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学位の種類	博士（理学）
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審査研究科	数理物質科学研究科
学位論文題目	Studies on Catalytic PO-R Bond Cleavages Generating Phosphonates (触媒的 PO-R 結合切断によるホスホン酸類合成に関する研究)

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## 論文の要旨

Ms. Chuanya Li's thesis described her achievements gained in studies on the development of new synthetic methods for organophosphorus compounds. Organophosphorus compound plays an important role in agricultural, pharmaceutical, organic synthesis, catalysts and materials chemistry. In this regard, a large number of these compounds have been prepared. However, only a limited number of synthetic methods have been developed. This is practically true for C-P bonding formation reactions. For example, the two widely employed classical methods for C-P bonding formation are the nucleophilic substitution reaction of a toxic halophosphorus compound with an organolithium or a Grignard reagent, and the Michaelis-Arbuzov reaction using a phosphite and an aliphatic halide, respectively. Tons of organophosphoryl compounds are prepared every year by these methods. However, these traditional methods suffer from drawbacks, such as low atomic efficiency and poor selectivity. Therefore, new methods for the preparation of organophosphorus compounds that can solve the current drawbacks are highly desirable.

In the thesis, the applicant studied new methods for the preparation of hydrogen phosphonates  $\text{H-P(O)(OR)}_2$ , alkylphosphonates  $\text{R-P(O)(OR)}_2$ , arylphosphonates  $\text{Ar-P(O)(OAr)}_2$ , and phosphonic acids  $\text{RP(O)(OH)}_2$ , via catalytic cleavages of PO-R bonds of the commercially available starting chemicals. Currently, hydrogen phosphonates  $\text{H-P(O)(OR)}_2$  is prepared by the reactions of  $\text{PCl}_3$  with ROH. Alkylphosphonates  $\text{R-P(O)(OR)}_2$  are prepared from  $(\text{RO})_3\text{P}$  with RX (the Michaelis-Arbuzov reaction) under high temperatures. All these two reactions produce a lot of wastes. On the other hand, there is no general method for the preparation of arylphosphonates  $\text{Ar-P(O)(OAr)}_2$ . Phosphonic acids  $\text{R-P(O)(OH)}_2$  are most generally prepared by the hydrolysis of dialkyl phosphonates using hot concentrated hydrochloric acids (HCl).

Firstly, the applicant disclosed efficient Brønsted acids-catalyzed PO-R cleavage of P(III) esters that

selectively producing P(O)–H and P(O)–R compounds, respectively. Although, the reaction of P(OR)<sub>3</sub> with Brønsted acids to give HP(O)(OR)<sub>2</sub> was known, its synthetic applications have not been fully explored. Alkylphosphonates have long been prepared by the Michaelis–Arbuzov reaction. However, this reaction was usually conducted under harsh conditions accompanied with a lot of side products. This Brønsted acid-catalyzed mild Michaelis–Arbuzov rearrangement of P(OR)<sub>3</sub> discovered by the applicant is unprecedented. TfOH was used as the catalyst for the reactions. For reactions in the presence of water, trialkyl, triallyl, tribenzyl and triphenyl phosphites also afforded the corresponding H-phosphonates in quantitative yields. Alkyl diphenylphosphinites, despite having different alkyl groups, all afforded the same H-phosphine oxide quantitatively. In the case of dimethyl phenyl phosphite, C–O cleavage could occur at both the MeO and PhO moieties, leading to a mixture of products. On the other hand, in the absence of water, substrates with methyl, ethyl, *n*-butyl, allyl, benzyl groups all gave the corresponding alkylphosphonates in high yields under the standard conditions. Unsymmetrical phosphites underwent C–O cleavage at the MeO moiety selectively and gave the corresponding phosphonates in high yields. Selective transformation was also achieved with substrates having both bulky and small alkoxy groups, the reactions selectively occurred at the smaller MeO group. A recyclable solid acid Nafion also showed excellent catalytic activity for these reactions. Based on a series control experiments and a theoretical calculation, the applicant proposed a possible mechanism for these reactions that involves phosphonium salt formed via the protonation of the phosphite by TfOH.

Then, the applicant studied palladium-catalyzed Michaelis–Arbuzov reaction of (ArO)PZ<sub>2</sub> to aryl phosphonates, phosphinates and phosphine oxides. Michaelis–Arbuzov reaction, the formation of P(V) phosphonates RP(O)(OR)<sub>2</sub> by the rearrangement of P(III) phosphites via a combination of (RO)<sub>3</sub>P/RX, was discovered more than 120 years ago. However, the most challenging preparation of Ar'P(O)(OAr)<sub>2</sub> from (ArO)<sub>3</sub>P/Ar'X still remained unsolved yet. The applicant discovered that a simple palladium–ArX catalyst system can efficiently catalyze the transformation of (ArO)<sub>3</sub>P to ArP(O)(OAr)<sub>2</sub> from a combination of (ArO)<sub>3</sub>P/ArX. The reaction was rather general. Thus, all the reactions with an electron-donating group (Me, *t*-Bu, MeO) took place efficiently to give the phosphonates in high yields. However, a substrate with an electron-withdrawing group, tris(4-fluorophenyl) phosphite, for example, gave a low yield of the product under similar conditions. This transformation can also be readily extended to aryl phosphinites to synthesize the corresponding aryl phosphinates. Similarly, aryl phosphine oxides can be prepared by the isomerization of phosphinites in moderate yields. Aliphatic phenyl dibutylphosphinite and the bulky phenyl dicyclohexylphosphinite also served well as the substrates. Not only phenylphosphites, other arylphosphites also underwent similar reactions to produce the corresponding phosphonates in excellent yields. Based on a series control experiments, the applicant proposed a possible mechanism for the Pd-catalyzed *sp*<sup>2</sup>C–O cleavage reactions of P(III) esters. Firstly, Pd(0) (Pd<sub>2</sub>(dba)<sub>3</sub>) may react with (ArO)PZ<sub>2</sub> to give a new palladium catalyst Pd[PZ<sub>2</sub>(OAr)]<sub>3</sub>, which then undergoes oxidative addition with PhX (X = I, OTf) to give palladium-aryl complex PhPd[PZ<sub>2</sub>(OAr)]<sub>2</sub>X. The reductive elimination of this complex afforded the phosphonium salt PhP<sup>+</sup>Z<sub>2</sub>(OAr)X<sup>–</sup> and regenerate Pd(0). The Pd(0) catalyst then reacts with (ArO)PZ<sub>2</sub> to produce Pd[PZ<sub>2</sub>(OAr)]<sub>3</sub> again. X<sup>–</sup> may attack the ArO moiety of PhP<sup>+</sup>Z<sub>2</sub>(OAr)X<sup>–</sup> through an intramolecular S<sub>N</sub>2

reaction to give  $sp^2C-O$  cleaved and rearranged  $Ph-P(O)Z_2$  and generate the corresponding  $ArX$ .

Finally, the applicant studied the conversion of the phosphoryl esters prepared above to phosphonic acids and related compounds. The applicant discovered that Brønsted acids catalyzed wet and dry processes for the selective transformation of phosphonates to phosphonic acids. In the presence of water, alkyl, alkenyl and aryl substituted phosphonates can be hydrolyzed to the corresponding phosphonic acids in good to excellent yields catalyzed by trifluoromethyl sulfonic acid at 140 °C. On the other hand, with specific substituents of the phosphonate esters, the conversion to the corresponding phosphonic acids can be achieved under milder conditions in the absence of water (the dry process). For example, the conversion of dibenzyl phosphonates to the corresponding phosphonic acids took place smoothly at 80 °C in toluene or benzene in high yields. The dealkylation via the generation of isobutene of *ditert*-butyl phosphonate and related catalyzed by TfOH took place even at room temperature to give the corresponding phosphonic acids in good to high yields. In addition, three plausible mechanisms of the hydrolysis of dialkyl phosphonates via C-O cleavage catalyzed by Brønsted acid in water and toluene were studied.

## 審 査 の 要 旨

〔批評〕

The applicant discovered three new reactions in her thesis, that is, (a) Brønsted acids-catalyzed PO-R cleavage of P(III) esters selectively producing P(O)-H and P(O)-R compounds, (b) palladium-catalyzed Michaelis-Arbuzov reaction of  $(ArO)PZ_2$  to aryl phosphonates, phosphinates and phosphine oxides, and (c) Brønsted acids-catalyzed wet and dry processes for the selective transformation of phosphonates to phosphonic acids. The applicant cited the backgrounds of the study correctly, conducted the researches logically, and analyzed the results reliably, as evidenced by her two papers published in renowned international journals.

〔最終試験結果〕

令和 2 年 7 月 31 日、数理物質科学研究科学学位論文審査委員会において審査委員の全員出席のもと、著者に論文について説明を求め、関連事項につき質疑応答を行った。その結果、審査委員全員によって、合格と判定された。

〔結論〕

上記の論文審査ならびに最終試験の結果に基づき、著者は博士（理学）の学位を受けるに十分な資格を有するものと認める。