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General and Stereoselective Method for the Synthesis of Sterically Congested and Structurally Diverse *P*-Stereogenic Secondary Phosphine Oxides

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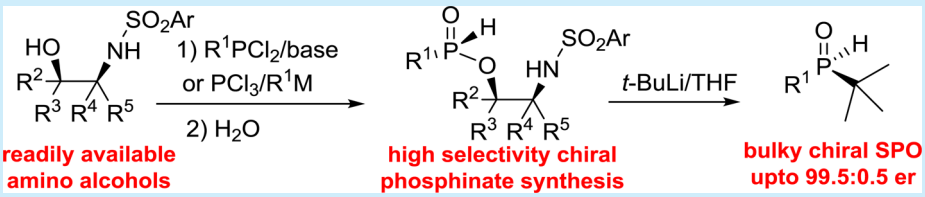
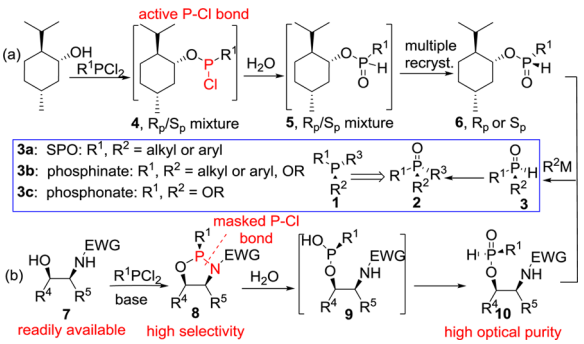
Supporting Information



ABSTRACT: A general and efficient method for the synthesis of bulky and structurally diverse *P*-stereogenic chiral secondary phosphine oxides (SPOs) by using readily available chiral amino alcohol templates is described. These chiral SPOs could be used as chiral building blocks for the synthesis of difficult-to-access bulky *P*-stereogenic phosphine compounds or ligands for organic catalysis.

P-Stereogenic chiral phosphines (*P*-SCPs, **1**, Scheme 1) have been demonstrated as effective ligands in enantioselective organometallic catalysis.[1] However, their development has been significantly hindered due to the synthetic challenges.[2,3] *P*-Stereogenic chiral tertiary phosphine oxides (TPOs, **2**, Scheme 1), on the other hand, are attractive precursors of *P*-SCPs due to their air- and moisture-stability and can be prepared in high chemical and optical purity.[4] Elegant work has been carried out recently for the synthesis of certain types of **2**, but the synthesis of sterically hindered variations, such as those containing a *tert*-butyl functionality, still remains a significant challenge.[3,5]

Scheme 1. Strategies for Synthesis of Enantiomerically Enriched SPOs and Their Applications



Secondary phosphine oxides (SPOs, **3**, Scheme 1) are promising precursors of **2** since the P−H bond can be readily functionalized, thus offering a handle for differentiation. As SPOs are inherently less sterically demanding, the incorporation of sterically demanding substituents (e.g., *t*-Bu) should be more facile, thus providing an alternative avenue for the synthesis of sterically hindered TPOs.[6−9] Moreover, SPOs themselves have been found to be effective ligands for a number of transformations (nonenantioselective).[10] Despite the wide range of potential applications of SPOs, their synthesis has met with limited success. Buono, Han, and co-workers have reported pioneering work on the asymmetric synthesis of SPOs by employing menthol as a chiral auxiliary (Scheme 1a).[3c,5c] Chemical and kinetic resolution are other means of preparation that have also been described recently,[8] but only a limited scope of *P*-stereogenic SPOs has been prepared. Therefore, an effective asymmetric synthesis of chiral **3** entities with diverse structures needed to be developed in order to better understand the properties of SPOs and to further expand their synthetic utilities.

Aiming to develop a practical and stereoselective SPO synthesis, we focused on using readily available chiral 1,2-amino alcohols as templates. On the basis of our previous work,[3d] we envisioned that the reaction of R^1PCl_2 with **7** would provide intermediate **8** in optically pure form (Scheme 1b). The more reactive P−N bond should selectively react with water to afford phosphinate **10** in a stereospecific fashion. The subsequent reaction of a nucleophile R^2 M with **10** would afford the chiral nonracemic SPO. Herein, we report the development of a general and stereoselective method for the synthesis of structurally diverse, sterically demanding, *P*-stereogenic SPOs

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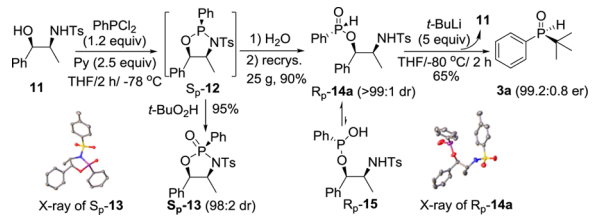
based on the above-mentioned concept. The application of chiral SPO in the synthesis of bulky *P*-stereogenic TPO under catalytic conditions is also described.

To evaluate our strategy, (1*R*,2*S*)-norephedrine **11** was first used for the study. Recently, we reported that either R_p-**13** or S_p-**13** 1,3,2-benzoxazaphosphinine-2-oxide is useful for the synthesis of *P*-stereogenic phosphine oxides (Scheme 2).[3d] The

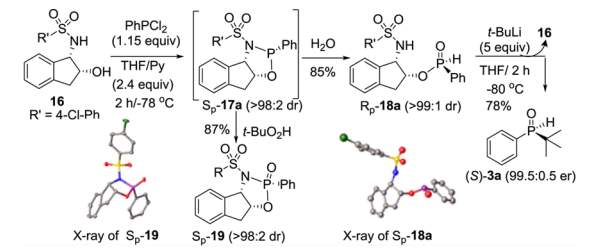
Scheme 2. Stereochemistry and Synthesis of (*S*)-*t*-Bu(Ph)-phosphine Oxide 3a Using 11 as Template



synthesis of **13** using $PhP(O)Cl_2$ generally provided the R_p-isomer preferentially, except when pyridine was used as base when the S_p-isomer was the major product but in low selectivity (63:37 dr). Later studies demonstrated that S_p-**13** could be obtained in high selectivity (98:2 dr) by first treating **11** with $PhPCl_2$ instead of $PhP(O)Cl_2$ to yield S_p-**12**, followed by oxidation with *t*-BuO_2H. S_p-**13** is a crystalline product, and its enantiomerically pure form was obtained by recrystallization from EtOAc/hexanes. On the other hand, in situ treatment of S_p-**12** with water afforded a stable crystalline product phosphinate R_p-**14a** in 98:2 dr, and its enantiomeric pure form was obtained via a single crystallization in 90% yield. The stereochemistry of R_p-**14a** was determined by single-crystal X-ray crystallography. It was reasoned that R_p-**14a** was formed through R_p-**15** that was obtained by nucleophilic addition of water on phosphorus by cleaving the active P−N bond via an S_N2 mechanism. Interestingly, treatment of R_p-**14a** with *t*-BuLi gave a clean reaction and afforded the highly enantiomerically enriched SPO (*S*)-*tert*-butyl(phenyl)phosphine oxide **3a**[5c] in good isolated yield with full recovery of **11**.

Encouraged by the above results, the potential of other chiral amino alcohols as auxiliaries for the synthesis of chiral SPO was explored such as the readily available (1*S*,2*R*)-aminoindanol **16** that has been previously used in the synthesis of *P*-stereogenic phosphanamine and chiral sulfinamides.[5b,11] Using the same protocol, treatment of **16** with $PhPCl_2$ in THF at −78 °C yielded S_p-**17a** in high selectivity of >98:2 dr, and its stereochemistry was determined by the single-crystal X-ray of its oxidation product S_p-**19** (Scheme 3). In situ treatment of S_p-**17a** with water afforded R_p-**18a** in high selectivity of >98:2 dr. R_p-**18a** is a crystalline product, and one crystallization from EtOAc/hexanes yielded its enantiomerically pure form in 85%

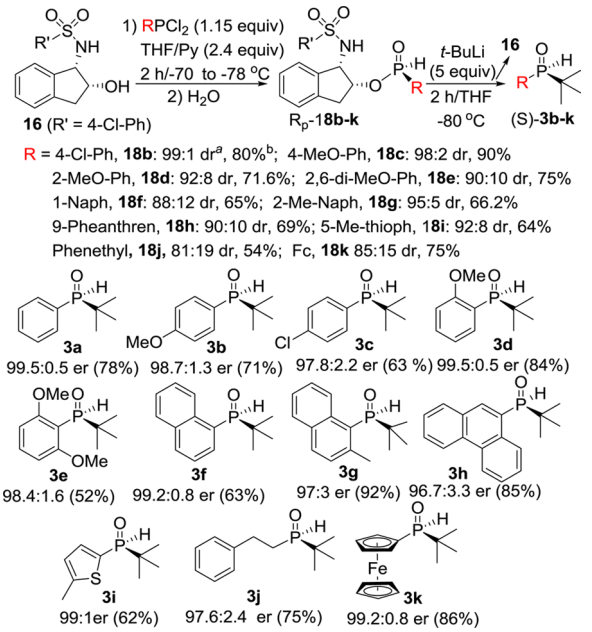
Scheme 3. Asymmetric Synthesis of 3a by Using 16



overall yield. As expected, reaction of R_p-**18a** with *t*-BuLi in THF at −80 °C provided highly enantiomerically enriched (*S*)-**3a** in 78% isolated yield with the full recovery of template **16**.

Having identified the optimal reaction conditions, the scope of the synthesis of diastereomerically pure **18** was examined. The results in Table 1 show that a broad scope of *H*-

Table 1. Substrate Scope for the Synthesis of *P*-Stereogenic SPOs Using (1*S*,2*R*)-Aminoindanol Derivative 16



[a]Selectivity based on NMR analysis or LC/MS. [b]Isolated yield after recrystallization for enantiomerically pure product.

phosphinate products **18** can be obtained with good-to-excellent selectivities and high yields. Products with phenyl substituents (**18b−e**), naphthalene substituents, phenanthrenes (**18f−h**), heterocycles (**18i**), ferrocene (**18k**), and alkyl substituents (**18j**) all proceeded with high selectivities and were readily prepared. *All of the reaction products were crystalline, and their optically pure forms were readily obtained via a single crystallization and prepared on multigram scale.*

The synthesis of *P*-stereogenic SPOs is straightforward using the above protocol of treatment of **18** with *t*-BuLi in THF. Clean reactions were observed in all cases (Table 1). The scope of the *P*-stereogenic SPOs products that can be synthesized range from ones containing phenyl with diverse substituents (**3b−e**), polycyclic aromatics (**3f−h**), and even heterocycle-substituted (**3i**) and dialkyl SPO (**3j**). It should be noted that the hindered **3g** was accessed previously only by chromatographic separation.[10c]

The efficient synthesis of chiral phosphinates using readily available PCl_3 and an organometallic reagent was next explored, and the success of this approach would avoid the synthesis of phosphine dichloride reagents such as $ArPCl_2$ (Scheme 4).

The stereochemistry of the process was first examined by the synthesis of **18d**. Treatment of **16** with PCl_3 in THF in the presence of pyridine at −78 °C for 2 h afforded **20**, and its reaction with water afforded **21** in high isolated yield. Interestingly, treatment of **20** with 2-MeO-PhMgBr in situ followed by addition of water provided **18d** in 82% yield and >85:15 dr. Recrystallization of crude **18d** from EtOAc/hexanes afforded the enantiomerically pure R_p-**18d** with an (*R*)-

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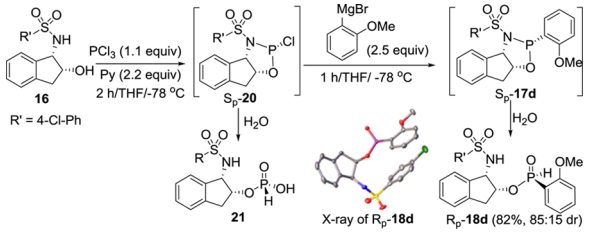
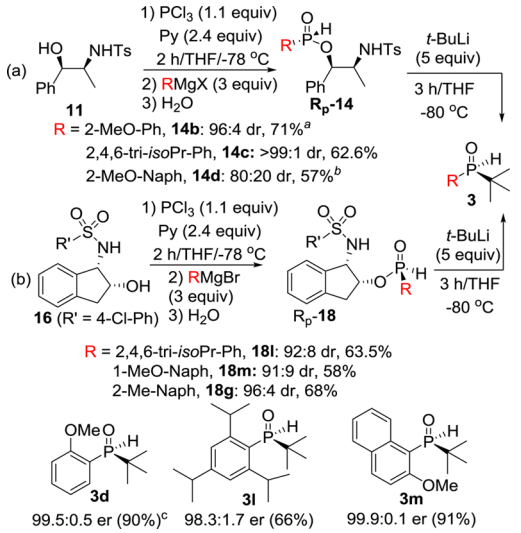
Scheme 4. Synthesis of *P*-Stereogenic Phosphinates via PCl_3 and an Organometallic Reagent



configuration at phosphorus as confirmed by single-crystal X-ray analysis. It was envisioned that R_P-**18d** was obtained through intermediate S_P-**17d** as described in Scheme 3, and therefore, it was rationalized that the configuration of **20**,[12a] formed supposedly via *N*-tosylsulfonamide attacks on phosphorus from the less hindered side, was retained in the reaction with 2-MeO-PhMgBr as observed in a similar system by Xiao et al.[12b] Similarly, treatment of **11** with PCl_3 followed by 2-MeO-PhMgBr and water afforded phosphinate **14b** in 94:6 dr and 71% isolated yield and in enantiomerically pure form after recrystallization (Table 2).

Table 2. Synthesis of More Hindered P-Stereogenic SPOs

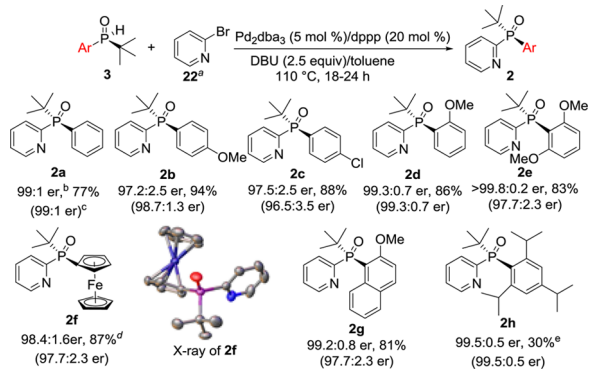


[a]Isolated yield after recrystallization for enantiomerically pure products. [b]Combined yields for both diastereomers.[13] See the Supporting Information for details. [c]Prepared from **13b**.

This strategy was first applied for the synthesis of bulky *P*-stereogenic SPO *tert*-butyl(2,4,6-triisopropylphenyl)phosphine oxide **3l** (Table 2). When either **11** or **16** was used, treatment with PCl_3 followed by 2,4,6-triisopropyl-PhMgBr and water afforded the corresponding phosphinates **14c** and **18l** with excellent selectivity of >99:1 dr and 98:2 dr, respectively. Both compounds are crystalline products, and gram quantities of enantiomerically pure products were isolated in good yield after a single recrystallization. The subsequent reaction of **14c** or **18l** with *t*-BuLi provided the bulky **3l** in high enantiomeric purity and good yield (Table 2). The scope of this approach was demonstrated in the synthesis of other chiral phosphinates **14d**, **18g**, and **18m** in good-to-excellent selectivities, from which *P*-stereogenic SPOs such as 2-MeO-naphthalene **3m** were prepared successfully in high stereoselectivities.

Use of these SPOs in the synthesis of *P*-stereogenic tertiary phosphine oxides (TPOs) by transition-metal-catalyzed coupling reactions was investigated. Transition-metal-catalyzed SPO coupling with aryl halides via P−C bond formation has been reported for the synthesis of racemic substrates,[14] but few reports have dealt with the reactions of chiral nonracemic or sterically unhindered chiral SPOs.[14b,c] Our interest in the synthesis of chiral phosphine ligands with heterocycle functionality led us to explore the coupling of 2-bromopyridine **22** with chiral SPOs. Reaction conditions were surveyed first for the synthesis of **2a**. Treatment of **22** with **3a** in the presence of 5 mol % of Pd_2dba_3 and 20 mol % of dppp (1,3-bis(diphenylphosphino)propane) in toluene gave a reaction that was only complete after 18 h at 110 °C. It afforded **2a** in good isolated yield without enantiopurity erosion. Single-crystal X-ray analysis of **2f** revealed that the reaction proceeded with retention of stereochemistry as observed by Herzon et al.[14b] Following this protocol, a variety of pyridine-containing *P*-stereogenic TPOs with diverse functionalities were readily prepared (Table 3). Moreover, very bulky TPOs such as **2e−g**

Table 3. Synthesis of Chiral TPOs via Coupling Reaction



[a]1.2 equiv of **22** used except where indicated. [b]er based on chiral HPLC analysis. [c]er of SPOs used for the reaction. [d]2.4 equiv of **22** used. [e]20 mol % of catalyst used.

were all obtained in high yields and excellent enantiomeric purities. The exceedingly bulky phosphine oxide **2h** was also synthesized in excellent selectivity of 99.5:0.5 er albeit in diminished yield due to the severe steric hindrance. It is worth noting that the synthesis of such bulky *P*-stereogenic phosphine oxides was not possible using previously reported methods. We believe that the newly developed method should greatly facilitate the design and synthesis of more efficient *P*-stereogenic P,N ligands, which are an important class of phosphine ligand in catalysis.[15]

Furthermore, the synthesis of *P*-stereogenic bis-phosphine oxides was also achieved by using this coupling strategy. Reaction of 2,6-dibromopyridine with **3d** afforded **23** in good yield and excellent selectivity. Subsequent reaction of **23** with another equivalent of **3d** furnished bis-phosphine oxide **24** efficiently and in highly enantiomerically enriched form. The latter is a key precursor for the synthesis of a *P*-stereogenic P, N, P ligand (Scheme 5 (a)). Phosphine oxide **26** was also prepared successfully via this method, which can be used for the synthesis of *P*-stereogenic version of QUINAP type of P, N ligands (Scheme 5(b)).

The application of SPOs in the synthesis of a phosphine ligand was demonstrated in the synthesis BI-DIME, which finds many applications in catalysis chemistry.[3d,16] Following the

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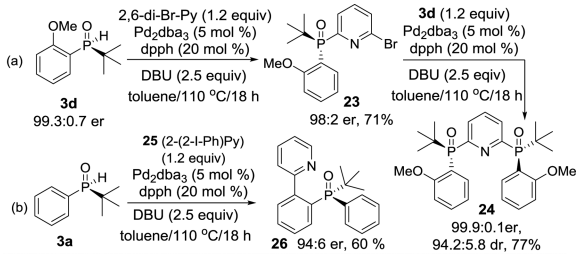
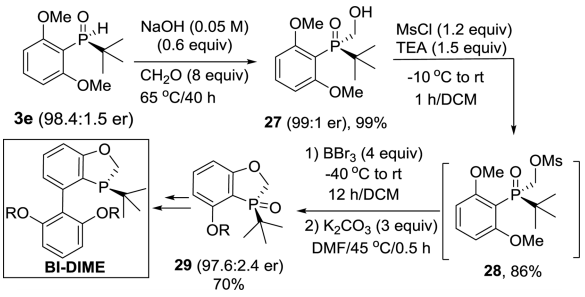
Scheme 5. Synthesis of Phosphine Oxides Used for P,N Ligand Precursors



reaction shown in Scheme 6,[8a] **3e** was converted to **29**, a key precursor for BI-DME, in high yield with high enantiomerica purity (Scheme 6).

Scheme 6. Synthesis of BI-DIME Precursor



In summary, a general and stereoselective methodology has been developed for the synthesis of *P*-stereogenic chiral SPOs. The method relies on the efficient synthesis of chiral secondary phosphinates using the readily available amino alcohols as chiral templates. These chiral phosphinates are readily prepared on a multigram scale, from which a variety of sterically hindered and structurally diverse chiral SPOs were prepared. The chiral templates can be recovered after the reaction and can be reused. These SPOs were successfully employed for the synthesis of hindered TPOs with high stereospecificities. We believe that this method offers a new avenue for the design and synthesis of versatile *P*-stereogenic chiral phosphine ligands for asymmetric catalysis, and these and other related applications are under investigation in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00568.

Experimental procedures, detailed reaction condition survey results, and spectroscopic data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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