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学位論文題目 ヨウ化テトラフルオロポリスチレン誘導体の合成と不均一系求
核触媒反応への応用:4-アミノピリジンペンダント型高分子触
媒の開発

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博士論文の要旨

氏 名：堀 達暁

論文題目：

ヨウ化テトラフルオロポリスチレン誘導体の合成と不均一系求核触媒反応への応用：4-アミノピリジンペンダント型高分子触媒の開発

The development of polymer-immobilized heterogeneous organocatalysts is an important research area for advancing the molecular transformation in organic synthesis. 4-Dimethylaminopyridine (DMAP) is one of the most frequently used organocatalysts; its immobilization onto polymers has been extensively investigated over the past 50 years. Among the polymer-immobilized DMAP catalysts reported to date, the covalent bond-based strategy is commonly used to immobilize DMAP on polymer side chain. However, this widespread strategy often decreases their catalytic activities by the side-chain on the amino nitrogen of DMAP. This longstanding issue is well-known in the field; a new strategy is desired to achieve high catalytic activity in polymer-immobilized DMAP catalysts. In the context of this doctoral thesis, polymer matrix possessing perfluorohalogenated aryl motifs was developed and applied to DMAP-pendant polymer ($\text{PDPX}_{\text{DMAP}}$) as a nucleophilic catalyst. It was revealed that $\text{PDPX}_{\text{DMAP}}$ catalysts efficiently promoted the acyl rearrangement reactions of benzofuranones and azlactones.

In Chapter 1, a comprehensive overview is provided, including previously reported polymer-immobilized DMAP catalysts, the underlying framework of the developed strategy focused on polymers with halogen-bonding (XB) donor motifs, and the scope of this thesis. At first, polymers with XB donor are exemplified based on literature reviews. Subsequently, the design concept in the doctoral study is described in detail. The thesis focuses on the synthesis of DMAP-pendant polymers and the catalysis through halogen bonding. The developments in the doctoral study would provide a good alternative to previously reported polymer-immobilized DMAP catalysts.

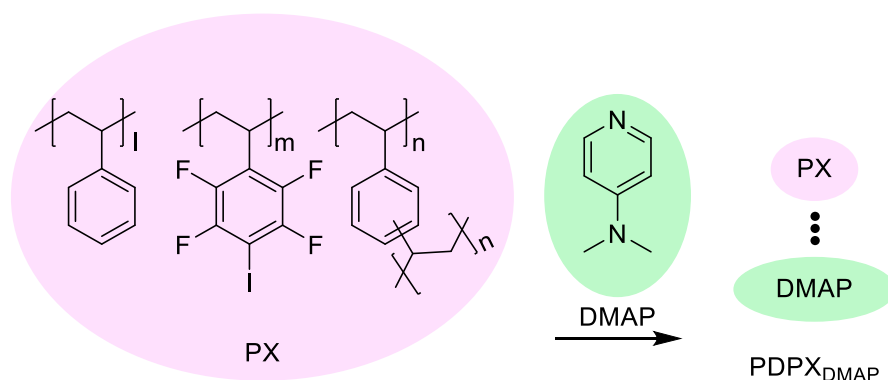
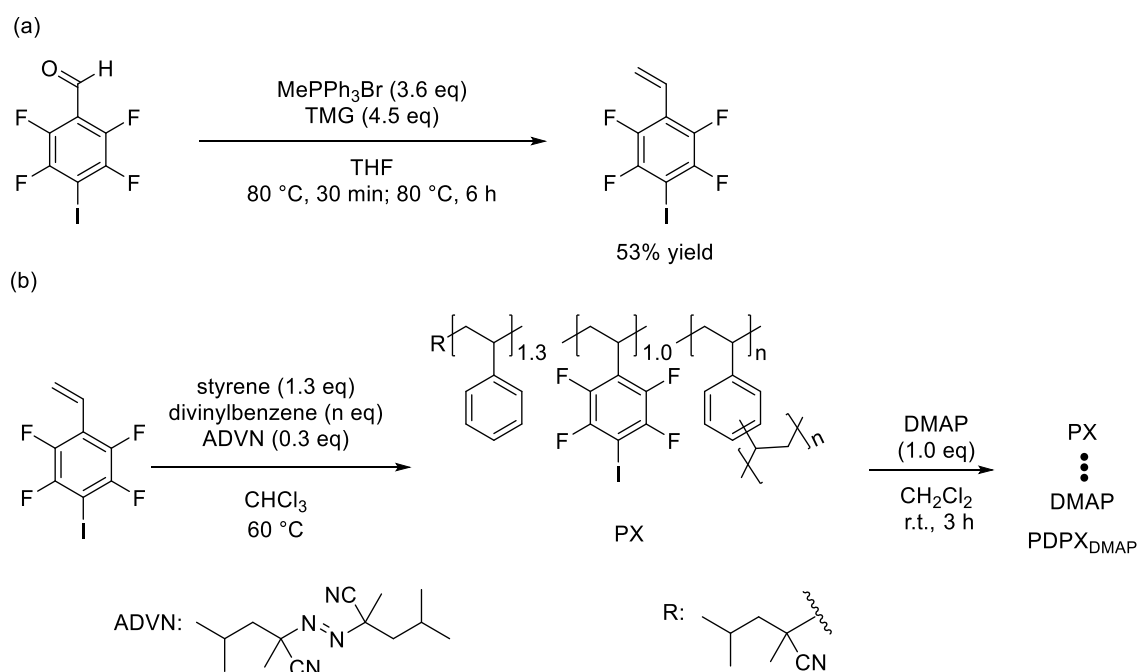


Figure 1. Design of DMAP-pendant polymer catalyst using halogen bond donor motifs

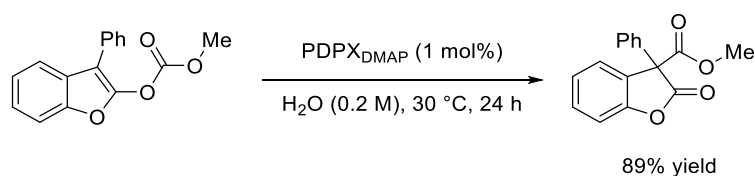
In Chapter 2, the synthesis of DMAP-pendant polymer is provided in detail. As an initial study, syntheses of 2,3,5,6-tetrafluoro-4-halostyrene (TFXS) as functional monomers were examined. Particularly, the Wittig reaction, which is the final step in the synthesis of TFXS, was systematically investigated. The base, reaction time, reaction temperature, solvent, and equivalents of reagents were explored using 2,3,5,6-tetrafluoro-4-iodobenzaldehyde. It was found that 1,1,3,3-tetramethylguanidine (TMG) was the optimal base, resulted in a 53% yield of TFIS (Scheme 1a). The number of nitrogen atoms as halogen bonding acceptors in the organic base played an important role in the production of TFXS. The radical polymerization of TFIS as functional monomer, styrene, and divinylbenzene as a crosslinking reagent was carried out with using the 2,2'-azobis-2,4-dimethylvaleronitrile (ADV N) as an initiator to obtain the halogen-bond donor-introduced polymer (PX). Elemental analysis and energy dispersive X-ray spectroscopy (EDS) confirmed the presence of perfluoroiodobenzene units. Subsequently, DMAP was introduced to yield PDPX_{DMAP} catalysts (Scheme 1b). Dynamic nuclear polarization (DNP) ¹⁵N-NMR of PDPX_{DMAP} might indicate interactions between DMAP and PDPX. Further, details on the optimization of the Wittig reaction, the radical polymerization, and preparation of polymer catalysts are provided in Chapter 2.



Scheme 1. (a) Wittig reaction of 2,3,5,6-tetrafluoro-4-iodobenzaldehydes;
(b) Preparation of DMAP-pendant polymer catalyst

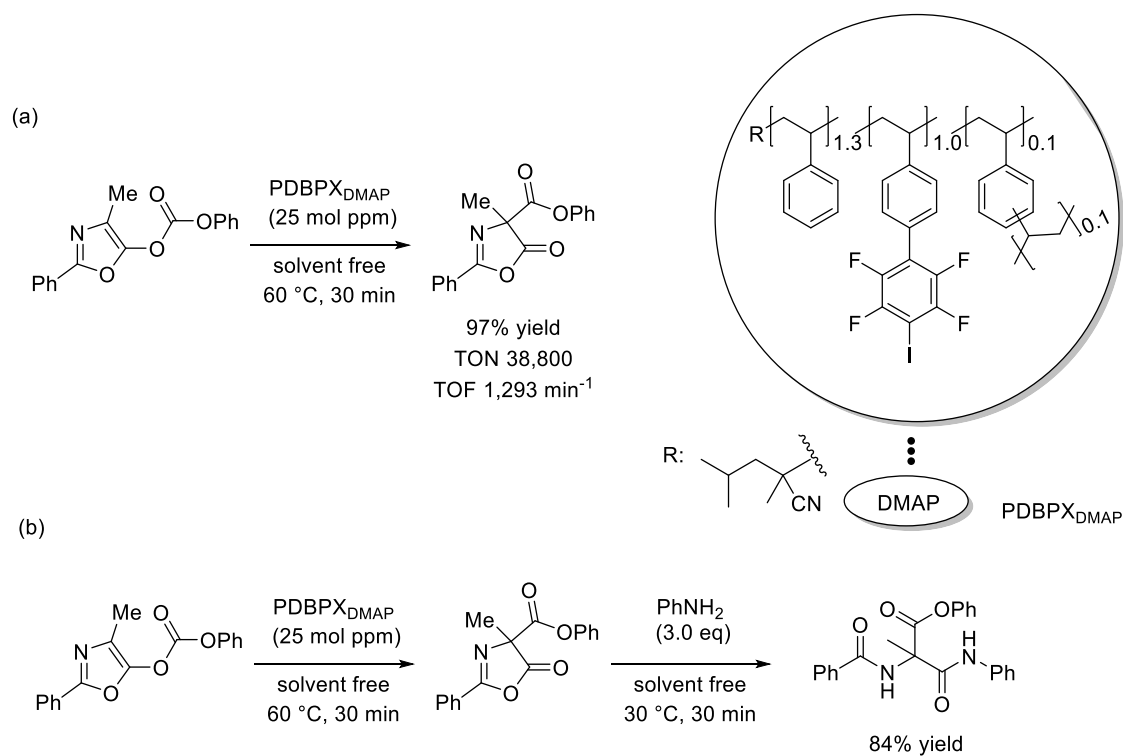
In Chapter 3, the application of PDPX_{DMAP} to heterogeneous catalysis are summarized, with a focus on the acyl rearrangement reaction of benzofuranones (Scheme 2). The PXs derived from different amounts of divinylbenzene (DVB) as a cross-linking reagent for TFIS, *i.e.* 0.01, 0.1, 1,

and 15 equivalents of DVB, were evaluated to develop the heterogeneous catalysis, particularly in H₂O. Among them, PDPX_{DMAP} from 15 equivalents of DVB afforded the desired product in higher yield compared to the ones derived from 0.01 and 1 equivalent ones. In sharp contrast, DMAP without a polymer matrix and commercially available polystyrene-based catalyst (PS_{DMAP}) did not promote the reaction, resulting in the desired products with yields of less than 10%. Investigation into the scope of this heterogeneous catalysis revealed that a variety of substituents on *O*-acyl benzofuranones was tolerated, providing the corresponding acyl-rearranged products in good to high yields. Further details on the initial study, substrate scope, reuse of PX, and reaction mechanism are described in Chapter 3.



Scheme 2. Representative results for acyl rearrangement reaction of benzofuranones in H₂O catalyzed by PDPX_{DMAP}

In Chapter 4, application of PDPX_{DMAP} to solvent-free heterogeneous catalysis is summarized, with a focus on acyl rearrangement reaction of azlactones (Scheme 3a). Similar to Chapter 3, the PXs derived from different amounts of divinylbenzene (DVB) as a cross-linking reagent for TFIS, *i.e.* 0.01, 0.1, 1, and 15 equivalents of DVB, were evaluated to develop solvent-free heterogeneous catalysis where PX is used as the reaction mediator. Among these, PDPX_{DMAP} prepared from 0.1 or 0.01 equivalents of DVB provided the desired product in higher yields compared to those obtained from 1 and 15 equivalents of DVB. Under a 25 mol ppm catalyst loading, the rearranged product was obtained in high yield, high TON (turnover number), and high TOF (turnover frequency) (97% yield, TON 38,800, TOF 1,293 min⁻¹ at 60 °C for 30 min). The catalytic activity of PS_{DMAP} was lower than that of PDPX_{DMAP}. To simplify the preparation of functional monomer TFIS for PX, 4'-ethenyl-2,3,5,6-tetrafluoro-4-iodo-1,1'-biphenyl was selected as an alternative functional monomer and applied to the halogen-bond donor-introduced polymer DMAP catalyst, affording PDBPX_{DMAP}. It was revealed that the catalytic activity of PDBPX_{DMAP} was similarly to that of PDPX_{DMAP}. Therefore, PDBPX_{DMAP} was used for further study. It was found that PDBPX_{DMAP} exhibited excellent catalytic activity for a wide range of substrates. To demonstrate the utilities of solvent-free heterogeneous catalysis for acylated azlactones, the rearranged products were subjected to aminolysis conditions to afford tetrasubstituted amino acid derivatives in a one pot reaction (Scheme 3b). Furthermore, this system was applicable to asymmetric catalysis. Detailed studies on reaction optimization, substrate scope, application to amino acid derivatives, and asymmetric acyl rearrangement reaction of azlactones are described in Chapter 4.



Scheme 3. (a) Representative results for solvent-free acyl rearrangement reaction of azlactone catalyzed by PDBPX_{DMAP}; (b) Representative results for synthesis of amino acid derivatives in one pot

In Chapter 5, the studies conducted for this thesis are summarized, and perspective of DMAP-pendant polymer catalysts is described.

博士論文審査結果

Name in Full
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Title
論文題目 ヨウ化テトラフルオロポリスチレン誘導体の合成と不均一系求核触媒反応への応用：4-アミノピリジンペンダント型高分子触媒の開発

4-アミノピリジンに代表される求核触媒は、アシル化など多くの有機分子変換で汎用されている。均一系反応から不均一系反応まで、様々な求核触媒が開発されてきた。不均一系の求核触媒は、求核部位を含む触媒母骨格が高分子担体の側鎖に共有結合により固定されるため、均一系の求核触媒よりも触媒活性が低下する。不均一系求核触媒の開発研究において、共有結合を介した高分子固定化法に代わる新たな方法論の開発が望まれてきた。申請者は、ヨウ化テトラフルオロポリスチレン誘導体の非共有結合性相互作用を活用することで、極めて高活性な不均一系求核触媒反応の開発に成功した。

本学位論文は、第1章を序論、第2章から第4章を本論、第5章を総括と展望とする、全5章から構成されている。

第1章では、高分子固定化求核触媒の先行研究を踏まえ、不均一系求核触媒の問題点が示されている。続いて、その解決に向けて、ヨウ化テトラフルオロポリスチレン誘導体に着目した経緯と意義、さらに本研究の内容が簡潔に論じられている。

第2章では、申請者が開発した4-ジメチルアミノピリジンペンダント型高分子触媒の合成について、詳細が述べられている。申請者は、有機塩基を用いる Wittig 反応を開発し、市販で入手可能なテトラフルオロ安息香酸からヨウ化テトラフルオロスチレンの合成工程および精製方法を確立した。さらに、高純度のヨウ化テトラフルオロスチレンを用いることで、テトラフルオロヨウ化ベンゼン部位を十分に有する高分子の合成と高分子求核触媒の調製に成功した。

第3章では、開発した高分子触媒による *O*-アシル化ベンゾフラノンの転位反応について、作業仮説と実験結果の詳細が論じられている。申請者は、ヨウ化テトラフルオロポリスチレンによるハロゲン結合が水中で反応基質の捕捉に有効に機能するとの作業仮説のもと、水中での不均一系求核触媒反応の開発を進めた。開発した高分子触媒が水中で *O*-アシル化ベンゾフラノン転位反応に有効であることを見出し、その要因について、対照実験の結果と開発した高分子触媒の組成に基づいて考察した。

第4章では、開発した高分子触媒による *O*-アシル化アズラクトンの転位反応について、作業仮説と実験結果の詳細が論じられている。申請者は、無溶媒触媒反応の重要性を述べたうえで、開発した高分子触媒の特長をもとに、無溶媒での不均一系求核触媒反応の開発を進めた。開発した触媒を用い、標的する転移反応が ppm レベルの触媒量で円滑に進行することを見出した。また、本反応が、4 置換型アミノ酸誘導体合成や触媒的不斉反応に展開可能であることを示した。

第5章では、本学位論文を総括し、本研究の展望を述べている。

本博士論文の成果は、新たな不均一系求核触媒の設計・合成・機能開拓に留まらず、ハロゲン化ペルフルオロポリスチレンの機能性高分子材料研究に発展する契機となるものである。学術的に極めて重要な成果と判断された。また、本論文の内容は、申請者を筆頭著者とする学術論文として査読付き国際誌に掲載済みである。国際的にも高い水準の研究であると判定できる。

以上により、本学位論文は博士(理学)の学位授与に値すると、審査委員全員一致で判断した。