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A Simple Strategy for the Preparation of *P*-Chirogenic Trost Ligands with Different Absolute Configurations

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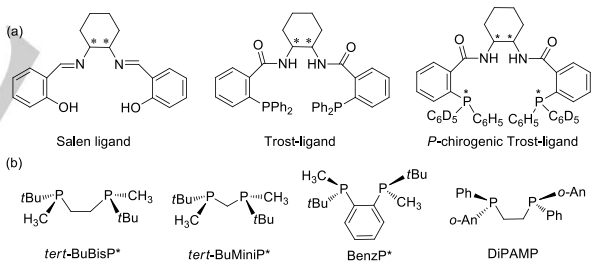
Abstract: *P*-chirogenic compounds are useful ligands and organocatalysts in asymmetric synthesis. However, the lack of preparative methods and their configurational instability have significantly hampered their development. Herein, we report a simple strategy for the preparation of enantiomerically pure *P*,*C*-chirogenic diphosphines. Amidation of the borane adducts of *rac*-phosphinobenzoic acids with enantiomerically pure *trans*-1,2-diaminocyclohexane afforded a 1:2:1 mixture of the diastereomers (C*,C*,R_p,R_p), (C*,C*,R_p,S_p), and (C*,C*,S_p,S_p), which were separated by column chromatography on silica gel. The prepared (C*,C*,R_p,R_p) and (C*,C*,S_p,S_p) stereoisomers were identical to those obtained from the enantiopure phosphines, which were synthesized by a multi-step route using chiral auxiliaries. Hence, this simple, short and convenient route towards *P*,*C*-chirogenic diphosphines obviates the use of chiral auxiliaries and enables the access to diphosphines with differently configured *P*-stereocenters.

Introduction

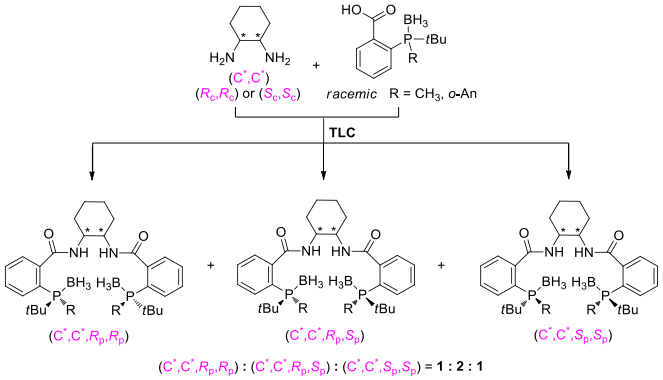
P-chirogenic phosphines are extensively employed in asymmetric catalysis as chiral ligands[1] and organocatalysts.[2] For example, the use of DiPAMP,[3] MiniPhos,[4,1g] BisPhos,[5] SMSPhos,[6] TangPhos,[7] and DuanPhos[8] has led to excellent enantioselectivities in various asymmetric transformations. In contrast to the extensive studies on *C*-chirogenic phosphines,[1a,1c,9] the development of *P*-chirogenic ligands has been hampered by the scarcity of general preparative methods and configurational instability of the *P*-stereocenter.

Previous studies revealed that *P*,*C*-chirogenic phosphine ligands provided higher levels of asymmetric induction than *C*-chirogenic ones because of the proximity between the chirogenic and catalyst activation centers.[7a,8,10] In addition, the chiral *C*-atom possibly stabilizes the configuration of the *P*-atom.[10b] Therefore, the presence of chiral *C*- and *P*-atoms in the same framework would be particularly advantageous for the asymmetric reactions because of the steric and electronic contributions of each chirogenic moiety. Nevertheless, only a few studies addressed the incorporation of both *P*- and *C*-stereocenters into phosphine ligands.[11]

Trans-1,2-diaminocyclohexane is a versatile chiral building block for the preparation of privileged chiral ligands such as salen,[12] Trost,[13] and other iminophosphine ligands[14] (Scheme 1a). In 1998, Imamoto et al. reported the superior enantioselectivity induced by *tert*-butyl and methyl substituted diphosphine ligands in transition metal catalyzed asymmetric reactions.[4a,5a,15] Later, the Lloyd-Jones group disclosed the stereoselective synthesis of *P*-chirogenic Trost ligands bearing a *D*-labelled phenyl ring at each *P*-atom, and combined computational and NMR studies to investigate the origin of the selectivity in asymmetric allylic alkylation reactions catalyzed by chiral palladium complexes.[16] These studies inspired the synthesis of several diphosphine ligands, including *tert*-BuBisPhos,[5] *tert*-BuMiniPhos,[4c,4d] BenzPphos, DioxyBenzPhos, and QuinoxPhos, and the evaluation of their performance in asymmetric hydrogenations.[17] Additionally, the successful commercial application of DiPAMP in the *L*-DOPA production by asymmetric hydrogenation in industrial scale further demonstrated the efficiency of *P*-chirogenic ligands (Scheme 1b).[3] Consequently, chiral *trans*-1,2-diaminocyclohexane-based diphosphine ligands bearing *P*-chirogenic phosphines are likely to exhibit excellent activities and enantioselectivities in asymmetric catalytic transformations.



Scheme 1. Representative ligands bearing *trans*-1,2-diaminocyclohexane (a) and *tert*-butyl or 2-methoxyphenyl (*o*-An) subunits (b).

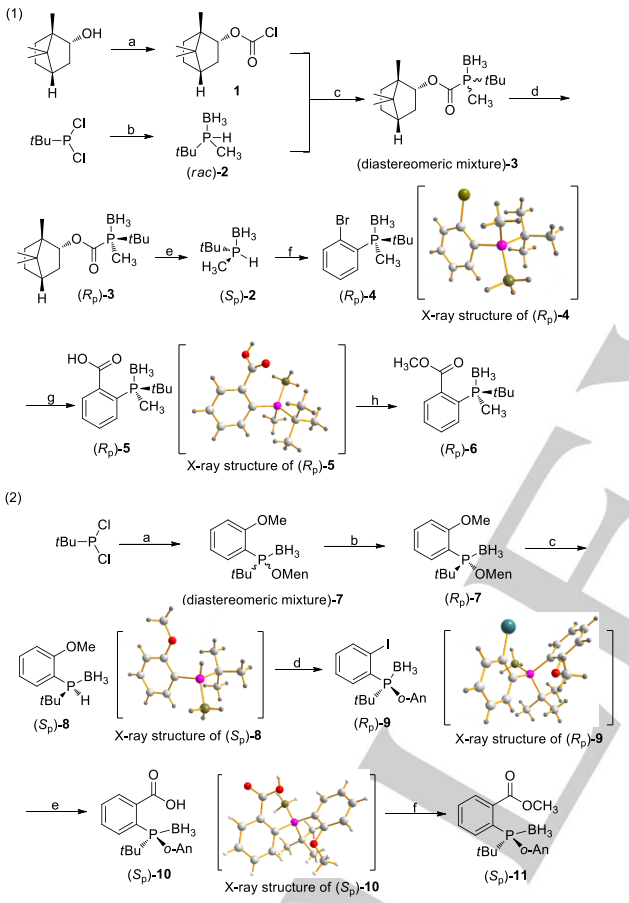


Scheme 2. Novel strategy for the preparation of *P*,*C*-chiral diphosphines.

Herein, we report a simple, chiral auxiliary-free strategy for the preparation of various *P*,*C*-chirogenic diphosphines by condensation of enantiopure *trans*-1,2-diaminocyclohexane with the borane adducts of *rac*-phosphinobenzoic acids followed by column chromatographic purification (Scheme 2).

Results and Discussion

Initially, the synthesis of *P*,*C*-chirogenic diphosphines bearing (*R,R*)- or (*S,S*)-*P*-stereocenters was adapted from modified methods of literatures[15,17c,18] using enantiopure (R_p)-(2-bromophenyl)*tert*-butylmethyl phosphine–borane adduct **4** or (R_p)-*tert*-butyl(2-iodophenyl)(2-methoxyphenyl)phosphine–borane adduct **9** as the key intermediates (Scheme 3).



Scheme 3. Preparation of the borane adducts of (R_p)-2-(*tert*-butyl(methyl)phosphino)benzoic **5** and (S_p)-2-(*tert*-butyl(2-methoxyphenyl)phosphino)benzoic acids **10** from *tert*-butyldichlorophosphine. OMen = (–)-menthyl. Reagents and conditions: (1) (a) triphosgene, quinoline, toluene, 0 to 60 °C; (b) (i) $LiAlH_4$, butyl diglyme, 0 °C, (ii) BH_3–THF, 0 °C, (iii) *n*-BuLi, −78 °C, (iv) CH_3I, −78 °C to rt; (c) *n*-BuLi, −78 °C to rt; (d) recrystallization from hexane, 60 °C to rt; (e) KOH, $CH_3CN/CH_3OH/H_2O$, rt; (f) (i) *n*-BuLi, −78 °C, (ii) *o*-$C_6H_4Br_2$, −78 °C to rt; (g) (i) *n*-BuLi, −78 °C, (ii) CO_2, −78 °C to rt, (iii) 1 M aq. HCl; (h) $TMSCHN_2$, CH_3OH/Et_2O, rt. (2) (a) (i) (1*R*,2*S*,5*R*)-menthoxide sodium, THF, −78 °C to rt, (ii) 2-methoxyphenyimagnesium bromide, 0 °C to rf, (iii) BH_3–THF, 0 °C to rt; (b) recrystallization from hexane, 60 °C to rt; (c) lithium naphthalenide, −40 °C, then 1M aq. HCl; (d) *s*-BuLi, −78 °C, (ii) *o*-$C_6H_4I_2$, −78 °C to rt; (e) (i) *n*-BuLi, −78 °C, (ii) CO_2, −78 °C to rt, (iii) 1 M aq. HCl; (f) $TMSCHN_2$, CH_3OH/Et_2O, rt.

To this end, *tert*-butyldichlorophosphine was consecutively reacted with $LiAlH_4$, BH_3–THF complex, and CH_3I to give *rac*-*tert*-butylmethylphosphine–borane adduct **2**. The resulting racemate was treated with *n*-BuLi and (–)-bornyl chloroformate **1** to afford bornyloxycarbonyl(*tert*-butyl)methylphosphine–borane adduct **3** as a mixture of diastereomers. Enantiopure (S_p)-**2** was obtained in 81% yield after recrystallization and hydrolysis.

Next, the lithium derivative of enantiopure (S_p)-**2** was reacted with *o*-dibromobenzene at –78 °C to furnish enantiopure (R_p)-**4** as a crystalline solid upon recrystallization from hexane. Furthermore, the borane adduct of (R_p)-2-(*tert*-butylmethylphosphino)benzoic acid **5** was achieved as a crystalline solid in 62% yield by bubbling CO_2 through a mixture of *n*-BuLi and (R_p)-**4**.[18d,19]

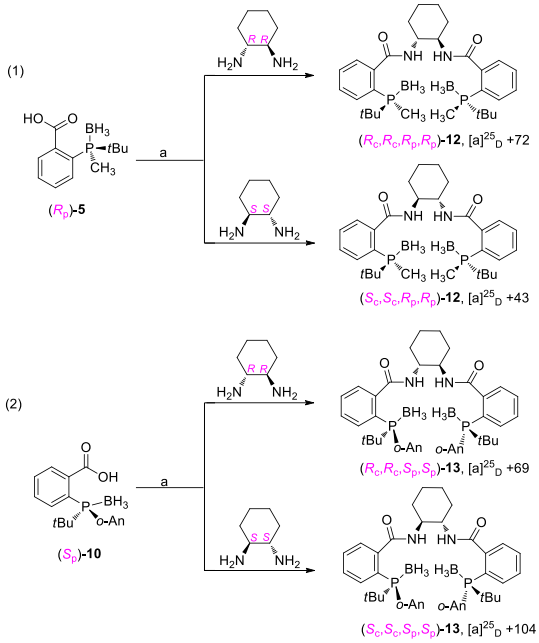
In addition, *tert*-butyl {[(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl]oxy}(2-methoxyphenyl)phosphine-borane adduct **7** was obtained as a diastereomeric mixture in 70% yield via a similar route involving successive reaction of *tert*-butyldichlorophosphine with sodium (1*R*,2*S*,5*R*)-menthoxide, (2-methoxyphenyl)magnesium bromide, and BH_3–THF complex.[18b] The crude product was subjected to chromatographic separation on silica gel and recrystallization from hexane to afford enantiopure (R_p)-**7** in 40% yield. Reductive cleavage of the P–O bond by lithium naphthalenide and subsequent addition of 1 M aq. HCl proceeded smoothly to produce (S_p)-*tert*-butyl(2-methoxyphenyl)phosphine–borane adduct **8** in 90% yield with inversion of configuration at the phosphorus atom.[18a]

The conversion of enantiopure (S_p)-**8** into its halogenated analog using *o*-dibromobenzene as a brominating reagent was inefficient, and the isolation of the small amount of brominated product was difficult. After extensive exploration of carefully controlled reaction conditions, we were delighted to find that the use of *o*-diiodobenzene led to the formation of (R_p)-*tert*-butyl(2-iodophenyl)(2-methoxyphenyl)phosphine **9** in 60% yield. Moreover, the haloarene moiety was efficiently converted to the corresponding benzoic acid by treatment with *n*-BuLi and CO_2 at low temperature, delivering (S_p)-2-(*tert*-butyl(2-methoxyphenyl)phosphino)benzoic acid–borane adduct **10** as a crystalline solid in 65% yield.

The absolute configuration of key intermediates such as (R_p)-**4**, (R_p)-**5**, (S_p)-**8**, (R_p)-**9**, and (S_p)-**10** was confirmed by X-ray crystallography and enantiopurities were determined by chiral HPLC analysis of the obtained compounds or their derivatives (R_p)-methyl-2-(*tert*-butyl(methyl)phosphino)benzoate–borane adduct **6** and (S_p)-methyl-2-(*tert*-butyl(2-methoxyphenyl)phosphino)benzoate–borane adduct **11**.

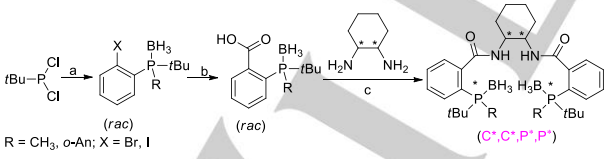
Next, (R_p)-**5** was activated with EDCI–HCl and HOBt, and subsequently reacted with each enantiomer of *trans*-1,2-diaminocyclohexane in the presence of 4-methylmorpholine,[16, 20] delivering diphosphines (R_c,R_c,R_p,R_p)- and (S_c,S_c,R_p,R_p)-**12** as white solids in 70% and 65% yields, respectively (Scheme 4). Although the similar condensation of *trans*-1,2-diaminocyclohexane and (S_p)-**10** in the presence of EDCI–HCl and HOBt led to the desired *P*,*C*-chirogenic diphosphines in low yields, the use of the more reactive EDCI enabled reaction at low temperatures. To this end, (S_p)-**10** reacted with EDCI and HOBt at –10 °C until the material was completely consumed. Subsequently, (1*S*,2*S*)- or (1*R*,2*R*)-diaminocyclohexane was carefully added to the activated intermediate at room temperature to furnish (S_c,S_c,S_p,S_p) and (R_c,R_c,S_p,S_p)-**13** 72% and 68% yields. Notably, racemization of the *C*-stereocenters

could be suppressed in the presence of HOBt at low temperature.



Scheme 4. Synthesis of (C*,C*,P*,P*)-diphosphines **12** and **13** from *trans*-1,2-diaminocyclohexane and (R_p)-2-(*tert*-butyl(methyl)phosphino)benzoic acid–borane adduct **5** or (S_p)-2-(*tert*-butyl(2-methoxyphenyl)phosphino)benzoic acid–borane adduct **10**. Reagents and conditions: (1) (a) (i) EDCI−HCl, HOBt, CH_2Cl_2, 0 °C, (ii) 4–methylmorpholine, (1*R*,2*R*)- or (1*S*,2*S*)-*trans*-diaminocyclohexane, 0 °C to rt. (2) (a) (i) EDCI, HOBt, CH_2Cl_2, −10 °C, (ii) (1*R*,2*R*)- or (1*S*,2*S*)-*trans*-diaminocyclohexane, 0 °C to rt.

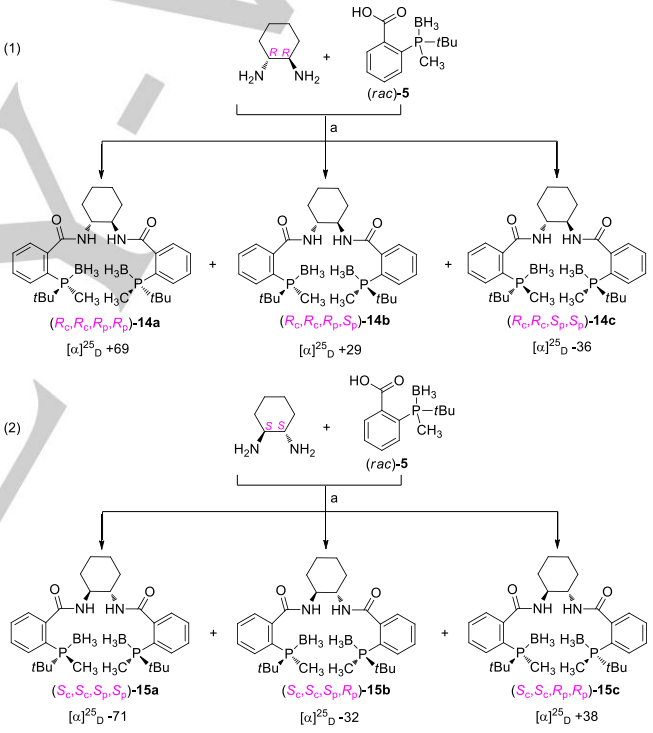
Although the (C*,C*,R_p,R_p)- and (C*,C*,S_p,S_p)-diphosphine stereoisomers could be synthesized by acylation of *trans*-1,2-diaminocyclohexanes with *P*-chirogenic phosphinobenzoic acids, their large-scale preparation is challenging because of the tedious synthesis of the enantiopure *P*-chirogenic compounds and the possibility of stereomutation of the *P*-stereocenters. Therefore, the development of convenient and efficient methods for accessing *P*,*C*-chirogenic diphosphines is highly desired.



Scheme 5. Synthesis of *P*,*C*-chirogenic diphosphines with different absolute configurations from *trans*-1,2-diaminocyclohexane and racemic carboxylic acid-substituted phosphine–borane adducts. Reagents and conditions: (a) (i) *i*-PrMgCl-LiCl, *o*-$C_6H_4Br_2$ or *o*-$C_6H_4I_2$, (ii) *t*-BuPCl$_2$, (iii) RMgBr, (iv) BH_3−THF; (b) (i) *n*-BuLi, (ii) CO_2, (iii) 1 M aq. HCl; (c) (i) EDCI−HCl/HOBt/4–methylmorpholine or EDCI/HOBt, (1*R*, 2*R*)- or (1*S*,2*S*)-*trans*-diaminocyclohexane.

During the optimization of the reaction conditions for the synthesis of enantiopure *P*-chirogenic phosphines (R_p)-**5** and (S_p)-**10**, materials obtained in low enantioselectivity were also employed in the condensation reaction with enantiopure *trans*-1,2-diaminocyclohexane, furnishing three different phosphine–borane adduct stereoisomers which could be conveniently separated by simple column chromatography. This unexpected finding prompted us to test the condensation of enantiopure *trans*-1,2-diaminocyclohexanes with racemic phosphinobenzoic acid–borane adducts for the straightforward preparation of different diastereoisomers of *P*,*C*-chirogenic diphosphines (Scheme 5).

Initially, we investigated the acylation of (1*R*,2*R*)-diaminocyclohexane and racemic **5** in the presence of EDCI–HCl and HOBt at room temperature. To our delight, the obtained mixture of diphosphines **14** could be separated by column chromatography on silica gel to deliver the enantiopure diastereomers (R_c,R_c,R_p,R_p)-**14a**, (R_c,R_c,R_p,S_p)-**14b** and (R_c,R_c,S_p,S_p)-**14c** in 18%, 34%, and 16% yield, respectively. Similarly, the reaction of (1*S*,2*S*)-diaminocyclohexane and racemic **5** afforded diphosphine diastereomers (S_c,S_c,S_p,S_p)-**15a**, (S_c,S_c,S_p,R_p)-**15b** and (S_c,S_c,R_p,R_p)-**15c** in 19%, 36%, and 18% (approximately 1:2:1 ratio) yield, respectively (Scheme 6).



Scheme 6. Synthesis of different diphosphine diastereomers from (1*R*,2*R*)- or (1*S*,2*S*)-*trans*-diaminocyclohexane and *rac*-2-(*tert*-butyl(methyl)phosphino)benzoic acid–borane adduct **5**. Reagents and conditions: (a) (i) EDCI−HCl, HOBt, CH_2Cl_2, 0 °C, (ii) 4–methylmorpholine, (1*R*,2*R*)- or (1*S*,2*S*)-diaminocyclohexane, 0 °C to rt.

The ^{1}H NMR spectra of the differently polar diastereomers indicated the presence of the secondary amide, methyl, and *tert*-butyl groups (see the Supporting Information for details). Additionally, the chemical shifts and amount of ^{31}P NMR signals showed that both *P*-atoms in (R_c,R_c,R_p,R_p)-**14a**, (R_c,R_c,S_p,S_p)-**14c**, (S_c,S_c,S_p,S_p)-**15a** and (S_c,S_c,R_p,R_p)-**15c** have the same absolute configuration, while (R_c,R_c,R_p,S_p)-**14b** and (S_c,S_c,S_p,R_p)-**15b** possess two differently configured *P*-atoms (Figure 1). While the optical rotations of diastereomers **14a**-**c**

and **15a-c** are different (Scheme 6), their molecular weight was the same as confirmed by HRMS.

By comparing the ^{31}P NMR spectra (Figure 1) and optical rotations of these diastereomers, we confirmed that (R_c,R_c,R_p,R_p)-**14a** is identical to (R_c,R_c,R_p,R_p)-**12** produced from the condensation of (R_p)-**5** and (1*R*,2*R*)-diaminocyclohexane, while (S_c,S_c,R_p,R_p)-**15c** is the same as (S_c,S_c,R_p,R_p)-**12** resulted from the corresponding reaction with (1*S*,2*S*)-diaminocyclohexane.

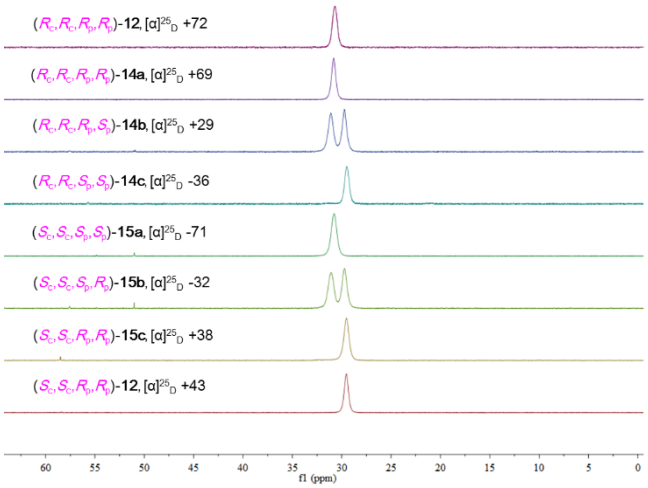
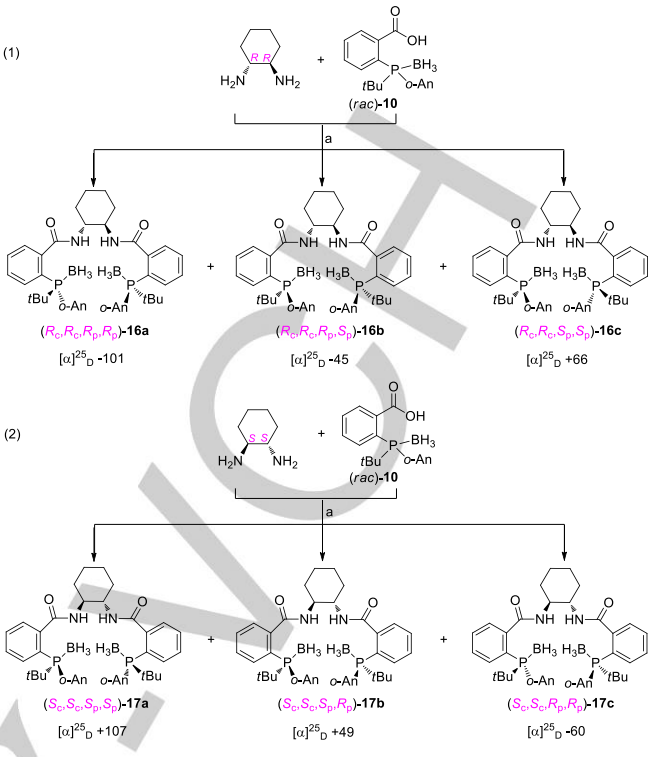


Figure 1. ^{31}P NMR spectra of the various diastereomers of diphosphines **12**, **14** and **15**.

Furthermore, this simple strategy was also employed to prepare *P*,*C*-chirogenic diphosphines **16** and **17** by the condensation of each enantiomer of *trans*-1,2-diaminocyclohexane with racemic **10** (Scheme 7). The diastereomers (R_c,R_c,R_p,R_p)-**16a**, (R_c,R_c,R_p,S_p)-**16b** and (R_c,R_c,S_p,S_p)-**16c** were obtained from (1*R*,2*R*)-diaminocyclohexane in 16%, 29%, and 18% yield, respectively, whereas (S_c,S_c,S_p,S_p)-**17a**, (Sc,Sc,Sp,*R*p)-**17b** and (S_c,S_c,R_p,R_p)-**17c** were produced from the corresponding (1*S*,2*S*)-enantiomer in 17%, 30%, and 15% isolated yield, respectively.

The ^{31}P NMR spectra (Figure 2) and optical rotations of these diastereomers demonstrated that (R_c,R_c,S_p,S_p)-**16c** was fully consistent with (R_c,R_c,S_p,S_p)-**13** obtained from (S_p)-**10** and (1*R*,2*R*)-diaminocyclohexane, whilst (S_c,S_c,S_p,S_p)-**17a** was identical to (S_c,S_c,S_p,S_p)-**13** generated by the reaction of (S_p)-**10** with (1*S*,2*S*)-diaminocyclohexane. Similarly, (R_c,R_c,R_p,S_p)-**16b** and (S_c,S_c,S_p,R_p)-**17b** possess two of different absolute configuration at *P*-atoms.

The corresponding free *P*,*C*-chirogenic diphosphines could be obtained by treatment of the diborane adducts of diphosphines using an excess of 1,4-diazabicyclo [2.2.2] octane (DABCO) in degassed toluene at 30 °C in excellent yield with retention of configuration at phosphorus (e.g., deboraned-(R_c,R_c,R_p,R_p)-**12**, see the Supporting Information for details). Owning to the mild conditions of the decomplexation, the epimerization of *P*-stereogenic could be effectively suppressed.[10c,18c,18d,21]



Scheme 7. Synthesis of different diphosphine diastereomersfrom (1*R*,2*R*)- or (1*S*,2*S*)-*trans*-diaminocyclohexane and *rac*-2-(*tert*-butyl(2-methoxyphenyl)phosphino)benzoic acid–borane adduct **10**. Reagents and conditions: (a) (i) EDCI, HOBt, CH_2Cl_2, −10 °C, (ii) (1*R*,2*R*)- or (1*S*,2*S*)-diaminocyclohexane, 0 °C to rt.

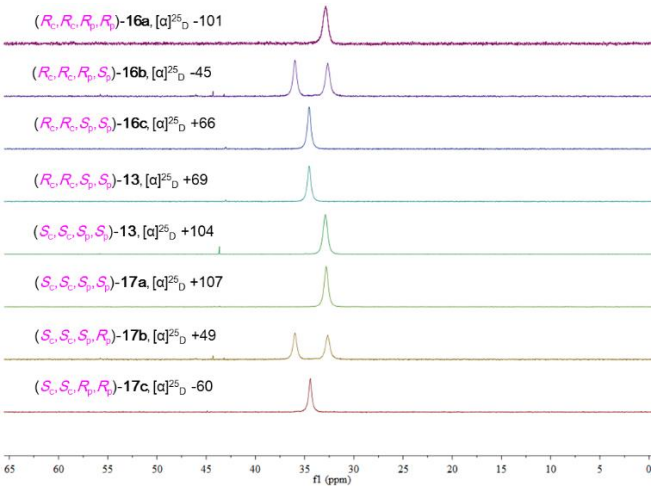


Figure 2. ^{31}P NMR spectra of the various diastereomers of diphosphines **13**, **16** and **17**.

Conclusion

In this paper, we reported a very simple and efficient strategy for preparing *P*-chirogenic Trost ligands with differently configured *P*-atoms from the borane adducts of racemic phosphinobenzoic acids without addition of any chiral auxiliary. The resulting diastereomers could be separated via simple column chromatography because of their different polarities. The

analytical data of the thus isolated (C*,C*,R_p,R_p) and (C*,C*,S_p,S_p) stereoisomers were identical to that of samples obtained from the condensation of each enantiomer of *trans*-1,2-diaminocyclohexane with the corresponding enantiopure *P*-chirogenic phosphines, which were in turn synthesized from *tert*-butyldichlorophosphine via a multi-step route using (–)-borneol and (–)-menthol as chiral auxiliaries. Moreover, this study largely facilitates the access to (C*,C*,R_p,S_p) stereoisomers with opposite configurations at the *P*-atoms, which are difficult to prepare by traditional methods involving the use of chiral auxiliaries. And, the free *P*,*C*-chirogenic diphosphines with retention of configuration at phosphorus atoms could be easily available under relatively mild conditions of the decomplexation. An exploration of the applications of the obtained *P*,*C*-chirogenic diphosphines as ligands in various asymmetric reactions are currently underway in our laboratory.

Experimental Section

General details can be seen in the online supporting information. The document contains detailed synthesis processes and analytical data of all reaction products, details about the NMR spectra, HPLC spectra of key intermediates (R_p)-**4**, (R_p)-**6**, (S_p)-**8**, (R_p)-**9**, (S_p)-**11** and X-ray crystallographic data of the (R_p)-**4** (CCDC No. 1996507), (R_p)-**5** (CCDC No. 1997211), (S_p)-**8** (CCDC No. 1997214), (R_p)-**9** (CCDC No. 1997213) and (S_p)-**10** (CCDC No. 1997212).

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Keywords: Chirality • Diastereoselectivity • Synthetic methods • Phosphine ligands • *P*-stereocenters

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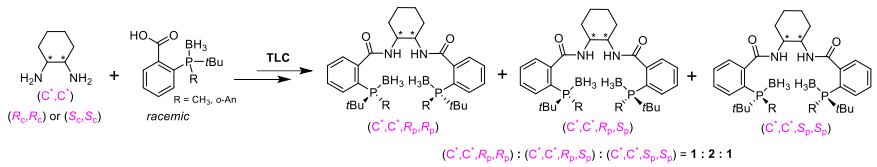

A simple, short and convenient route towards *P*-chirogenic Trost ligands obviates the use of chiral auxiliaries and enables the access to diphosphines with differently configured *P*-stereocenters.

Key Topic:

P,*C*-chirogenic Synthesis