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ARTICLE

# Access to P-Chiral Phosphine Oxides by Enantioselective Allylic Alkylation of Bisphenols

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A novel biscinchona alkaloid-catalyzed highly enantioselective desymmetrization reaction of bisphenol compounds with achiral Morita–Baylis–Hillman carbonate agents was developed. Through the asymmetric allylic alkylation strategy, a broad range of optically active P-stereogenic phosphine oxides were generated with excellent to good yields (up to 99%) and high enantioselectivities (up to 98.5:1.5 e.r.). The reaction was further investigated by the linear free energy relationship (LFER) analysis. A possible transition state was proposed and furthered verified by theoretical calculations.



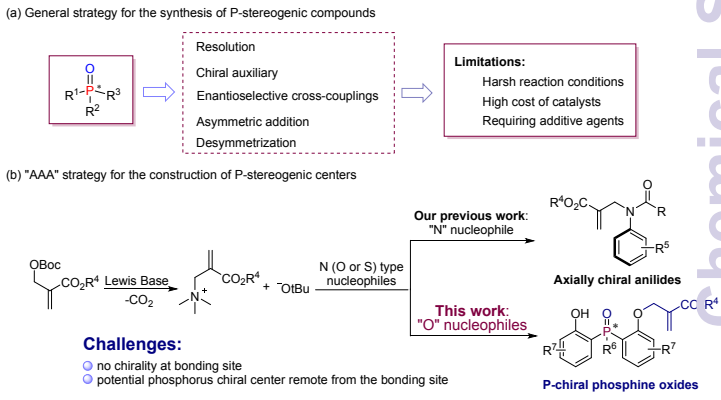


## Introduction

P-stereogenic compounds, in which the chirality is on the phosphorus atom, have been widely used as biologically active compounds,[1] chiral ligands[2] and useful building blocks[3]. The significance of this privileged structural motif with P-stereogenic center has led to a great demand for efficient synthetic methods. However, the methodologies used to synthesize such chiral structures were largely limited.[4] Early reports on P-stereogenic center synthesis comprise the resolution of diastereoisomers,[5] chiral auxiliary controlled asymmetric reactions,[6] transition-metal-catalyzed enantioselective cross-couplings,[7] asymmetric addition reactions of phosphorus nucleophiles,[8] and desymmetrization of prochiral phosphorus derivatives (Scheme 1a).[9] Among these above mentioned synthetic strategies of P-stereogenic centers, only two cases were achieved through organocatalysis.[10] Therefore, it is currently desirable and challenging to develop an organocatalysis-based synthetic methodology for P-stereogenic centers, and to expand the facile and extensive substrate adaptability.

Lewis base catalyzed asymmetric allylic alkylation (AAA) reaction with Morita–Baylis–Hillman (MBH) carbonates as electrophile precursors has been considered as one of the most attractive approach to build stereogenic centers. However, the AAA strategy currently was restricted to the build of chiral carbon centers because most frequently used allylation reagents are racemic MBH adducts. In fact, it is possible to expand the usage of AAA strategy to building other non-carbon center chirality when the reactions proceed between achiral MBH adducts and N (O or S) type nucleophiles. Our group recently developed a general and efficient method for atroposelective construction of axially chiral anilides (Scheme 1b).[12]

In continuation of our ongoing interest in AAA strategy, we speculated that the privilegedphosphorus compounds with P-stereogenic centers could be generated via AAA reaction between bis(2-hydroxyphenyl) phosphinates and achiral MBH carbonates (Scheme 1b). Thus, two challenges need to be solved in this scenario: i) the difficulty in controlling stereoselectivities due to the lack of chirality at the bonding site; ii) the difficulty in designing a proper chiral catalyst to induce enantiocontrol during the course of desymmetrization, because the targeted phosphorus center is remote from the enantiotopic site. Herein, we reported a biscinchona alkaloid-catalyzed enantioselective desymmetrization of bis(2-hydroxyphenyl) phosphine oxides. Utilizing the AAA strategy based method, a number of phosphine oxides processing chiral phosphorus (V) atoms were synthesized with good enantioselectivities.




**Scheme 1** Methods for the synthesis of P-stereogenic compounds.

## Results and discussion

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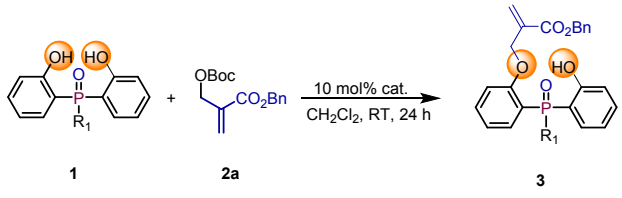
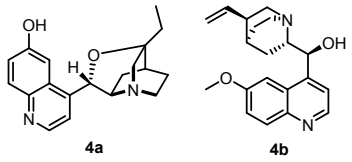
## Reaction optimization

**Table 1** Reaction optimization.[a]




**4c:** $(DHQD)_2PHAL$
**4d:** $(DHQD)_2AQN$
**4e:** $(DHQD)_2PYR$
**4f:** $(DHQ)_2PHAL$
**4g:** $(DHQ)_2AQN$
**4h:** $(DHQ)_2PYR$

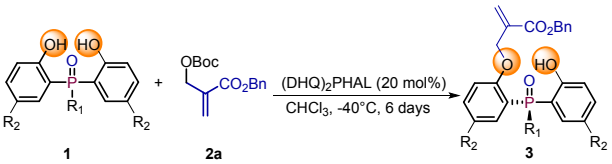
| entry | $R_1$ | Cat. | Solvent | Yield (%)[b] | e.r.[c] |
|---|---|---|---|---|---|
| 1 | **1a**: OMe | **4a** | $CH_2Cl_2$ | **3a**: 96 | 50:50 |
| 2 | **1a**: OMe | **4b** | $CH_2Cl_2$ | **3a**: 99 | 54.5:45.5 |
| 3 | **1a**: OMe | **4c** | $CH_2Cl_2$ | **3a**: 60 | 51.5:48.5 |
| 4 | **1a**: OMe | **4d** | $CH_2Cl_2$ | **3a**: 60 | 52:48 |
| 5 | **1a**: OMe | **4e** | $CH_2Cl_2$ | **3a**: 73 | 53.5:46.5 |
| 6 | **1a**: OMe | **4f** | $CH_2Cl_2$ | **3a**: 73 | 66:34 |
| 7 | **1a**: OMe | **4g** | $CH_2Cl_2$ | **3a**: 68 | 53:47 |
| 8 | **1a**: OMe | **4h** | $CH_2Cl_2$ | **3a**: 68 | 53.5:46.5 |
| 9 | **1b**: OEt | **4f** | $CH_2Cl_2$ | **3b**: 65 | 68.5:31.5 |
| 10 | **1c**: O*i*Pr | **4f** | $CH_2Cl_2$ | **3c**: 64 | 70.5:31.5 |
| 11 | **1d**: OAd | **4f** | $CH_2Cl_2$ | **3d**: 90 | 71.5:28.5 |
| 12 | **1e**: Ad | **4f** | $CH_2Cl_2$ | **3e**: 90 | 84:16 |
| 13[d] | **1e**: Ad | **4f** | $CH_2Cl_2$ | **3e**: 46 | 94:6 |
| 14[d] | **1e**: Ad | **4f** | $CHCl_3$ | **3e**: 60 | 94.5:5.5 |
| 15[d] | **1e**: Ad | **4f** | THF | **3e**: 36 | 94:6 |
| 16[d] | **1e**: Ad | **4f** | toluene | trace | Nd[f] |
| 17[d] | **1e**: Ad | **4f** | ether | trace | Nd[f] |
| 18[d, e] | **1e**: Ad | **4f** | $CHCl_3$ | **3e**: 84 | 94.5:5.5 |

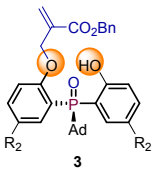
[a] Reaction conditions: phosphinate **1** (0.1 mmol), MBH carbonates **2a** (0.12 mmol), catalyst (10 mol %), in 1 mL of solvent. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] The reaction was conducted at -40 °C with 20 mol% $(DHQ)_2PHAL$ and reaction time was 6 days. [e] With 0.2 mmol **2a**. [f] Not determined.

Our initial investigation was carried out with bis(2-hydroxyphenyl) phosphinates **1a** and Boc protected MBH product **2a** as the model substrates, 10 mol% of cinchona alkaloid **4a** as catalyst in $CH_2Cl_2$ at room temperature. The reaction gave the desymmetrization product **3a** in 96% yield, albeit with racemic result (Table 1, entry 1). To improve the enantioselectivity, we next evaluated the different types of cinchona alkaloid catalysts. As shown in Table 1, the catalysts' backbone demonstrated remarkable impacts towards the outcome of the reaction (Table 1, entries 2-8), in which biscinchona alkaloid catalyst **4f** gave the best 66:34 e.r. (Table 1, entry 6). To further improve the enantioselectivity, we then screened different bisphenol substrates. To our delight, substrates **1b**-**1d**, which had large size of the ester groups, showed improved enantioselectivities (Table 1, entries 9-11). This result indicated that the enantioselectivity of the studied desymmetrization reaction may be closely related to the steric hindrance of substituent linked to pre-stereogenic P-center. This hypothesis was furthermore supported by reaction with substrate phosphine oxide **1e**, in which the enantioselectivity was obtained as 84:16 e.r. (Table 1, entry 12). A series of subsequent screenings (for example, temperature, solvent, and substrate ratio) kept enhancing the enantioselectivity. Lowering the reaction temperature to -40 °C can further increase e.r. value to 94:6, while increasing catalyst loading and prolonging the reaction time were necessary to ensure the conversion of reaction (Table 1, entry 13). The evaluation of the solvents showed that $CHCl_3$ was the best reaction medium in terms of reactivity and enantioselectivity (Table 1, entries 13-17). The reaction also favoured the increased amount of substrate of **2a** with an improved yield to 84% with the retaining 94.5:5.5 e.r. (Table 1, entry 18).

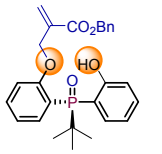
## Substrate evaluation

**Table 2** Substrate scope of phosphine oxide substrates.[a]

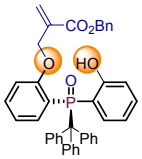



**3e** $R_1$ = Ad $R_2$ = H 84% yield, 94.5:5.5 e.r.
**3f** $R_1$ = Ad $R_2$ = Me 91% yield, 96:4 e.r.
**3g** $R_1$ = Ad $R_2$ = Et 75% yield, 96.5:3.5 e.r.
**3h** $R_1$ = Ad $R_2$ = *i*Pr 71% yield, 97:3 e.r.
**3i** $R_1$ = Ad $R_2$ = *c*Hex 64% yield, 95.5:4.5 e.r.
**3j** $R_1$ = Ad $R_2$ = *t*Bu 34% yield, 92.5:7.5 e.r.
**3k** $R_1$ = Ad $R_2$ = OMe 58% yield, 91.0:9.0 e.r.
**3l** $R_1$ = Ad $R_2$ = F 65% yield, 88.5:11.5 e.r.
**3m** $R_1$ = Ad $R_2$ = Cl 73% yield, 96:4 e.r.
**3n** $R_1$ = Ad $R_2$ = Br 71% yield, 97.5:2.5 e.r.
**3o** $R_1$ = Ad $R_2$ = I 66% yield, 98.5:1.5 e.r.




$R_1$ = *t*-Bu, $R_2$ = H
**3p**, 81% yield, 93:7 e.r.




$R_1$ = $Ph_3C$, $R_2$ = H
**3q**, 81% yield, 88.5:11.5 e.r.

[a] Reaction conditions: phosphine oxides **1** (0.1 mmol), MBH carbonates **2a** (0.2 mmol), catalyst (20 mol%), 1 mL $CHCl_3$. Isolated yields. e.r. values were determined by chiral HPLC analysis.

With the optimal reaction conditions in hand, we set out to explore the substrate generality of this desymmetrization strategy. Firstly, different substituted phosphine oxides were investigated. As shown in Table 2, substrates with electron-donating groups and electron-withdrawing groups on the phenyl ring were well tolerated in this reaction. The corresponding products **3e**-**3k** and **3l**-**3o** were afforded in 34-

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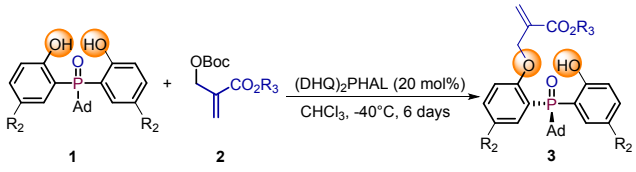
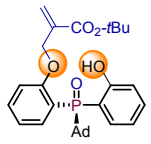
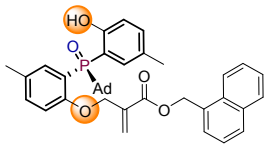
91% yields and 91.0:9.0-98.5:1.5 e.r. values. When the substituted atom was F, the enantioselectivity decreased to moderate level (**3l**, 65% yield and 88.5:11.5 e.r.). It is valuable to note that the steric hindrance of the substituent seems to also influence on the reactivity. For example, the substrate with $R_2$ as *tert*-butyl group only provided corresponding product **3j** with 34% yield under the optimized reaction conditions. Other two substrates with large steric hindrance phosphine oxides, in which the groups linked to P-center were tert-butyl and triphenyl methyl, were also examined. As a result, **3p** was obtained in 81% yield with 93:7 e.r. and **3q** was obtained in 81% yield with 88.5:11.5 e.r..

**Table 3** Substrate scope of MBH carbonate substrates. [a]

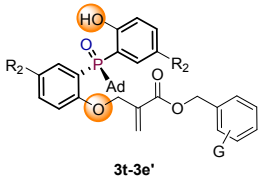



$R_2$ = H, $R_3$ = *t*-Bu
**3r**[b], 61% yield, 92:8 e.r.




$R_2$ = Me, $R_3$ =1-methylnaphthyl
**3s**, 93% yield, 95.5:4.5 e.r.

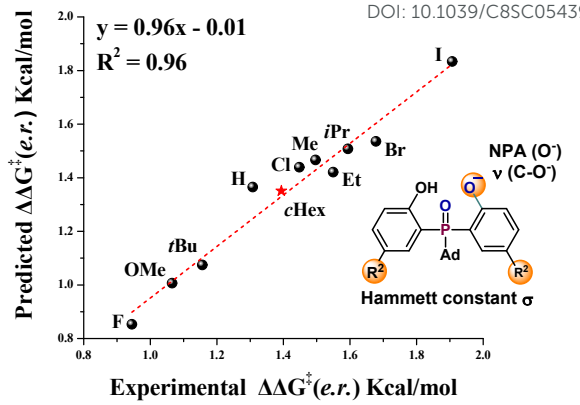


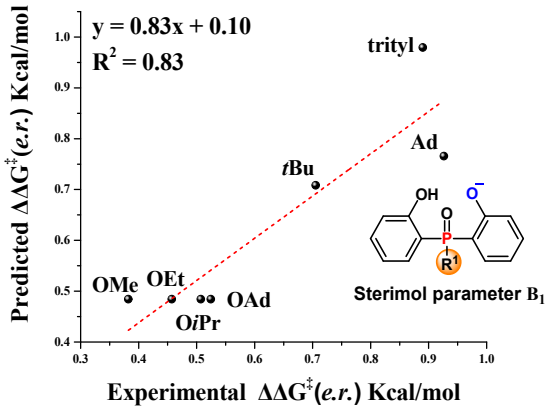

**3t-3e'**

**3t**, $R^2$ = Me, G = 2-$CF_3$, 99% yield, 96:4 e.r.
**3u**, $R^2$ = Me, G = 2-Me, 77% yield, 95.5:4.5 e.r.
**3v**, $R^2$ = Me, G = 2-MeO, 46% yield, 96.5:3.5 e.r.
**3w**, $R^2$ = Me, G = 2-Cl, 99% yield, 95.5:4.5 e.r.
**3x**, $R^2$ = Me, G =3-Me, 75% yield, 95:5 e.r.
**3y**, $R^2$ = Me, G = 3-MeO, 78% yield, 95:5 e.r.
**3z**, $R^2$ = Me, G =3-Cl, 88% yield, 96:4 e.r.
**3a'**, $R^2$ = Me, G =4-F,85% yield, 96:4 e.r.
**3b'**, $R^2$ = Me, G = 4-Cl, 99% yield, 96:4 e.r.
**3c'**, $R^2$ = Br, G = 2-Me, 52% yield, 96.5:3.5 e.r.
**3d'**, $R^2$ = Br, G =3MeO, 41%yield, 97.5:2.5 e.r.
**3e'**, $R^2$ = Br, G =4-F, 70% yield, 97:3 e.r.

[a] Reaction conditions: phosphine oxides **1** (0.1 mmol), MBH carbonates **2** (0.2 mmol), catalyst (20 mol%), 1 mL $CHCl_3$. Isolated yields. e.r. values were determined by chiral HPLC analysis. [b] The reaction was conducted at 0 °C

Further investigation of the substrate scope was focused on the Boc protected MBH carbonate substrates **2** (Table 3). The electronic nature or position of the substituent on the benzyl ring do not appear to affect the results, all the benzyl-substituted MBH carbonates afforded the target products **3t**-**3e'** in moderate to excellent yields (41-99%) with excellent enantioselectivities (95.5:4.5 to 97.5:2.5 e.r.). The 1-methylnaphthyl type MBH carbonate tolerated well under the optimal condition, gave **3s** in 93% yield with 95.5:4.5 e.r.. The *tert*-butyl substituted MBH carbonate is also transformed to the desired product **3r** in 61% yield and 92:8 e.r. by running the reaction at 0 °C albeit with the large steric hinderance. The absolute configuration of **3r** was determined by X-ray diffraction analysis and those of other products were assigned by analogy.[13]



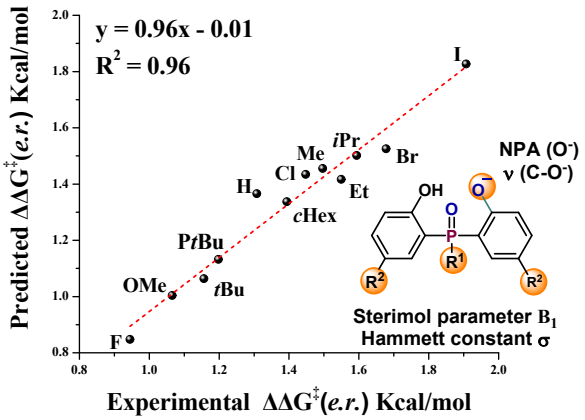




**Fig. 1** Correlation of enantioselectivity with substrate parameters.

## LFER researches

The substrate scope study reveals that, in general, product with large size of the substituent on the aromatic ring of phosphine has better enantioselectivity. To investigate the effect of steric factor on the enantioselectivity, we plotted the enantioselectivities towards Charton values.[14] Preliminary analysis revealed that substrates having large steric substituents $R_2$ gave better enantioselectivities (For $R^2$ = H, Me, Et, *i*Pr, see Fig. S1 in SI). This rule could be also expanded to

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substrates containing halogen substituent ($R^2$ = F, Cl, Br, I, see Fig. S2 in SI). It seemed that steric factor may play a role in enantioselectivity control. However, the steric correlation could not explain the stereoselectivity for the substrates containing other large hindrance substituents, such as $R^2$ = *t*Bu or *c*Hex. Thus, other factors, such as electronic effect, should also be considered.

Recently, Sigman and coworkers utilize multivariate linear regression (MLR) models to effectively predict the experimental reaction outcome based on both experimentally-derived and calculated physical organic molecular descriptors.[15] Inspired by their work and our previous related study,[12] we explored the factors that governing the stereoselectivity. The regression analysis was made with ten data and tested with one data. After evaluating various parameters, Hammett constant (σ), NPA charge ($O^-$) and ν ($C\text{-}O^-$),[15b and 15c] which can be used to embody the steric and electronic effect, were found to accurately predict the stereoselectivity (eq 1, Figure 1, slope = 0.96, intercept = -0.01, $R^2$ = 0.96). Besides, the effects of substituents linked to pre-stereogenic P-center were evaluated. The stereoselectivity is in good correlation with Sterimol parameter $B_1$ (eq 2).[16] The steric factor of substituents linked to phosphorous atom significantly affected the enantioselectivity. Finally, based on eq 2, the eq 1 could be expanded to substrates that have different substituents linked to pre-stereogenic P-center (eq 3, slope = 0.96, intercept = -0.01, $R^2$ = 0.96).

$$\Delta\Delta G^{\ddagger}(e.r.) = -3.04\sigma + 78.6NPA_{(O^-)} - 0.014\nu_{(C\text{-}O^-)} + 88.2 \quad (1)$$

$$\Delta\Delta G^{\ddagger}(e.r.) = 0.16B_1 + 0.24 \quad (2)$$

$$\Delta\Delta G^{\ddagger}(e.r.) = -3.03\sigma + 78.1NPA_{(O^-)} - 0.0144\nu_{(C\text{-}O^-)} + 0.828B_1 + 85.7 \quad (3)$$

### Theoretical calculations

Theoretical calculations were conducted to support the above analysis.[17,18] Extensive explorations of a variety of catalytic arrangements show that the most two stable transition state structures are TS1 and TS2 (Fig. 2). The free energy difference between TS1 and TS2 is 2.2 kcal/mol, which agrees with experiment data 85:15 e.r.. As shown in Figure 2, TS1 is stabilized by a C–H···π interaction between the methylene of quinuclidine ring and the aromatic ring of phenol. However, this interaction is missing in TS2, which would be a key factor that contributes to the energy difference between TS1 and TS2. Previous studies of C–H···π interactions showed that the interaction energies are correlated with Hammett constant ($\sigma_m$),[19] which supported our LFER analysis. The steric factor of substituents linked to pre-stereogenic P-center could be also explained by transition states. If the *tert*-butyl group linked to phosphorous atom is replaced by adamantyl group, the steric effect between catalyst and substrate will destabilize TS2, which is crucial for excellent enantioselectivity control.

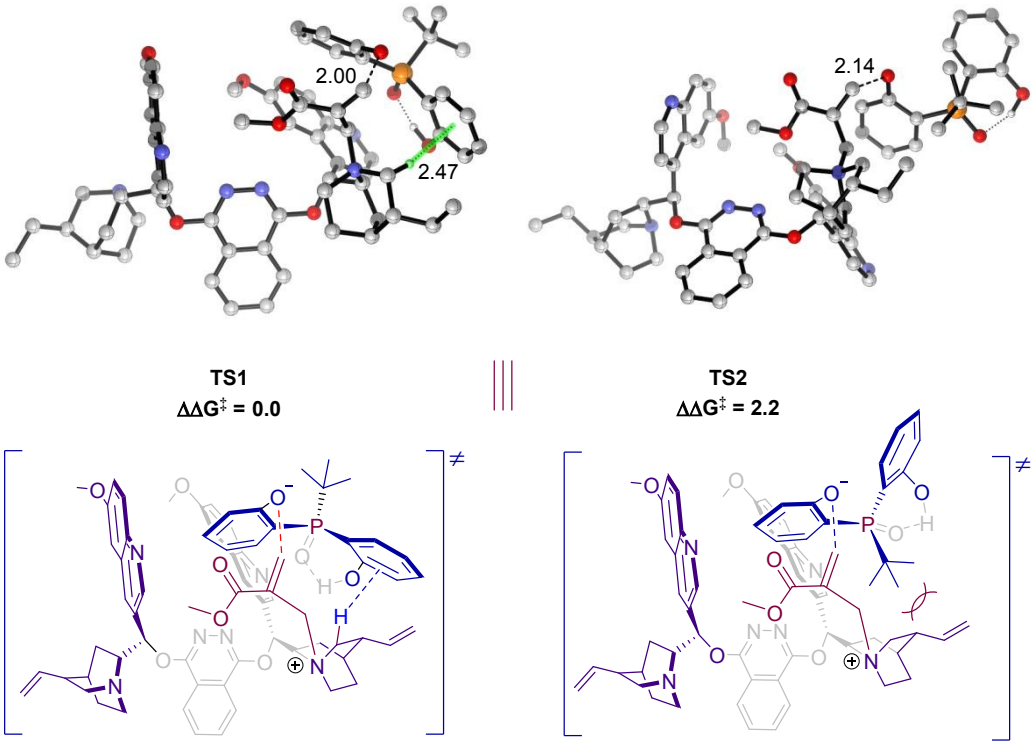
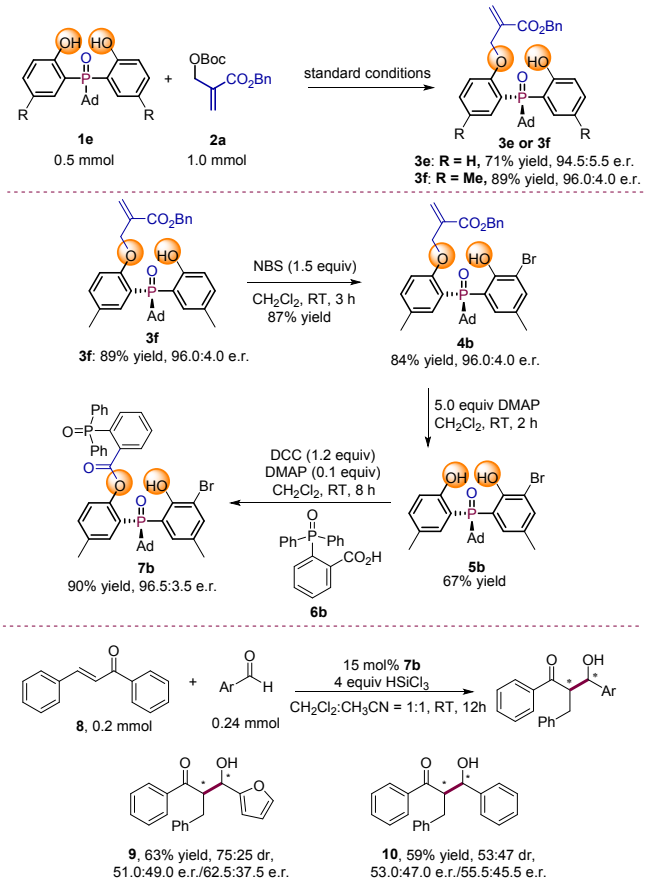



**Fig. 2**. Transition state structures and relative free energies (in Kcal/mol) for desymmetrization catalyzed by **4f**. Noncritical hydrogen atoms have been omitted for clarity. The C-H···π interaction in TS1 is highlighted.

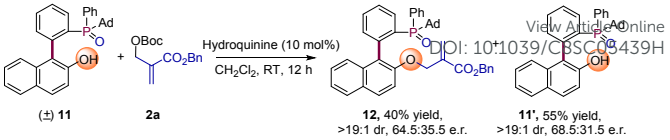
### Large scale reaction and product transformation

To probe the efficiency of current studied desymmetrization strategy in preparative synthesis, large scale reactions were investigated under the optimal conditions. To our delight, the desired products **3e** and **3f** were obtained without any loss of enantioselectivities (Scheme 2). Further bromation of **3f** by 1.5 equiv NBS afforded **4b**. Treated **4b** with 5 equivalent DMAP acquired **5b** in moderate yield with retentive enantioselectivity. Finally, product **7b** can be obtained in 90% yield with 96.5:3.5 e.r. under the conditions shown in Scheme 2. The preliminary application of the synthesized bidentate chiral phosphine oxide indicated that **7b** could be used as a catalyst in asymmetric reactions between enone and aldehydes (Scheme 2).[20]




**Scheme 2** Large scale reaction and synthetic transformations of the product.[21]

Moreover, we also made another kinetic resolution experiment with substrate (±)-**11**, which cotains both axial and phosphorous pre-chirality (Scheme 3). The reaction of (±)-**11** with **2a** proceed smoothly in the presence of 10 mol% hydroquinine under the standard conditions, resulting in **12** in 40% yield with 64.5:35.5 e.r. and **11'** in 55% yield with 68.5:31.5 e.r.. Further optimization of reaction conditions may lead to better enantioselectivities. This result again proves the universality of the strategy for the synthesis of P-stereogenic compounds.




**Scheme 3** Kinetic resolution experiment using AAA strategy..

## Conclusions

In summary, we have developed a catalytic enantioselective desymmetrization of bisphenols that hold pre-stereogenic P-centers, using a biscinchona alkaloid catalyst. This AAA strategy based method provides a novel and highly efficient way to the synthesis of P-stereogenic compounds, affording the desired functionalized phosphine oxides in good yields (up to 99%) and high enantioselectivities (up to 98.5:1.5 e.r.). A range of functional groups were tolerated under the mild reaction conditions. A possible transition state was proposed based on the linear free energy relationship analysis, which was further verified by theoretical calculations.

## Conflicts of interest

There are no conficts to declare.

## Acknowledgements

We are grateful to the NNSFC (Grant No. 21390400) for financial support.

## Notes and references

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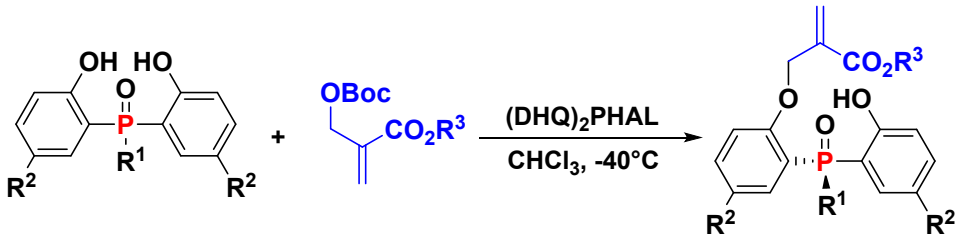
**AAA Strategy for the Construction of P-Stereogenic Centers**




**up to 99% yield**
**up to 98.5:1.5 *e.r.***

**Challenges:**

- no chirality at bonding site
- potential phosphorus chiral center remote from the bonding site

A biscinchona alkaloid-catalyzed AAA reaction for the construction of P-stereogenic center compounds was developed.