, RMSE = 0.149, $p = 1.76 \times 10^{-6}$

Equation 2 shows that the $\Delta\Delta G^{\ddagger}$ value strongly depends on the B_{1X} term because of its big coefficient compared to that of B_{5Y} (for details, see the Supporting Information). Therefore, a smaller proximal steric bulk of the X group will lead to a larger increase of the $\Delta\Delta G^{\ddagger}$ value. Obviously, a more positive value of $\Delta\Delta G^{\ddagger}$ indicates a higher enantioselectivity of the asymmetric Henry reaction for the (*R*)-alcohol product, and a more negative value of $\Delta\Delta G^{\ddagger}$ indicates a higher enantioselectivity of the asymmetric Henry reaction for the (*S*)-alcohol product. Therefore, the $NHCH_2$(*p*-MeC_6H_4) group of the chiral 1,2-amino phosphinamide ligand **2k** with the smallest B_{1X} value and the largest B_{5Y} value gave the (*R*)-alcohol product with the highest optical purity in the reaction among the 12 chiral ligands **2a**–**2l**. A plot of the predicted and experimentally determined $\Delta\Delta G^{\ddagger}$ values (Figure 2) is linear with a slope = 0.948, an intercept = 0.050, and $R^2 = 0.942$.

A leave-one-out cross-validation was performed to examine the predictive power of eq 2. The results are listed in Table 4, and the obtained q^2 value is 0.896. Tropsha[75,76] pointed out that an acceptable predictive model should satisfy the following criteria: $q^2 > 0.5$; $R^2 > 0.6$; $[(R^2 - R_0^2)/R^2] < 0.1$; and $0.85 \le k \le 1.15$ (see the Supporting Information for the definitions of R_0^2 and *k* as described by Tropsha). Our model well satisfies these criteria with $q^2 = 0.896$; $R^2 = 0.947$; $(R^2 - R_0^2)/R^2 = -0.056$; and $k = 0.999$. The result indicates that eq 2 is a well-accepted predictive model.

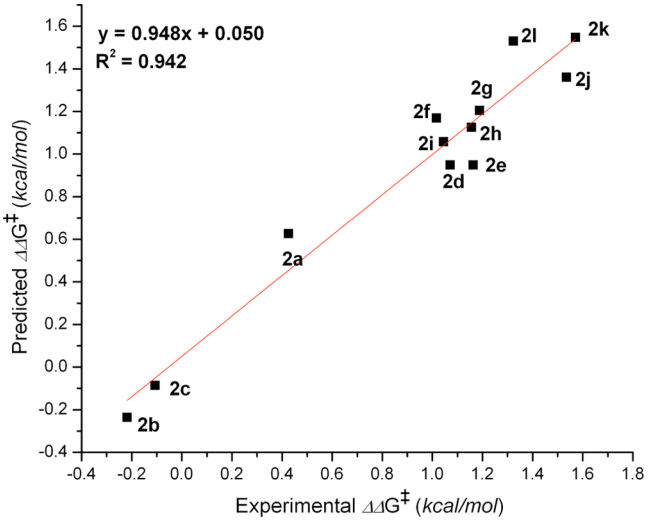

Figure 2. Plot of experimentally determined versus predicted $\Delta\Delta G^{\ddagger}$ values based on a Sterimol analysis.

Eq 2 reveals that B_{1X} and B_{5Y} are the key terms for the model construction; however, when B_{1X} was plotted on one axis and B_{5Y} was plotted along another axis, we found that the B_{1X} and B_{5Y} parameters of ligands **2a**–**2l** are unevenly spread as shown in Figure 3. We wondered if the removal of the chiral ligands **2e**, **2f** and **2l** from eq 2 to make these ligands spread more evenly in B_{5Y} dimension would have a positive effect on the predictive ability of the model. As shown below, the generated new eq 3 is different from eq 2 only in the values of the coefficients and constant with $q^2 = 0.953 > 0.5$; $R^2 = 0.984 > 0.6$; $(R^2 - R_0^2)/R^2 = -0.016 < 0.1$; and $0.85 \le k \approx 1.00 \le 1.15$. The above statistic paremeters are even better than those of eq 2, which implies that the omission of the uneven data may lead to better predictive model.

$$\Delta\Delta G^{\ddagger} = 2.468 - 1.839B_{1X} + 0.180B_{5Y} \quad (3)$$

$R^2 = 0.984$, $q^2 = 0.953$, $F = 183.036$, RMSE = 0.097, $p = 4.19 \times 10^{-6}$

To develop an even more efficient chiral ligand other than **2k** and at the same time to further evaluate the predictive power of eq 2, an additional seven chiral 1,2-diamino phosphinamide ligands **2m**–**2s** were synthesized and used in the asymmetric Henry reaction between benzaldehyde and nitromethane, and

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Table 4. Leave-One-out Cross-Validation Results for Eq 2

entry	ligand	measured $\Delta\Delta G^{\ddagger}$	predicted $\Delta\Delta G^{\ddagger}$	entry	ligand	measured $\Delta\Delta G^{\ddagger}$	predicted $\Delta\Delta G^{\ddagger}$
1	**2a**	0.426	0.807	7	**2g**	1.188	1.203
2	**2b**	−0.218	−0.257	8	**2h**	1.156	1.119
3	**2c**	−0.107	−0.067	9	**2i**	1.045	1.058
4	**2d**	1.071	0.924	10	**2j**	1.535	1.324
5	**2e**	1.163	0.907	11	**2k**	1.571	1.532
6	**2f**	1.016	1.184	12	**2l**	1.323	1.610

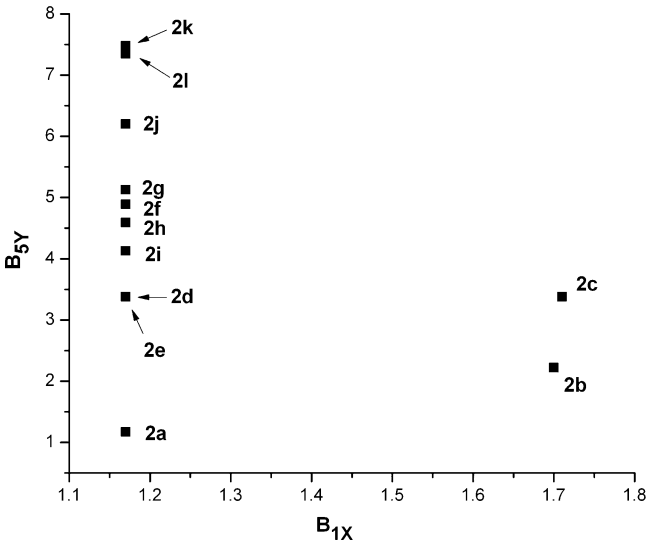


Figure 3. B_{1X} and B_{5Y} values for ligands **2a**−**2l**.

their measured enantioselectivities were compared to the values predicted by eq 2 and listed in Table 5.

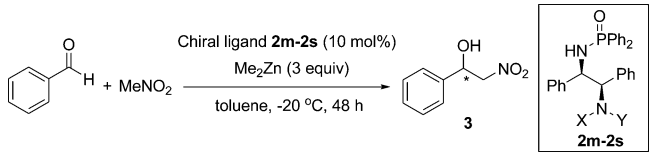
Notably, the appropriate assignment of the two different alkyl groups of the asymmetric N,N-disubstituted ligands **2m** and **2s** (Table 5, entries 1 and 7) to X and Y in Table 5 is important for a correct prediction. The predictive model of eq 2 was established on the basis of Y as the big alkyl group and X as the small alkyl group and gave a positive $\Delta\Delta G^{\ddagger}$ value to show the higher enantioselectivity of the asymmetric Henry reaction to the (*R*)-alcohol (Table 1). Therefore, for the N,N-disubstituted ligands that offered the (*S*)-alcohol as the main product, the big alkyl group should be assigned to X and the small alkyl group should be assigned to Y to give a negative $\Delta\Delta G^{\ddagger}$ value to show the higher enantioselectivity of the asymmetric Henry reaction to the (*S*)-alcohol. As shown in Table 5, just as predicted by eq 2, the chiral ligand **2r**, with the smallest B_{1X} value and largest B_{5Y} value, is the most efficient chiral ligand, which give the largest positive $\Delta\Delta G^{\ddagger}$ value and could promote the asymmetric Henry reaction to afford the (*R*)-alcohol product with 92% *ee*. In addition, the chiral ligand **2m** gives the largest negative $\Delta\Delta G^{\ddagger}$ value and could promote the asymmetric Henry reaction to afford the (*S*)-alcohol product with 32% *ee*.

The comparison between the measured $\Delta\Delta G^{\ddagger}$ and predicted $\Delta\Delta G^{\ddagger}$ values for **2m**−**2s** is depicted in Figure 4 with a slope = 0.995 between 0.6 and 1.4, which indicates that eq 2 is a highly predictive model.[27] For these testing sets, the corresponding statistical parameters are listed as follows: $q_{ext}^2 = 0.978 > 0.5$; $R^2 = 0.978 > 0.6$; $(R^2 - R_0^2)/R^2 = -0.02 < 0.1$; $0.85 \le k = 0.968 \le 1.15$. These parameters further demonstrate that eq 2 has good stability and predictive power. In addition, all of the residuals of the 19 chiral ligands in Table 1 and Table 5 distribute between −2RMSE and +2RMSE, which implies that no outlier exists in the model.

Moreover, as shown in Table 5, entries 4−6, CF_3-, Cl-, and CH_3O- substituted ligands gave 45%, 80%, and 99% yields of the corresponding alcohol products with similar *ee* values, respectively. This result indicates that the electronic effect affects the reaction activity dramatically but has little influence on the reaction enantioselectivity. Therefore, it is steric hindrance that plays a key role for the enantioselectivity of the asymmetric reaction.

Obviously, the steric differentiation between the X and Y groups is very important for the chiral ligands. For example, the catalytic efficiency of the chiral ligand **2m** with an N(Me)Et

Table 5. Experimental and Predicted *ee* Values of the Asymmetric Henry Reaction Catalyzed by Chiral Phosphinamide Ligands 2m−2s



entry	ligand	X	Y	yield (%)[a]	*er* (%)[b]	measured $\Delta\Delta G^{\ddagger}$[c]	predicted $\Delta\Delta G^{\ddagger}$[d]	residual[e]
1	**2m**	Et	Me	31	34:66	−0.332	−0.256	−0.076
2	**2n**	H	CH_2*i*-Pr	85	89.3:10.7	1.066	1.133	−0.067
3	**2o**	H	*s*-Bu	76	92.1:7.9	1.234	1.025	0.209
4	**2p**	H	CH_2(*p*-ClC_6H_4)	80	95.3:4.7	1.512	1.552	−0.04
5	**2q**	H	CH_2(*p*-$CF_3C_6H_4$)	45	95.1:4.9	1.490	1.624	−0.134
6	**2r**	H	CH_2(*p*-$MeOC_6H_4$)	99	95.9:4.1	1.584	1.717	−0.133
7	**2s**	CH_2Bu	Me	33	35:65	−0.311	−0.256	−0.055

[a]Isolated yields. [b]*er* is *R*/*S*, which was determined by a chiral HPLC analysis. [c]Estimated at 253 K (−20 °C); $\Delta\Delta G^{\ddagger} = RT \ln(R/S)$; $R = 0.001986$ kcal K^{-1} mol^{-1}. [d]Predicted $\Delta\Delta G^{\ddagger}$ was calculated by eq 2. [e]Residual = experimental $\Delta\Delta G^{\ddagger}$ − predicted $\Delta\Delta G^{\ddagger}$.

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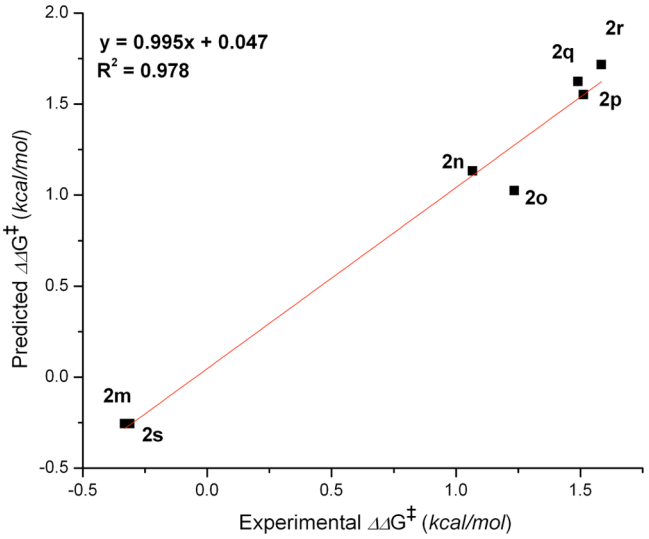


Figure 4. Plot of experimental $\Delta\Delta G^{\ddagger}$ values versus predicted $\Delta\Delta G^{\ddagger}$ values from eq 2 for ligands **2m**−**2s** in the asymmetric Henry reaction.

group is better than those of **2b** and **2c** with NMe_2 and NEt_2 groups, respectively. To evaluate the differential effect of X- and Y-substituted ligands **2d**−**2s** with different X and Y substituents, a new model of eq 4 was obtained (for details, see the Supporting Information) using subtractive Sterimol parameters (Table 6).

The subtracted Sterimol-based mathematical model of eq 4 shows that the $\Delta\Delta G^{\ddagger}$ value strongly depends on the B_{1S} and B_{5S} terms. The positive coefficients of B_{1S} and B_{5S} indicate that the larger the difference between B_1 and B_5 parameters of the X and Y substituents, the higher the enantioselectivity of the alcohol product would be observed. Eq 4 is also stable and predictive with $q^2 = 0.886$; $R^2 = 0.934$; $(R^2 - R_0^2)/R^2 = -0.071$; and $k = 0.999$.

$$\Delta\Delta G^{\ddagger} = 0.112 + 0.631B_{1S} + 0.165B_{5S} \quad (4)$$

$R^2 = 0.934$, $q^2 = 0.886$, $F = 92.493$, RMSE = 0.160, $p = 2.05 \times 10^{-8}$

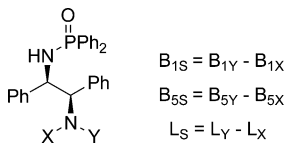
A plot of the predicted and experimentally determined $\Delta\Delta G^{\ddagger}$ values (Figure 5) is linear with a slope = 0.935, an intercept = 0.071, and $R^2 = 0.930$.

To evaluate the predictive power of eq 4, two chiral 1,2-diamino phosphinamide ligands **2t** and **2u** containing two different X and Y groups were synthesized and used in the asymmetric Henry reaction between benzaldehyde and nitromethane. Their measured enantioselectivities were compared to the values predicted by eq 4 and listed in Table 7. The predicted $\Delta\Delta G^{\ddagger}$ values are in good agreement with the measured $\Delta\Delta G^{\ddagger}$ values, which indicates that eq 4 is also reliable and powerful in prediction. Mechanistically, the validation of the subtracted Sterimol-based mathematical model of eq 4 indicates that a bigger steric differentiation between the X and Y groups could result in a better asymmetric environment of the transition state for a higher enantioselectivity.

3. CONCLUSION

In conclusion, we successfully developed a novel chiral 1,2-diamino phosphinamide-Zn(II) catalyzed asymmetric Henry reaction. The effects of the N-substituent sizes of chiral ligands on the enantioselectivities in the asymmetric Henry reaction were correlated using physical steric Sterimol parameters and a predictive QSAR model, which was constructed to guide the ligand optimization. For N,N-disubstituted ligands with two different alkyl groups, the appropriate assignment of the two different alkyl groups is important for a correct prediction. A highly correlated model was also established based on subtractive Sterimol parameters. In addition, the electronic effect of the substituent on the reaction activity is dramatic, but it has little influence on the enantioselectivity. An investigation is currently under way to apply the quantitative methodology of

Table 6. Calculated Subtractive Sterimol Parameters (B_{1S}, B_{5S}, L_S)



$B_{1S} = B_{1Y} - B_{1X}$
$B_{5S} = B_{5Y} - B_{5X}$
$L_S = L_Y - L_X$

entry	ligand	X	Y	B_{1S}	B_{5S}	L_S
1	**2d**	H	Et	0.54	2.21	2.13
2	**2e**	H	*i*-Pr	0.93	2.21	2.07
3	**2f**	H	Bu	0.54	3.72	4.19
4	**2g**	H	CH_2Bu	0.54	3.96	5.06
5	**2h**	H	*c*-Hex	0.91	3.42	3.26
6	**2i**	H	$CHEt_2$	1.09	2.96	3.21
7	**2j**	H	Bn	0.53	5.03	3.24
8	**2k**	H	$CH_2(p\text{-}CH_3C_6H_4)$	0.53	6.31	3.53
9	**2l**	H	$CH_2(1\text{-}NapCH_2)$	0.53	6.18	2.03
10	**2m**	Et	Me	−0.01	−1.16	−1.29
11	**2n**	H	CH_2i-Pr	0.54	3.48	3.01
12	**2o**	H	*s*-Bu	0.95	2.74	3.10
13	**2p**	H	$CH_2(p\text{-}ClC_6H_4)$	0.55	6.35	2.87
14	**2q**	H	$CH_2(p\text{-}CF_3C_6H_4)$	0.54	6.84	3.54
15	**2r**	H	$CH_2(p\text{-}CH_3OC_6H_4)$	0.53	7.48	2.70
16	**2s**	CH_2Bu	Me	−0.01	−2.91	−4.22
17	**2t**	H	$CH_2(p\text{-}FC_6H_4)$	0.53	5.92	2.45
18	**2u**	CH_2i-Pr	Me	−0.01	−2.43	−2.17

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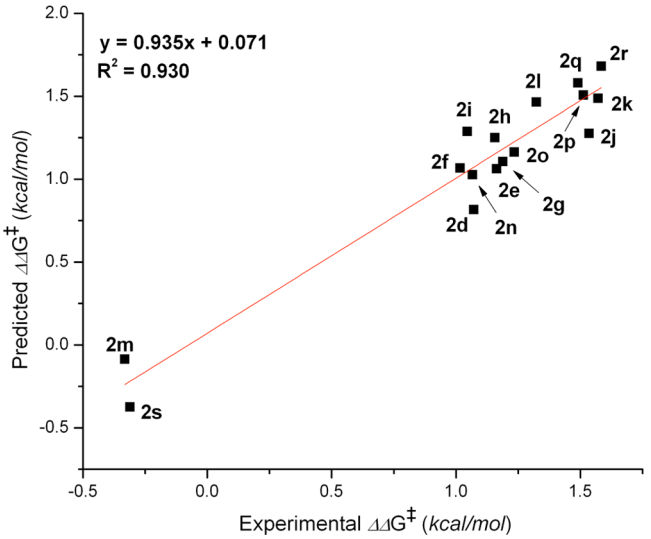


Figure 5. Plot of experimental $\Delta\Delta G^{\ddagger}$ values versus predicted $\Delta\Delta G^{\ddagger}$ values from eq 4 for ligands **2d**–**2s** in the asymmetric Henry reaction.

the design and optimization of catalysts in other catalytic asymmetric reaction systems.

4. EXPERIMENTAL SECTION

4.1. General Methods. All of the 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), ^{31}P NMR (162 MHz), and ^{19}F NMR (376 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 of the solvents were purified and dried prior to use according to standard methods.[77] Optical rotations were measured on a polarimeter and reported as follows: $[\alpha]_D^T$ (c g/100 mL, solvent). The high performance liquid chromatography (HPLC) analysis was performed using Chiralcel columns. High resolution mass spectra (HRMS) were obtained by electrospray ionization (ESI) sources using the time-of-flight mass spectrometry (TOF MS) technique.

4.2. Synthesis of Chiral Ligands 1, 2a–2h, and 2m–2o. Chiral ligand **1** was synthesized according to the reported procedure.[29] Mp, 113–114 °C; $[\alpha]_D^{22.0}$, −41.2 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89–0.98 (m, 1H), 1.02 (d, J = 6.1 Hz, 3H), 1.06 (d, J = 6.3 Hz, 3H), 1.12–1.27 (m, 3H), 1.49–1.76 (m, 3H), 1.97–2.10 (m, 2H), 2.22–2.37 (m, 1H), 2.73–3.00 (m, 2H), 3.90 (s, 1H), 7.33–7.55 (m, 6H), 7.79–8.01 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 24.5, 24.8, 25.0, 32.4, 34.4, 45.7, 56.0, 60.0 (d, J = 6.8 Hz), 128.3, 128.4, 128.5, 131.52, 131.54, 131.62, 131.7, 132.0, 132.1, 133.1, 133.3, 134.3, 134.6.

Chiral ligands **2a**–**2h** and **2m**–**2o** were synthesized according to the reported procedure.[30] Chiral ligand **2a**: Mp, 217–218 °C; $[\alpha]_D^{31.1}$, −48.2 (c 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (s, 2H), 4.23–4.32 (m, 1H), 4.33–4.37 (m, 1H), 4.43–4.54 (m, 1H), 7.11–7.6 (m, 18H), 7.62–7.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.3, 61.4, 126.8, 127.1, 127.2, 127.5, 128.1, 128.18, 128.23, 131.2, 131.32, 131.34, 131.49, 131.52, 132.0, 132.13, 132.17, 132.28, 132.5, 133.6, 141.5, 142.4.

Chiral ligand **2b**: Mp, 197–198 °C; $[\alpha]_D^{31.4}$, 48.1 (c 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.24 (s, 6H), 3.72 (d, J = 10.7 Hz, 1H), 4.84 (t, J = 10.9 Hz, 1H), 5.37 (s, 1H), 6.79–6.91 (m, 3H), 6.92–6.99 (m, 2H), 7.01–7.11 (m, 4H), 7.12–7.25 (m, 4H), 7.39–7.64 (m, 5H), 7.86–7.98 (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, 127.3, 127.37, 127.39, 127.49, 127.52, 128.3, 128.5, 128.6, 129.9, 130.69, 130.72, 131.2, 131.3, 131.4, 131.47, 132.5, 133.5, 134.8, 140.8.

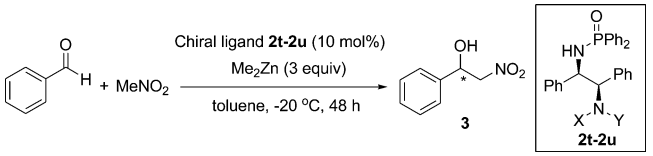
Chiral ligand **2c**: Mp, 167–168 °C; $[\alpha]_D^{31.4}$, 68.1 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, J = 7.0 Hz, 6H), 2.09–2.24 (m, 2H), 2.78–2.98 (m, 2H), 3.97 (d, J = 10.7 Hz, 1H), 4.91 (t, J = 10.7 Hz, 1H), 5.65 (s, 1H), 6.79–6.90 (m, 3H), 6.94–7.01 (m, 2H), 7.03–7.26 (m, 8H), 7.40–7.53 (m, 3H), 7.54–7.64 (m, 2H), 7.84–8.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 42.7, 54.5, 69.8 (d, J = 9.0 Hz), 126.6, 127.2, 127.4, 127.5, 127.6, 128.3, 128.4, 128.6, 128.8, 130.62, 130.65, 131.1, 131.2, 131.39, 131.42, 131.7, 132.3, 132.4, 133.0, 133.6, 134.6, 134.9, 140.9.

Chiral ligand **2d**: Mp, 202–203 °C; $[\alpha]_D^{30.8}$, −55.9 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (t, J = 7.1 Hz, 3H), 1.56–2.20 (br, 1H), 2.27–2.40 (m, 1H), 2.44–2.57 (m, 1H), 3.97 (d, J = 6.0 Hz, 1H), 4.26–4.41 (m, 1H), 4.47–4.60 (m, 1H), 7.06–7.20 (m, 5H), 7.21–7.33 (m, 9H), 7.34–7.43 (m, 2H), 7.46–7.56 (m, 2H), 7.67–7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.0, 41.4, 60.8, 68.6 (d, J = 6.5 Hz), 126.8, 127.1, 127.75, 127.8, 127.9, 128.0, 128.1, 131.2, 131.5, 131.68, 131.73, 131.77, 132.0, 132.1, 132.8, 133.0, 140.3, 140.76, 140.78.

Chiral ligand **2e**: Mp, 206–207 °C; $[\alpha]_D^{29.9}$, −19.6 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (d, J = 6.2 Hz, 3H), 0.96 (d, J = 6.4 Hz, 3H), 1.32–1.87 (br, 1H), 2.52–2.67 (m, 1H), 4.02 (d, J = 6.3 Hz, 1H), 4.29–4.38 (m, 1H), 4.48–4.65 (m, 1H), 7.05–7.17 (m, 5H), 7.17–7.22 (m, 2H), 7.22–7.34 (m, 7H), 7.34–7.45 (m, 2H), 7.50–7.60 (m, 2H), 7.63–7.76 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 24.3, 45.5, 61.0, 66.1 (d, J = 6.9 Hz), 127.0, 127.3, 127.4, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 131.38, 131.40, 131.49, 131.52, 131.8, 131.9, 132.3, 132.4, 133.21, 133.25, 140.80, 140.82, 140.88.

Chiral ligand **2f**: Mp, 201–202 °C; $[\alpha]_D^{31.3}$, −48.6 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.81 (t, J = 7.3 Hz, 3H), 1.12–1.25 (m, 2H), 1.29–1.42 (m, 2H), 1.61–2.11 (br, 1H), 2.26–2.35 (m, 1H), 2.40–2.55 (m, 1H), 3.92 (d, J = 5.8 Hz, 1H), 4.24–4.41 (m, 1H), 4.44–4.55 (m, 1H), 7.10–7.22 (m, 5H), 7.22–7.26 (m, 2H), 7.26–7.36 (m, 7H), 7.36–7.44 (m, 2H), 7.44–7.55 (m, 2H), 7.65–7.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 20.2, 32.0, 47.0, 61.1, 68.9 (d, J = 6.7 Hz), 127.1, 127.28, 127.33, 128.0, 128.14, 128.19, 128.21,

Table 7. Experimental and Predicted *ee* Values of the Asymmetric Henry Reaction Catalyzed by Chiral Phosphinamide Ligands 2t and 2u



entry	ligand	X	Y	yield (%)[a]	*er* (%)[b]	measured $\Delta\Delta G^{\ddagger}$[c]	predicted $\Delta\Delta G^{\ddagger}$[d]	residual[e]
1	**2t**	H	$CH_2(p\text{-}FC_6H_4)$	81	95.0:5.0	1.479	1.423	0.056
2	**2u**	CH_2i-Pr	Me	52	36.7:63.3	−0.274	−0.295	0.021

[a]Isolated yields. [b]*er* is *R*/*S*, which was determined by a chiral HPLC analysis. [c]Estimated at 253 K (−20 °C); $\Delta\Delta G^{\ddagger} = RT \ln(R/S)$; R = 0.001986 kcal K^{-1} mol^{-1}. [d]Predicted $\Delta\Delta G^{\ddagger}$ was calculated by eq 4. [e]Residual = experimental $\Delta\Delta G^{\ddagger}$ − predicted $\Delta\Delta G^{\ddagger}$.

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128.26, 128.4, 131.5, 131.7, 131.9, 132.0, 132.2, 132.3, 132.9, 133.3, 140.6, 140.96, 140.98.

Chiral ligand **2g**: Mp, 176−177 °C; $[\alpha]_D^{31.5}$, −73.4 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.82 (t, J = 7.3 Hz, 3H), 1.11−1.24 (m, 4H), 1.31−1.41 (m, 2H), 1.56−1.71 (br, 1H), 2.18−2.37 (m, 1H), 2.37−2.52 (m, 1H), 3.92 (d, J = 5.3 Hz, 1H), 4.25−4.52 (m, 2H), 7.11−7.26 (m, 7H), 7.28−7.36 (m, 7H), 7.37−7.52 (m, 4H), 7.65−7.76 (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 = 6.8 Hz), 127.1, 127.29, 127.34, 128.01, 128.03, 128.14, 128.76, 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.

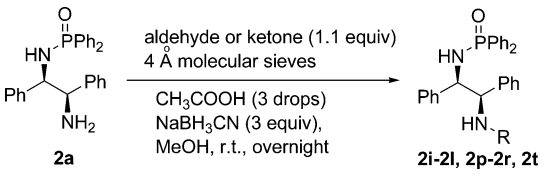
Chiral ligand **2h**: Mp, 204−205 °C; $[\alpha]_D^{31.6}$, −51.4 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.78−0.89 (m, 1H), 0.96−1.20 (m, 4H), 1.40−1.70 (m, 5H), 1.73−1.85 (m, 1H), 2.16−2.32 (m, 1H), 4.07 (d, J = 6.1 Hz, 1H), 4.25−4.35 (m, 1H), 4.48−4.60 (m, 1H), 7.08−7.19 (m, 5H), 7.19−7.25 (m, 2H), 7.25−7.35 (m, 7H), 7.36−7.46 (m, 2H), 7.46−7.54 (m, 2H), 7.64−7.75 (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, 128.1, 128.12, 128.14, 128.3, 128.4, 131.4, 131.5, 131.8, 131.9, 132.0, 132.1, 132.2, 132.3, 133.1, 133.4, 140.9, 141.2.

Chiral ligand **2m**: Mp, 177−178 °C; $[\alpha]_D^{28.9}$, 96.4 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.09 (t, J = 7.1 Hz, 3H), 2.24 (s, 3H), 2.25−2.34 (m, 1H), 2.49−2.62 (m, 1H), 3.82 (d, J = 10.8 Hz, 1H), 4.87 (t, J = 10.8 Hz, 1H), 5.52 (s, 1H), 6.79−6.86 (m, 3H), 6.91−6.98 (m, 2H), 6.99−7.10 (m, 4H), 7.10−7.21 (m, 4H), 7.39−7.61 (m, 5H), 7.82−7.92 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 36.1, 47.3, 54.5, 73.6 (d, J = 8.8 Hz), 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.

Chiral ligand **2n**: Mp, 214−215 °C; $[\alpha]_D^{31.3}$, −26.6 (c 0.50, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.76 (d, J = 6.6 Hz, 6H), 1.55−1.68 (m, 2H), 2.06−2.16 (m, 1H), 2.18−2.28 (m, 1H), 3.86 (d, J = 5.8 Hz, 1H), 4.26−4.48 (m, 1H), 5.52 (s, 1H), 7.08−7.24 (m, 7H), 7.24−7.33 (m, 7H), 7.35−7.49 (m, 4H), 7.62−7.73 (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, 127.30, 128.0, 128.03, 128.13, 128.16, 128.2, 128.3, 131.4, 131.9, 132.0, 132.3, 140.7, 140.9.

Chiral ligand **2o**: Mp, 203−204 °C; $[\alpha]_D^{26.0}$, −56.9 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.55−0.84 (m, 3H), 0.84−0.92 (m, 3H), 1.07−1.45 (m, 3H), 2.20−2.58 (m, 1H), 3.96−4.10 (m, 1H), 4.27−4.39 (m, 1H), 4.54−4.68 (m, 1H), 7.07−7.17 (m, 5H), 7.17−7.21 (m, 1H), 7.21−7.33 (m, 8H), 7.33−7.44 (m, 2H), 7.44−7.61 (m, 2H), 7.62−7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 8.7, 10.4, 19.0, 20.7, 27.3, 30.8, 50.8, 61.1, 65.8 (d, J = 7.2 Hz), 66.2 (d, J = 7.1 Hz), 127.0, 127.3, 127.4, 127.43, 127.87, 127.91, 128.0, 128.07, 128.12, 128.14, 128.26, 128.38, 128.4, 131.4, 131.5 (m), 131.8 (m), 131.9 (m), 132.1, 132.2, 132.22, 132.3, 133.1, 133.2, 133.3, 133.4, 140.7, 140.8, 140.9, 141.2.

4.3. General Procedure for Preparing Chiral Ligands 2i−2l, 2p−2r, and 2t. *4.3.1. [(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenylethyl](pentan-3-yl)amine (2i).* To a stirred solution of **2a** (412 mg, 1.0 mmol) in dried methanol (10 mL) and 4 Å molecular sieves (1g), 3-pentanone (94 mg, 1.1 mmol) was added followed by 3 drops of glacial acetic acid. The reaction mixture was monitored by thin-layer chromatography (TLC) until the imine was formed, then $NaBH_3CN$ (189 mg, 3.0 mmol) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred overnight. The molecular sieves were filtered through filter paper, and the solution was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (20 mL), washed by saturated Na_2CO_3 solution (20 mL), and then dried over anhydrous Na_2SO_4. The solvent was removed to give the crude product, which was subjected to silica gel column chromatography (EtOAc/hexane = 1/2) and afforded 314 mg (65%) of **2i** as a white solid. Mp, 188−189 °C; $[\alpha]_D^{24.8}$, −40.5 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.53 (t, J = 7.4 Hz, 3H), 0.77 (t, J = 7.4 Hz, 3H), 1.21−1.30 (m, 5H), 2.18−2.30 (m, 1H), 3.96 (d, J = 5.9 Hz, 1H), 4.27−4.33 (m, 1H), 4.55−4.58 (m, 1H), 7.06−7.17 (m, 5H), 7.20−7.32 (m, 9H), 7.33−7.50 (m, 4H), 7.62−7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 7.8, 10.4, 23.8, 26.6, 55.5, 61.3, 65.8 (d, J = 7.2 Hz), 127.0, 127.2, 127.3, 127.9, 128.0, 128.07, 128.1, 128.2, 128.25, 128.3, 131.3, 131.36, 131.4, 131.43, 131.8, 132.0, 132.1, 132.2, 133.1, 133.6, 140.9, 141.1; ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.0; HRMS (ESI): (m/z) [M + H]$^+$ calcd for $C_{31}H_{36}N_2OP$, 483.2560; found, 483.2560.



4.3.2. Benzyl[(1R,2R)-2-[(diphenylphosphoroso)amino]-1,2-diphenylethyl]amine (2j). Following the general procedure described for **2i** on the same scale, benzaldehyde (117 mg, 1.1 mmol) was used to replace 3-pentanone and **2j** was obtained as a white solid with the yield of 427 mg (85%). Mp, 204−205 °C; $[\alpha]_D^{20.8}$, −54.2 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20−2.32 (s, 1H), 3.42 (d, J = 13.7 Hz, 1H), 3.74 (d, J = 13.7 Hz, 1H), 3.91 (d, J = 6.1 Hz, 1H), 4.23−4.43 (m, 2H), 7.07−7.18 (m, 7H), 7.22−7.35 (m, 12H), 7.37−7.45 (m, 2H), 7.53−7.60 (m, 2H), 7.71−7.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.7, 60.8, 67.6 (d, J = 6.5 Hz), 126.7, 127.1, 127.3, 127.8, 127.86, 127.91, 128.0, 128.07, 128.11, 128.15, 128.20, 128.24, 131.4, 131.5, 131.6, 131.7, 131.8, 132.1, 132.2, 132.8, 132.9, 139.9, 140.1, 140.59, 140.61; ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.6; HRMS (ESI): (m/z) [M + H]$^+$ calcd for $C_{33}H_{32}N_2OP$, 503.2240; found, 503.2247.

4.3.3. [(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenylethyl][(4-methylphenyl)methyl]amine (2k). The general procedure described for **2i** was followed on the same scale; p-tolualdehyde (132 mg, 1.1 mmol) was used to replace 3-pentanone, and **2k** was obtained as a white solid with a yield of 413 mg (80%). Mp, 198−199 °C; $[\alpha]_D^{26.0}$, −57.2 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 2.37 (d, J = 8.8 Hz, 1H), 3.36 (d, J = 13.6 Hz, 1H), 3.68 (d, J = 13.6 Hz, 1H), 3.90 (d, J = 5.8 Hz, 1H), 4.20−4.38 (m, 2H), 6.93−7.00 (m, 2H), 7.01−7.09 (m, 4H), 7.10−7.17 (m, 3H), 7.21−7.35 (m, 9H), 7.37−7.50 (m, 4H), 7.64−7.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 50.6, 61.0, 67.7 (d, J = 6.3 Hz), 127.0, 127.1, 127.3, 127.5, 127.9, 128.0, 128.1, 128.2, 128.4, 129.0, 131.5, 131.7, 131.9, 132.0, 132.3, 132.4, 133.0, 133.2, 136.4, 137.0, 140.3, 140.8; ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.3; HRMS (ESI): (m/z) [M + H]$^+$ calcd for $C_{34}H_{34}N_2OP$, 517.2402; found, 517.2403.

4.3.4. [(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenylethyl](naphthalen-1-ylmethyl)amine (2l). The general procedure described for **2i** was followed on the same scale; 1-naphthaldehyde (172 mg, 1.1 mmol) was used to replace 3-pentanone, and **2l** was obtained as a white solid with a yield of 414 mg (75%). Mp, 248−249 °C; $[\alpha]_D^{30.1}$, −39.4 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.69 (br, 1H), 3.80−4.04 (m, 2H), 4.10−4.46 (m, 3H), 6.94−7.14 (m, 5H), 7.20−7.55 (m, 17H), 7.58−7.69 (m, 2H), 7.71−7.79 (m, 1H), 7.80−7.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 49.0, 61.0, 68.4 (d, J = 6.8 Hz), 123.6, 125.3, 125.5, 126.1, 126.2, 127.1, 127.3, 127.5, 127.8, 127.95, 128.0, 128.1, 128.25, 128.3, 128.4, 128.6, 131.5, 131.7, 131.8, 131.9, 132.2, 132.4, 132.97, 133.0, 133.8, 135.4, 140.2, 140.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.6; HRMS (ESI): (m/z) [M + H]$^+$ calcd for $C_{37}H_{34}N_2OP$, 553.2405; found, 553.2403.

4.3.5. [(4-Chlorophenyl)methyl][(1R,2R)-2-[(diphenylphosphoroso)amino]-1,2-diphenylethyl]amine (2p). The general procedure described for **2i** was followed on the same scale; p-chlorobenzaldehyde (154 mg, 1.1 mmol) was used to replace 3-pentanone, and **2p** was obtained as a white solid with a yield of 311 mg (58%). Mp, 215−217 °C; $[\alpha]_D^{26.0}$, −45.6 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97 (br, 1H), 3.38 (d, J = 14.0 Hz, 1H), 3.68 (d, J = 13.9 Hz, 1H), 3.84 (d, J = 6.4 Hz, 1H), 4.05−4.21 (m, 1H), 4.25−4.38 (m, 1H), 6.95−7.08 (m, 4H), 7.10−7.22 (m, 7H), 7.27−7.35 (m, 5H), 7.37−7.76 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.1, 61.1, 67.8 (d, J = 6.0 Hz), 127.19, 127.23, 127.5, 128.07, 128.13, 128.3, 128.35, 128.43, 128.48, 129.3, 131.5, 131.6,

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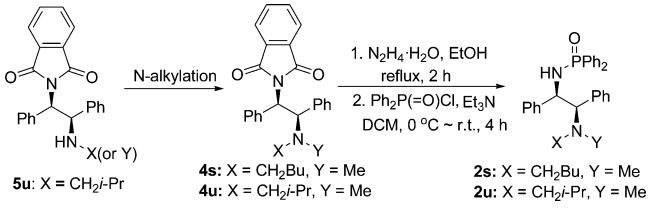
131.66, 131.68, 131.7, 131.8, 131.9, 132.3, 132.4, 132.5, 132.8, 133.0, 138.6, 139.9, 140.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.9; HRMS (ESI): (m/z) [M + H]$^+$ calcd for $C_{33}H_{31}ClN_2OP$, 537.1859; found, 537.1853.

*4.3.6. [(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenylethyl]({[4-(trifluoromethyl)phenyl]methyl})amine (**2q**).* The general procedure described for **2i** was followed on the same scale; 4-trifluoromethylbenzaldehyde (192 mg, 1.1 mmol) was used to replace 3-pentanone, and **2q** was obtained as a white solid with a yield of 354 mg (62%). Mp, 220−222 °C; $[\alpha]_D^{26.2}$, −37.3 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.46 (br, 1H), 3.49 (d, J = 14.3 Hz, 1H), 3.76 (d, J = 14.4 Hz, 1H), 3.87 (d, J = 6.6 Hz, 1H), 4.10−4.20 (m, 1H), 4.22−4.35 (m, 1H), 6.95−7.06 (m, 2H), 7.09−7.16 (m, 3H), 7.16−7.21 (m, 2H), 7.21−7.36 (m, 9H), 7.37−7.64 (m, 6H), 7.64−7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.4, 61.2, 68.0 (d, J = 5.7 Hz), 125.2 (q, J = 3.6 Hz), 127.21, 127.23, 127.6, 128.1, 128.2, 128.27, 128.3, 128.35, 128.4, 128.5, 128.9, 129.2, 131.4, 131.7, 131.8, 131.9, 132.4, 132.5, 132.7, 133.0, 139.8, 140.7, 144.3; ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.1; ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.3; HRMS (ESI): (m/z) [M + H]$^+$ calcd for $C_{34}H_{31}F_3N_2OP$, 571.2119; found, 571.2121.

*4.3.7. [(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenylethyl][(4-methyloxyphenyl)methyl]amine (**2r**).* The general procedure described for **2i** was followed on the same scale; *p*-methoxylbenzaldehyde (150 mg, 1.1 mmol) was used to replace 3-pentanone, and **2r** was obtained as a white solid with a yield of 431 mg (81%). Mp, 223−225 °C; $[\alpha]_D^{25.6}$, −49.7 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.89 (br, 1H), 3.34 (d, J = 13.4 Hz, 1H), 3.65 (d, J = 13.4 Hz, 1H), 3.78 (s, 3H), 3.87 (d, J = 6.1 Hz, 1H), 4.18−4.38 (m, 2H), 6.68−6.81 (m, 2H), 6.97−7.08 (m, 4H), 7.09−7.18 (m, 3H), 7.19−7.25 (m, 2H), 7.27−7.32 (m, 6H), 7.34−7.52 (m, 5H), 7.63−7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.2, 55.3, 61.0, 67.6 (d, J = 6.5 Hz), 113.7, 127.1, 127.3, 127.4, 128.0, 128.1, 128.19, 128.22, 128.3, 128.4, 129.1, 131.5, 131.7, 131.9, 132.0, 132.1, 132.3, 132.4, 133.0, 133.1, 140.2, 140.8, 158.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.3; HRMS (ESI): (m/z) [M + H]$^+$ calcd for $C_{34}H_{34}N_2O_2P$, 533.2352; found, 533.2352.

*4.3.8. [(1R,2R)-2-[(Diphenylphosphoroso)amino]-1,2-diphenylethyl][(4-fluorophenyl)methyl]amine (**2t**).* The general procedure described for **2i** was followed on the same scale; *p*-fluorobenzaldehyde (136.5 mg, 1.1 mmol) was used to replace 3-pentanone, and **2t** was obtained as a white solid with a yield of 266 mg (51%). Mp, 216−217 °C; $[\alpha]_D^{29.1}$, −39.2 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.20 (br, 1H), 3.41 (d, J = 13.6 Hz, 1H), 3.70 (d, J = 13.6 Hz, 1H), 3.87 (d, J = 6.3 Hz, 1H), 4.10−4.29 (m, 1H), 4.30−4.45 (m, 1H), 6.85−7.00 (m, 2H), 7.01−7.13 (m, 4H), 7.13−7.27 (m, 5H), 7.28−7.38 (m, 7H), 7.39−7.48 (m, 2H), 7.49−7.60 (m, 2H), 7.63−7.82 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 50.1, 61.1, 67.8 (d, J = 6.2 Hz), 115.0, 115.2, 127.2, 127.3, 127.5, 128.1, 128.13, 128.3, 128.4, 128.5, 129.46, 129.54, 131.7, 131.8, 131.9, 132.38, 132.45, 132.9, 133.0, 135.8, 140.1, 140.8; ^{31}P NMR (162 MHz, $CDCl_3$): δ 22.6; ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.2; HRMS (ESI): (m/z) [M + H]$^+$ calcd for $C_{33}H_{31}FN_2OP$, 521.2153; found, 521.2154.

4.4. Synthesis of Chiral Ligands 2s and 2u. Compound **4s** was synthesized according to the reported procedure.[78] **4s**: Mp, 129−130 °C; $[\alpha]_D^{29.0}$, −105.6 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.63 (t, J = 7.3 Hz, 3H), 0.91−1.37 (m, 6H), 2.07 (s, 3H), 2.20−2.30 (m, 1H), 2.32−2.42 (m, 1H), 5.27 (d, J = 12.3 Hz, 1H), 6.04 (d, J = 12.3 Hz, 1H), 7.06−7.29 (m, 8H), 7.52−7.62 (m, 2H), 7.65−7.73 (m, 2H), 7.79−7.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 27.5, 29.3, 36.5, 53.7, 54.8, 66.2, 123.0, 127.1, 127.5, 127.7, 128.2, 129.3, 129.6, 132.5, 133.5, 133.8, 137.4, 168.5, 168.7.



Compound **5u** was synthesized according to the reported procedure.[30] Mp, 116−117 °C; $[\alpha]_D^{28.9}$, 10.1 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.69 (d, J = 6.7 Hz, 3H), 0.72 (d, J = 6.7 Hz, 3H), 1.33−1.59 (m, 2H), 2.17−2.24 (m, 1H), 2.24−2.31 (m, 1H), 5.01 (d, J = 11.5 Hz, 1H), 5.48 (d, J = 11.5 Hz, 1H), 7.09−7.20 (m, 4H), 7.20−7.30 (m, 4H), 7.41−7.52 (m, 2H), 7.66−7.73 (m, 2H), 7.82−7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.4, 28.4, 55.1, 61.1, 62.2, 123.1, 127.1, 127.5, 127.8, 128.1, 128.2, 129.3, 132.0, 133.8, 137.7, 141.2, 168.8.

*2-[(1R,2R)-2-[Methyl(2-methylpropyl)amino]-1,2-diphenylethyl]-2,3-dihydro-1H-isoindole-1,3-dione (**4u**).* A mixture of **5u** (1.20 g, 3 mmol), 98% formic acid (1.38 g, 30 mmol), and 36% formaldehyde solution (2.31 mL, 30 mmol) was stirred under reflux (oil bath, 90 °C) overnight. The solvent was removed under reduced pressure followed by the addition of saturated K_2CO_3 (50 mL) solution and extracted with CH_2Cl_2 (15 mL × 3). Then, the organic layer was dried over anhydrous $MgSO_4$ and concentrated in vacuo to give the crude product, which was subjected to silica gel column chromatography (EtOAc/hexane = 1/30) to afford 977 mg (79%) of **4u** as a white solid. Mp, 151−152 °C; $[\alpha]_D^{29.2}$, −75.4 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.55−0.69 (m, 6H), 1.49−1.68 (m, 1H), 2.05 (s, 3H), 2.06−2.16 (m, 2H), 5.28 (d, J = 12.3 Hz, 1H), 6.04 (d, J = 12.3 Hz, 1H), 7.05−7.13 (m, 1H), 7.14−7.22 (m, 3H), 7.22−7.30 (m, 4H), 7.52−7.62 (m, 2H), 7.65−7.73 (m, 2H), 7.76−7.91 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.2, 20.4, 25.4, 36.2, 54.8, 62.6, 66.7, 122.9, 123.1, 127.1, 127.6, 127.7, 128.2, 129.4, 129.7, 131.8, 132.6, 133.6, 133.8, 137.5, 168.6, 168.8; HRMS (ESI): (m/z) [M + H]$^+$ calcd for $C_{27}H_{29}N_2O_2$, 413.2220; found, 413.2223.

*(Diphenylphosphoroso)[(1R,2R)-2-[methyl(pentyl)amino]-1,2-diphenylethyl]amine (**2s**).* To a solution of **4s** (853.1 mg, 2.0 mmol) in ethanol (2 mL), hydrazine monohydrate (0.97 mL, 20 mmol) was added, and the reaction mixture was stirred at reflux (oil bath, 80 °C) for 4 h. After the resultant mixture was cooled to room temperature, diethyl ether (20 mL) and CH_2Cl_2 (20 mL) were added to form precipitates, which were removed by filtration. The filtrate was dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure to afford 533 mg of white solid, which was used in the next step without further purification. A reaction mixture of the white solid in CH_2Cl_2 (10 mL) with Et_3N (545 mg, 5.4 mmol) was stirred at room temperature for 10 min. After being cooled to 0 °C, it was added the solution of diphenylphosphinic chloride (1.06 g, 4.5 mmol) in dry CH_2Cl_2 (10 mL) dropwise and was stirred for 30 min at 0 °C. Then, the temperature was allowed to warm to room temperature and was kept at room temperature for about 4 h. After the reaction mixture was cooled to 0 °C, water (20 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was dried over anhydrous $MgSO_4$ and concentrated. The crude product was subjected to silica gel column chromatography (EtOAc/hexane = 1/1), which afforded 616.8 mg (62%) of **2s** as a white solid. Mp, 168−169 °C; $[\alpha]_D^{30.4}$, 79.5 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, J = 6.7 Hz, 3H), 1.26−1.35 (m, 4H), 1.41−1.55 (m, 2H), 2.25 (s, 3H), 2.27−2.36 (m, 1H), 2.38−2.48 (m, 1H), 3.83 (d, J = 10.7 Hz, 1H), 4.91 (t, J = 10.9 Hz, 1H), 5.59 (s, 1H), 6.77−6.89 (m, 3H), 6.94−7.42 (m, 10H), 7.40−7.64 (m, 5H), 7.81−7.97 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 27.5, 29.4, 35.9, 53.6, 54.5, 73.9 (d, J = 8.9 Hz), 126.6, 127.3, 127.4, 127.5, 127.6, 128.3, 128.5, 128.7, 129.8, 130.7, 131.2, 132.24, 131.5, 132.3, 132.4, 132.8, 133.2, 133.6, 134.9, 140.7; ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.7; HRMS (ESI): (m/z) [M + H]$^+$ calcd for $C_{32}H_{38}N_2OP$, 497.2701; found, 497.2716.

*(Diphenylphosphoroso)[(1R,2R)-2-[methyl(2-methylpropyl)-amino]-1,2-diphenylethyl]amine (**2u**).* The same procedure described for **2s** was followed on the same scale; **4u** (824 mg, 2 mmol) was used to replace **4s**, and **2u** was obtained as a white solid with a yield of 771 mg (80%). Mp, 206−208 °C; $[\alpha]_D^{29.1}$, 64.9 (c 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.83 (d, J = 3.9 Hz, 3H), 0.85 (d, J = 3.9 Hz, 3H), 1.70−1.86 (m, 1H), 2.11 (d, J = 7.4 Hz, 3H), 2.21 (s, 1H), 3.80 (d, J = 10.8 Hz, 1H), 4.92 (t, J = 10.7 Hz, 3H), 5.63 (s, 1H), 6.74−6.85 (m, 3H), 6.93−7.07 (m, 6H), 7.07−7.18 (m, 4H),

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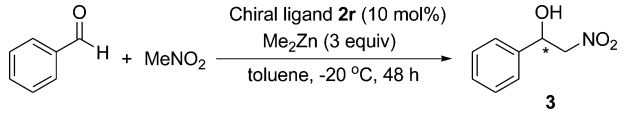
7.37−7.49 (m, 3H), 7.49−7.61 (m, 2H), 7.83−7.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.56, 20.64, 25.7, 35.6, 54.5, 62.6, 74.2 (d, J = 9.2 Hz), 126.6, 127.27, 127.34, 127.38, 127.47, 127.57, 128.3, 128.4, 128.7, 129.9, 130.59, 130.61, 131.1, 131.2, 131.4, 131.5, 131.6, 132.3, 132.4, 132.9, 133.1, 133.7, 134.9, 140.5; ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.4; HRMS (ESI): (m/z) $[M + H]^+$ calcd for $C_{31}H_{36}N_2OP$, 483.2552; found, 483.2557.

4.5. Typical Procedure for the Catalytic Asymmetric Henry Reaction between Benzaldehyde and Nitromethane.



3

To a solution of chiral phosphinamide ligand **2r** (53.2 mg, 0.1 mmol) in toluene (1 mL), Me_2Zn (3.0 mL, 1 M in toluene, 3.0 mmol) was added, and the resulting mixture was stirred for 30 min at −50 °C under an atmosphere of nitrogen. Then, nitromethane (0.54 mL, 10 mmol) was added in one portion, followed by benzaldehyde (106 mg, 1.0 mmol). The reaction temperature was allowed to warm to −20 °C, and the mixture was stirred for 48 h. The reaction was quenched by the addition of a saturated NH_4Cl solution (15 mL), and the mixture was extracted with EtOAc (15 mL × 3). The combined organic layer was dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane/EtOAc = 8/1) to give 166 mg of the corresponding product **3** of (*R*)-2-nitro-1-phenylethanol (99% yield, 92% *ee*). The *ee* value was determined by HPLC analysis with a Chiralcel OD-H column (Hexane/2-propanol = 90/10, 1.0 mL/min, 230 nm). The major enantiomer t_R = 11.7 min, and the minor enantiomer t_R = 12.5 min. $[\alpha]_D^{17.6}$, −30.40 (c 1.00, CH_2Cl_2) [Literature[61] $[\alpha]_D^{16.0}$, −40.16 (c 1.00, CH_2Cl_2) for 93% *ee* (*R*)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (s, 1H), 4.48 (dd, J = 4.8 Hz, 13.2 Hz, 1H), 4.59 (dd, J = 3.2 Hz, 13.2 Hz, 1H), 5.41 (dd, J = 3.2 Hz, 9.6 Hz, 1H), 7.30−7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.8, 81.1, 125.8, 128.7, 128.8, 138.1.

■ ASSOCIATED CONTENT

Supporting Information

Asymmetric Henry reaction of benzaldehyde, the Sterimol analysis, Tropsha's criteria on evaluating the constructed model, copies of ^{1}H and ^{13}C NMR spectra of products, and HPLC data of chiral 2-Nitro-1-phenylethanol. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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