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The first asymmetric synthesis of trialkyl phosphates on the basis of dynamic kinetic resolution in the phosphite method using a chiral source in a catalytic manner†

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The first asymmetric synthesis of trialkyl phosphates having stereogenic phosphorus atoms on the basis of dynamic kinetic resolution using a chiral source in a catalytic manner; achieved through the stereospecific oxidation of a trialkyl phosphite enantioselectively obtained by the condensation of a racemic unsymmetrically substituted dialkyl phosphorochloridite and an alcohol using a chiral amine as a catalytic promoter.

There exist many biologically and chemically attractive chiral organophosphorus compounds with stereogenic centers on the phosphorus atoms (*P*-chiral organophosphorus compounds); these include phospono,[1] EPN[2] and profenofos.[3] Studies on these substances have shown that their properties are affected by the chirality of the phosphorus atoms. Thus, it is important to prepare such *P*-chiral organophosphorus compounds in an enantioselective manner.[4] However, we cannot easily achieve the asymmetric synthesis of these compounds because of the lack of usable methods for attaining this purpose. Therefore we have aimed to invent a new tool useful for the asymmetric synthesis of *P*-chiral organophosphorus compounds. Among the various methodologies for asymmetric synthesis developed so far, dynamic kinetic resolution is the most effective, because it can use racemic starting materials. Thus, it would be most favorable if a method was developed for asymmetric synthesis by means of dynamic kinetic resolution.

To the best of our knowledge, there have been three reports on the enantioselective preparation of *P*-chiral organophosphorus compounds based on this strategy. One example is the production of *P*-chiral methyl *p*-nitrophenyl alkylphosphonates *via* treatment of alkylphosphonyl dichlorides with *p*-nitrophenol followed by methanol in the presence of a stoichiometric amount of ethyl L-prolinate.[5] The second example is the formation of *P*-chiral alkyl(*tert*-butyl)phenylphosphine–boranes through alkylation of *tert*-butylphenylphosphine–boranes with butyllithium and alkyl halides or triflates in the presence of a stoichiometric amount of (−)-sparteine as a chiral auxiliary.[6] The third example is the preparation of *P*-chiral phosphinic acid esters through the condensation of phosphinyl chlorides and alcohols by the assistance of a stoichiometric amount of (−)-$C_6H_5CH(CH_3)N(CH_3)_2$ as a promoter.[7] However, these methodologies have some problems. For example, though the catalytic use of the chiral reagent is universally desirable for asymmetric synthesis, these three strategies have to use a stoichiometric amount of the chiral source. Further, these methods do not provide a sufficient synthetic flexibility and are only useful for the preparation of a limited class of substances. Accordingly, there is a strong need for development of a new method which is achievable by the use of a chiral source in a catalytic manner and is applicable to the synthesis of a variety of compounds. Among the organophosphorus compounds, phosphites serve as precursors for the preparation of a wide range of substances, including phosphates, phosphorothioates, phosphoroselenoates, and boranophosphates. Therefore, it would be greatly significant to develop a method for the asymmetric synthesis of *P*-chiral trialkyl phosphites using the dynamic kinetic resolution strategy, in which the chiral source is used in a catalytic manner. This communication discloses the first example of such a type of asymmetric synthesis of a *P*-chiral trialkyl phosphate *via* a phosphite intermediate which is obtained by the condensation of a dialkyl phosphorochloridite and an alcohol using a catalytic chiral amine (the phosphite method).

We carried out the asymmetric synthesis of the trialkyl phosphate **8** according to the following procedure. To a mixture of the racemic phosphorochloridite **1**‡ (1.0 mmol) and the chiral amine **3**[8] (0.1 mmol, a promoter) in THF (10 mL) was added at −78 °C over 5 min a mixture of benzyl alcohol (1.0 mmol) and diisopropylethylamine (1.0 mmol, a scavenger of hydrochloric acid generated in the progress of the reaction). The mixture was warmed up to 25 °C over 12 h. To this was added a 3.0 M solution of *tert*-butyl hydroperoxide in toluene (2.0 mmol) and stirring was continued for an additional 30 min at 25 °C. The resulting mixture was subjected to the usual extractive workup to afford a crude product of the trialkyl phosphate **8** (an 88% yield based on the ^{31}P NMR assay). Chromatography of this crude material on silica gel gave pure **8**‡ in an 80% yield. HPLC analysis using a chiral column indicated that this chromatographed material consists of an 88 : 12 ratio of two enantiomers (76% ee, see Fig. 1). The small-scale HPLC separation of these enantiomers gave the major isomer in a pure form,§ but the minor isomer could not be obtained in a pure form. The optical purity of the pure major enantiomer was not changed by exposure to the extractive workup and chromatography conditions. This result indicated that the chiral phosphate **8** is configurationally stable under these conditions. The $[\alpha]_D$ of the 88 : 12 mixture of the two enantiomers§ was −25.8° (d = 1.13, neat, 25 °C).

The enantioselectivity and yield of this synthesis was strongly affected by the amount and type of the promoter, the

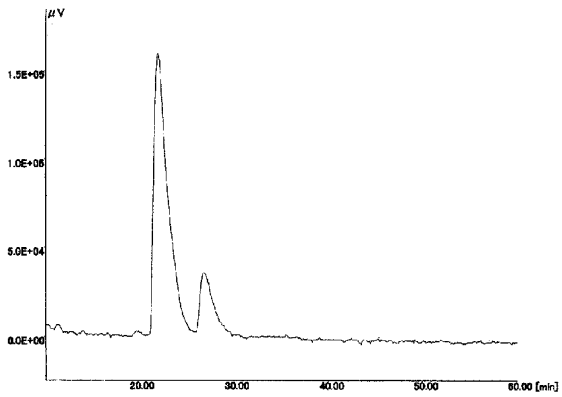

Fig. 1 HPLC profile of **8** obtained by the synthesis using promoter **3**. *Conditions*: DAICEL CHIRALCEL OJ column (4.6 × 250 mm); eluent, hexane : 2-propanol = 9 : 1, detection 254 nm, flow rate 0.5 mL min^{-1}, temperature 25 °C.

† Electronic supplementary information (ESI) available: procedures for the preparation of compounds **1**, **2**, **4**, **8**, **9** and **10** and their ^{1}H-, ^{13}C- and ^{31}P-NMR spectra. See http://www.rsc.org/suppdata/cc/b3/b304163h/

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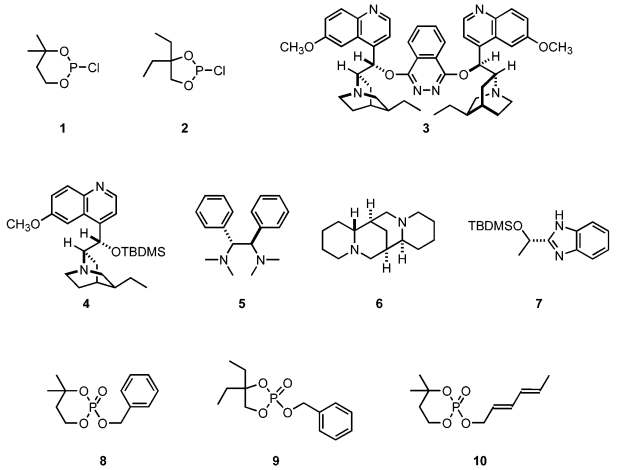
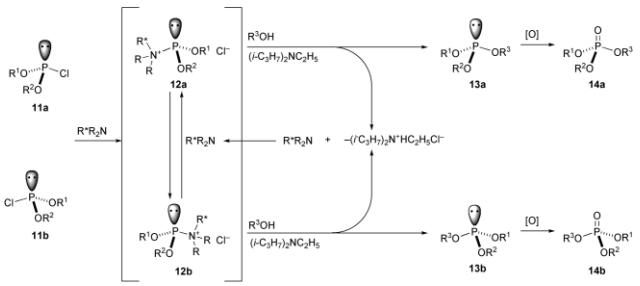
type of reaction solvent, and the type of amine used for trapping the acid. In the synthesis of 0.05 or 0.01 molar equivalents of **3** toward **1** and benzyl alcohol, the optical yield of the product **8** dropped to 29 or 6% ee, respectively. As the promoter, **3** was most effective. The use of **4**‡, **5**,[9] **6**¶ or **7**[10] in place of **3** decreased the optical yield and the chemical yield of the product **9** to 4–20% ee and 11–48%, respectively. As the reaction solvent, THF was the best choice. The use of acetonitrile, dichloromethane, and toluene lowered the enantioselectivity and yield to 11–15% ee and 62–71%, respectively. As the acid scavenger, the use of pyridine or 2,4,6-tri-*tert*-butylpyridine in place of diisopropylethylamine showed an extremely low degree of enantioselectivity (less than 10% ee). Asymmetric induction was also observed in the synthesis using **2** as the phosphorochloridite or (*E*,*E*)-2,4-hexadien-1-ol as the alcohol, but the optical yield of the product was rather low. Thus, synthesis *via* the condensation of **2** and benzyl alcohol (1.0 equiv. each) assisted by **3** (0.1 equiv.) followed by the TBHP oxidation gave **9** with a 24% ee of optical purity in 49% yield. In the synthesis using the hexadienyl alcohol and **1** as building blocks, the phosphate **10** was obtained in a 69% yield and its optical purity was 64% ee.



In the present synthesis of the trialkyl phosphate, the oxidation of the trialkyl phosphite to the phosphate is carried out in a stereospecific manner. Therefore, we consider that the asymmetric reaction is occurring in the formation of trialkyl phosphite intermediates as shown in Scheme 1. Thus, the chiral amine promoter initially reacts with racemic dialkyl phosphorochloridites **11a** and **11b** to form a diastereomeric mixture of the cationic phosphoramidite derivatives **12a** and **12b**. Judging from related reactions, **12a** and **12b** would be convertible to each other by the assistance of the amine, and this interconversion would be faster than their following reaction with alcohol, giving phosphites **13a** and **13b**. Here, the thermodynamic stability of **12a** and **12b** is different, and thus one of the isomers would exist in a much higher concentration. Further, these two diastereomers must have different reactivities. Consequently, the difference in stability and/or reactivity of the two diastereomers of **13** causes the dynamic kinetic resolution allowing the asymmetric reaction.‖



Scheme 1 A possible mechanism for the asymmetric synthesis of a trialkyl phosphate through a trialkyl phosphite on the basis of dynamic kinetic resolution in the condensation of a dialkyl phosphorochloridite and an alcohol using a chiral amine as promoter in a catalytic manner.

In conclusion, we have revealed the first example of the asymmetric synthesis of a *P*-chiral trialkyl phosphate *via* a trialkyl phosphite, in which the keystone is dynamic kinetic resolution in the condensation of a dialkyl phosphorochloridite and an alcohol by the catalytic assistance of a chiral amine. The present method has the following advantages. The chiral source can be catalytically utilized, and the dialkyl phosphorochloridite is usable in a racemic form. Further, the synthetic applicability is high, because the phosphites can be derived to a wide class of *P*-chiral organophosphorus compounds by means of a suitable oxidative treatment. This strategy may allow the asymmetric synthesis of not only the phosphates demonstrated here but also phosphorothioates by sulfurization,[11] phosphoroselenoates through selenation[12] and boranophosphates by boranation.[13] These three derivatives are unable or difficult to prepare using other methods, particularly the existing dynamic kinetic resolution methods. Thus, though the method described here does not provide numerous products and the optical yields of products are not high, the present strategy appears to possess strong potential and can be expected to serve as a major tool for the symmetric synthesis of *P*-chiral organophosphorus compounds in the future.

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Notes and references

‡ New compounds **1**, **2**, **4**, **8**, **9** and **10** showed ^{1}H-, ^{13}C- and ^{31}P-NMR spectroscopic data and MS data in agreement with their structures.

§ We attempted the large-scale separation of two enantiomers by preparative HPLC under several conditions to obtain a sufficient amount of the pure sample for measuring the $[\alpha]_D$, but so far have been unsuccessful. Therefore, the $[\alpha]_D$ was measured using the 88 : 12 mixture of two enantiomers.

¶ The material supplied from Aldrich was used without purification.

‖ At present, it has not been elucidated which difference in stability or reactivity of the two diastereomers of **12** is the main factor causing the asymmetric synthesis. We are investigating this subject and will report the results at a later date.

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