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学位論文題目 Development of Catalytic Membrane-Installed
Microchannel Devices and Their Application to
Organic Transformations

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Instantaneous catalytic molecular transformation is an important goal in chemical synthesis. Recently, microreactor systems offering many fundamental as well as practical advantages have been considered as innovative devices for chemical experimentation. Molecular transformations with catalyst-immobilized microflow reactors are representative examples of these systems, in which the efficiency of various reactions has been found to increase because of the vast interfacial area and the close distance of the molecular diffusion path in the narrow space of the microreactors. Considering that the majority of chemical reactions are carried out by mixing two unique solutions of reactants, it is not surprising that the catalyst-immobilized microreactor for liquid–solid–liquid triphase reaction systems would be an eagerly awaited device. If a catalyst were installed as a membranous composite at the center of the microchannel, two reactants could be oppositely charged into and flow through the divided channel all the while in contact with the vast interfacial surface of the catalytic membrane from both front and back sides, thereby realizing an instantaneous chemical reaction. This concept is shown schematically in Figure 1 (a), where a catalytic cross-coupling reaction is depicted as a typical example. Uozumi and co-workers reported a preliminary result of the preparation of a polymeric Pd-membrane-installed microchannel reactor for the Suzuki-Miyaura reaction.¹ The catalytic membrane was constructed inside the microchannel via “molecular convolution”, a novel concept for catalyst-immobilization to achieve the one-step preparation of the insoluble polymeric metal

composite, at the interface between the organic and aqueous phases flowing laminarily (Figure 1 (b)). While the catalytic membrane-installed microchannel reactor was a promising system to accomplish the instantaneous catalytic molecular transformation, only one catalytic microdevice was prepared and only five entries of the

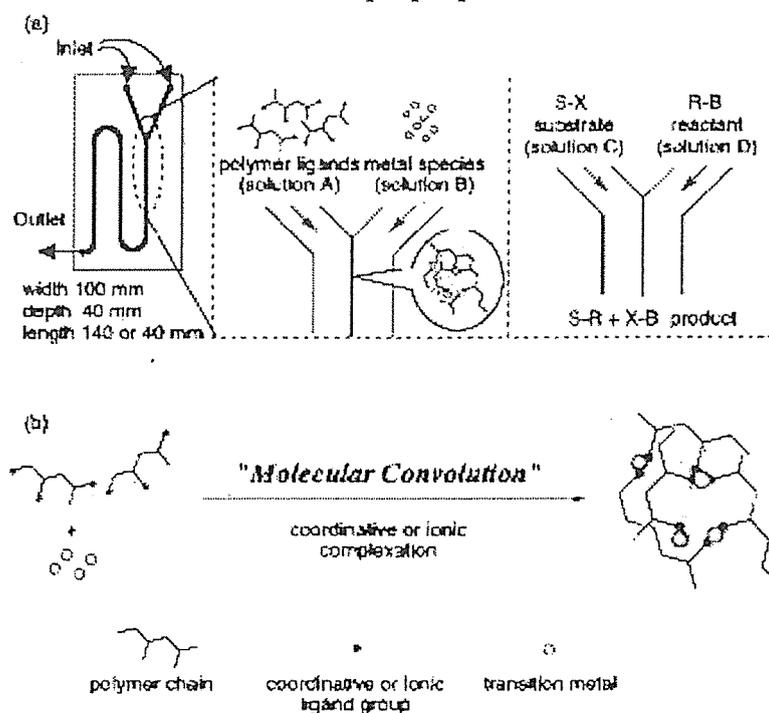


Figure 1. Catalytic membrane-installed microchannel reactor system (a); Concept of 'Molecular Convolution' (b)

Suzuki-Miyaura coupling of aryl iodides and arylboronic acids were described in the preliminary communication.

In this thesis, this author describes the development of various polymeric palladium membranes-installed microchannel reactors (Chapter II), and their application to not only the Suzuki-Miyaura coupling (Chapter III and IV) but also the allylic arylation (Chapter V) and hydrodechlorination using the first polymeric Pd-nanoparticle membrane-installed microchannel devices (Chapter VI), in which instantaneous and complete conversion was achieved efficiently.²

Chapter II reports details of the formation of three catalytic membranes using a microchannel reactor having a channel pattern of 100 μm wide, 40 μm deep, 40 or 140 mm long, and a Y-junction. Thus, the coordinative convolution of palladium species and a polymeric phosphine ligand was performed by the installation of an EtOAc solution of poly(*N*-isopropylacrylamide-triarylphosphine) (solution A, Figure 1) and an aqueous solution of $(\text{NH}_4)_2\text{PdCl}_4$ (solution B, Figure 1) oppositely into the microchannel at 50 $^\circ\text{C}$ with a flow rate of 20 $\mu\text{l}/\text{min}$. The two-phase parallel laminar flow was readily formed under the flowing conditions, and a polymer membrane was precipitated at the interface of the laminar flow (the μ -device 1, Figure 2). The palladium-immobilized membranes of poly(4-vinylpyridine) and poly[4,4'-bipyridyl-*co*-1,4-bis(bromomethyl)benzene] were also installed into the Y-junction microchannel via ionic convolution (the μ -devices 2,3, Figure 2).

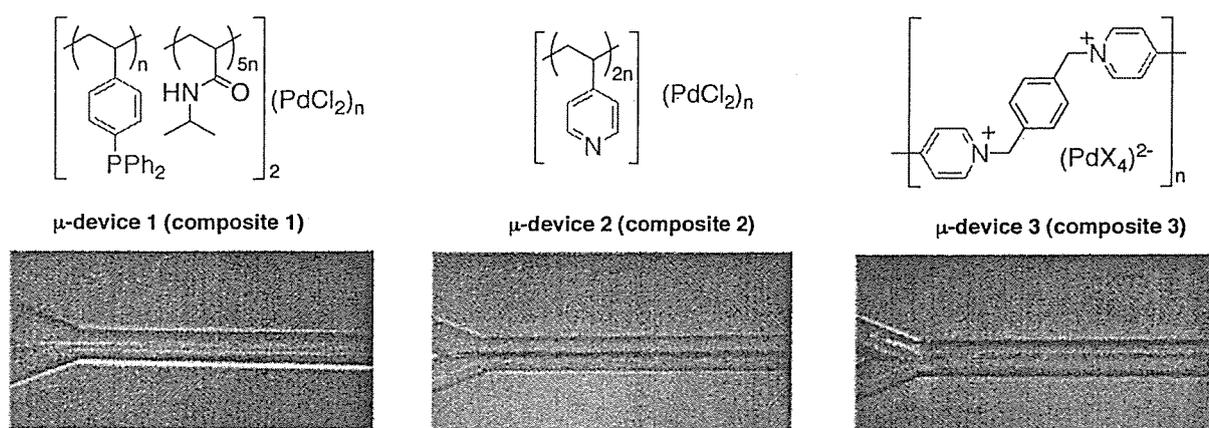
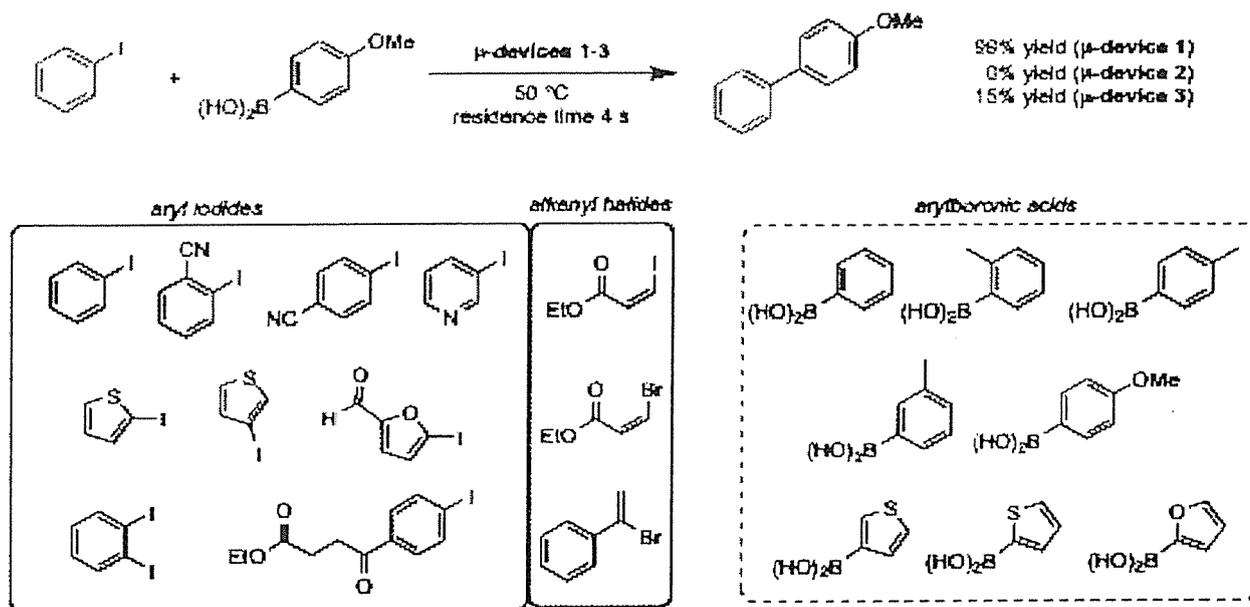


Figure 2. Structure and microscopic view of catalytic membranes in the μ -devices 1-3 (composite 1-3)

In chapter III, the synthetic ability of the three types of microchannel devices prepared above (the μ -devices 1-3) were examined for the Suzuki-Miyaura reaction (Scheme 1). Thus, a solution of iodobenzene in EtOAc/*i*-PrOH (solution C, Figure 1) and an aqueous solution of 4-methoxyphenylboronic acid with Na_2CO_3 (solution D, Figure 1) were oppositely introduced into the membrane-divided channels, the μ -devices 1-3, at 50 $^\circ\text{C}$, with a flow rate of 2.5 $\mu\text{l}/\text{min}$ (for solution C) and 5.0 $\mu\text{l}/\text{min}$ (for solution D), respectively. The μ -device 1 gave 4-methoxybiphenyl in 99% yield

within 4 seconds of residence time through the continuous 120 min of the flow reaction, whereas the μ -devices 2 and 3 in 0% and 15% yields, respectively. The reaction system of the μ -device 1 was applied to the cross-coupling reaction of a variety of heteroaryl halides, alkenyl halides and heteroarylboronic acids.

Scheme 1. The Suzuki-Miyaura reaction using the μ -devices 1-3

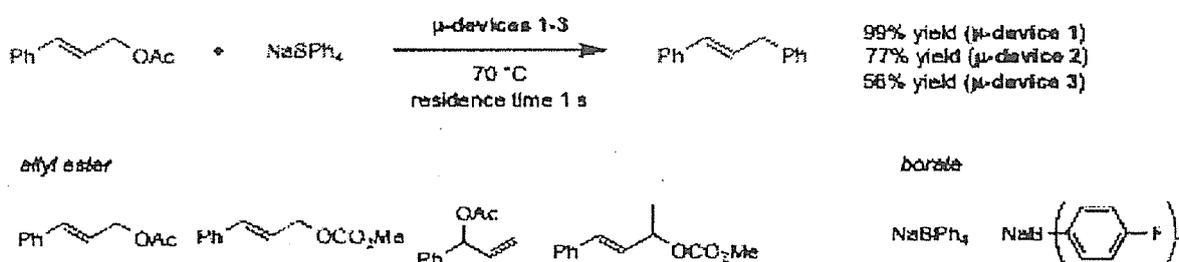


Application to the preparation of intermediates of bioactive compounds as well as functional materials using μ -device 1 was also described in chapter IV. Thus, the Suzuki-Miyaura reaction of 4-cyano-1-iodobenzene with 4-pentylphenylboronic acid was carried out with the μ -device 1 at 50 °C with 4 sec of residence time to afford, a liquid crystal compound 5CB, 4-cyano-4'-pentylbiphenyl in 99% yield. A variety of medicinal intermediates and functional materials were obtained with similar conditions.

In chapter V, the synthetic ability of the three types of microchannel devices prepared above (the μ -devices 1-3) was also examined for allylic arylation of allyl esters with arylboron reagents. While numerous reports on aryl-aryl couplings with arylboron reagents (the Suzuki-Miyaura coupling) have appeared so far, the allyl-aryl coupling, which often requires relatively high reaction temperatures, has received only scant attention. The successful results for the aryl-aryl coupling using the microchannel reactor with a catalytic membrane (*vide supra*) led us to the idea that the microchannel devices might also promote the allyl-aryl coupling with high efficiency. The allyl-aryl coupling reaction was examined with cinnamyl acetate and sodium tetraphenylborate using the μ -devices 1-3 (Scheme 2). Thus, a solution of cinnamyl acetate in *i*-PrOH (solution C) and an aqueous solution of tetraphenylborate (solution D) were oppositely introduced into the membrane-divided

channels, the μ -devices 1-3 (40 mm long), at 70 °C with a flow rate of 3.0 μ l/min. Two parallel laminar layers flowed through the channel in 1 second, and the resulting organic/aqueous micro stream was collected from the outlet to afford (*E*)-1,3-diphenylpropene. Thus, the μ -devices 1-3 promoted the allyl-aryl coupling reaction to give (*E*)-1,3-diphenylpropene in 99%, 77%, and 56% yield, respectively. The turnover frequency of the μ -device 1 in the catalytic reaction reached to 1,000 h^{-1} . A variety of allyl esters and arylboronic acid were also carried out under the similar conditions to give the corresponding products in high yield (Scheme 2).

Scheme 2. Allylic Arylation using the μ -devices 1-3



Hydrodechlorination of aryl chlorides has been an important chemical transformation in organic synthesis as well as an environmental point of view. Accomplishment with instantaneous and continuous flow system would become an attractive method for this purpose. In typical results, it is known that several palladium-nanoparticle catalysts promote the hydrodechlorination of aryl halide. Therefore, this author made a thorough investigation on the preparation of the first polymeric Pd-nanoparticle membrane-installed microchannel devices by reduction with sodium formate (HCO₂Na) or thermal decomposition at 250 to 300 °C. Furthermore, the application of polymeric palladium particle-installed microchannel devices to the instantaneous hydrodechlorination of aryl halides with sodium formate was described in chapter VI. Thus, the composites 1-3 were reduced with saturated aqueous sodium formate at 50 °C for 30 min to give insoluble powders 4-6 in 96%, 99% and 30%, respectively (Figure 3, left). Optical microscopic observation showed that color of 5 and 6 was changed from yellow to black whereas that of 4 remained unchanged (Figure 3, left). High resolution TEM analysis of 5 and 6 revealed that the Pd nanoparticles in 5 and 6 had a mean diameter of 2.0±0.3 nm and 10.0±2.0 nm respectively (Figure 3, right). In contrast, nanoparticles were not observed in 4. This result suggested that microflowing of HCO₂Na in the μ -devices 2 and 3 at 50 °C should in-situ provide a polymeric palladium-nanoparticle membrane inside a microchannel reactor.

For the thermal decomposition of palladium species, the complexes 1-3 were heated at 250, 325 and 300 °C for 0.5 h in an electric furnace under batch conditions to afford black powders 4'-6' in 93%, 90%, and 79%, respectively.

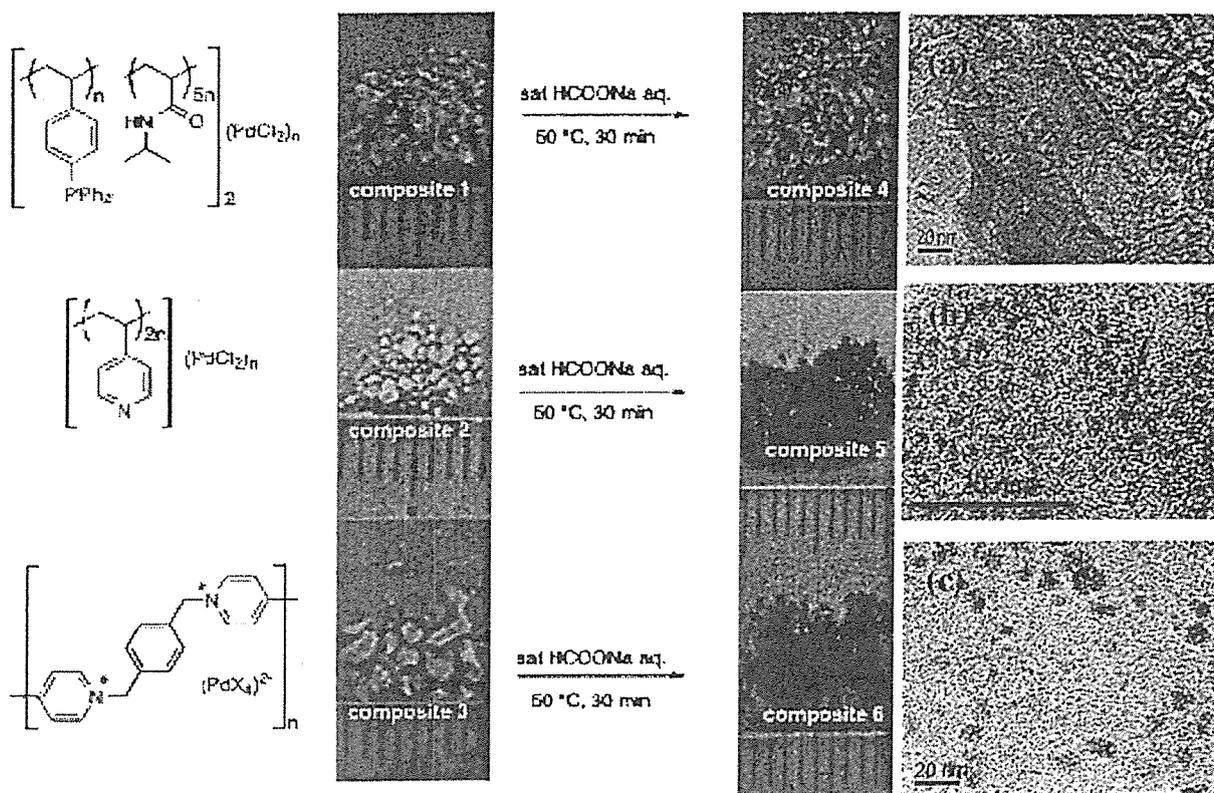
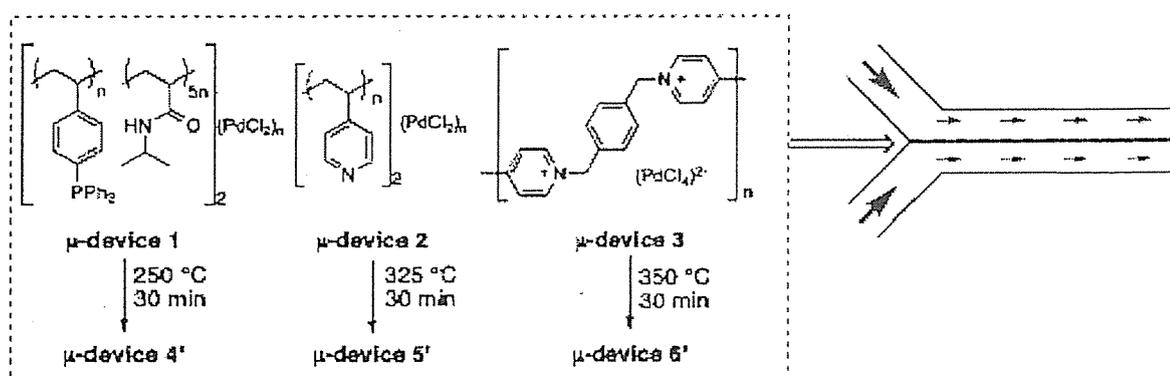
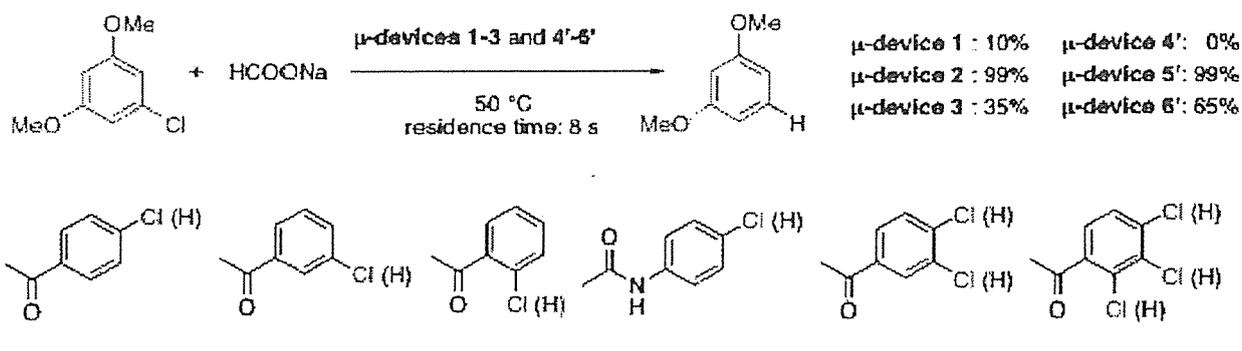


Figure 3. (left) Optical microscopic images of polymeric palladium composites 4-6 prepared by reduction of the composite 1-3 with HCO_2Na ; (right) TEM images of the three types of palladium composite 4 (a), 5 (b) and 6 (c)

Scheme 3. Hydrodechlorination using the μ -devices 1-3 and 4'-6'



The catalytic activity of six types of microchannel devices prepared was also examined for the hydrodechlorination of an electron-rich substrate,

3,5-dimethoxychlorobenzene, with HCO_2Na by using the μ -devices 1-3 (μ -devices 4-6 generated in-situ) and the μ -devices 4'-6'. Thus, a solution of 3,5-dimethoxychlorobenzene in *i*-PrOH (5.0 mM) and an aqueous solution of HCO_2Na (saturated) were oppositely introduced into the membrane-divided channels, the μ -devices 1-3 and 4'-6' (40 mm long), at 50 °C with a flow rate of 0.5 $\mu\text{l}/\text{min}$ for 2 hours. Two parallel laminar layers flowed through the channel in 8 sec, and the resulting organic/aqueous micro stream was collected from the outlet to afford 1,3-dimethoxybenzene (Scheme 3). The μ -devices 1-3 and 4'-6' promoted the hydrodechlorination to give 1,3-dimethoxybenzene in 10%, 99%, 35%, 0%, 99%, and 65% yield, respectively (Scheme 3). Since the μ -device 2 (the μ -device 5 generated in-situ) was found to be the most active and the most readily prepared, the reaction system of the μ -device 2 was applied to the hydrodechlorination of a variety of aryl chlorides. The μ -device 2 promoted the hydrodechlorination of various aryl chlorides in 8 seconds of residence time with the formation of a palladium nanoparticle-installed catalytic membrane in-situ.

In summary, this author developed a variety of palladium membrane-installed microchannel devices via "coordinative and ionic convolution" and demonstrated that these microchannel devices efficiently promoted the instantaneous Suzuki-Miyaura reaction and allylic arylation within 4-5 and 1 seconds of residence time, respectively to afford the corresponding products quantitatively. Moreover, the first polymeric Pd-nanoparticle membrane-installed microchannel devices were prepared by reduction with HCO_2Na or thermal decomposition in chapter VI. The polymeric Pd-nanoparticle membrane-installed microchannel devices μ -device 1-3 (4'-6') was applied to the hydrodechlorination of aryl halides with sodium formate. Especially, the μ -device 2 promoted the hydrodechlorination of various aryl chlorides in 8 seconds of residence time with the formation of a palladium nanoparticle-installed catalytic membrane in-situ.

References

- (1) Uozumi, Y.; Yamada, Y. M. A.; Beppu, T.; Fukuyama, N.; Ueno, M.; Kitamori, T. *J. Am. Chem. Soc.* **2006**, *128*, 15994.
- (a) Yamada, Y. M. A.; Watanabe, T.; Torii, K.; Uozumi, Y. *Chem. Commun.* **2009**, 5594. (b) Yamada, Y. M. A.; Watanabe, T.; Beppu, T.; Fukuyama, N.; Torii, K.; Uozumi, Y. *Chem. Eur. J.* *accepted*.

博士論文の審査結果の要旨

本博士論文は、触媒膜導入型マイクロリアクターデバイスの調製とその有機変換反応への応用について論述されたものである。第1章が序論、第2章―第6章までが本論、第7章が結論の7章立てで構成されている。

第1章では、固定化触媒担持型マイクロリアクターデバイスの開発における背景、現状について述べられている。過去の問題点を提示しつつ、高分子金属触媒膜のマイクロリアクター内層流界面への導入の意義、重要性が提起され、本論文の学術的な位置づけが記載されている。

第2章では、高分子パラジウム膜導入型マイクロリアクターデバイスの設計と調製について述べられている。マイクロリアクター内への poly(acrylamide-triarylphosphine-palladium) 触媒膜が、Y字導入部のチャンネルパターンを有するマイクロリアクターに、poly(acrylamide-triarylphosphine) の酢酸エチル溶液と $(\text{NH}_4)_2\text{PdCl}_4$ の水溶液が相対してY字導入部より注入されることで調製された。電子顕微鏡、エネルギー分散型X線分析等により、膜厚1 mm、高さ40 mm、長さ4 cmもしくは14 cm（流路長）の高分子パラジウム膜が、マイクロリアクター層流界面に生成していることが明らかにされた (device 1)。同様の手法により、poly(vinylpyridine-palladium) 触媒膜 (device 2)、poly(viologen-palladium) 触媒膜 (device 3) のマイクロリアクター層流界面への導入に初めて成功した。

第3章では、3種類のマイクロ反応デバイス devices 1-3 が鈴木-宮浦クロスカップリングに適用され、デバイスの触媒能が評価された。その結果、device 1 の優位性が見出され、iodobenzene と 4-methoxyphenylboronic acid とのカップリング反応が反応温度50 °C、滞留時間4秒で定量的に進行する事が示された。さらに、種々のハロゲン化複素環化合物、ハロゲン化アルケニルとアリールボロン酸、ヘテロアリールボロン酸との反応が行われ、いずれの場合でも反応温度50 °C、滞留時間4-5秒で対応するカップリング化合物が高い収率で得られ、触媒膜導入型マイクロリアクターデバイスの合成的有用性が提示された。

第4章では、device 1 により数々の医薬品・機能材料合成中間体が調製され、本デバイスのプロセス化学的実用性が示された。

第5章では、devices 1-3 がアリルエステルと有機ホウ素化合物とのアリル位アリール化反応に適用された。その結果、cinnamyl acetateとsodium tetraphenylborateとの反応では devices 1-3 いずれにおいても触媒活性があることが確認され、特に device 1 において、対応する1,3-diphenylpropeneが反応温度70 °C、滞留時間1秒で定量的に得られる事が見出された。本デバイスは様々な基質においても機能し、同様の条件で対応する生成物が定量的に得られることが示され、マイクロリアクターでの初めてのアリル位アリール化反応が確立された。

第6章では、devices 1-3 が塩化アリのルの水素化脱塩素反応に適用された。本反応は有機合成化学のみならずPCB、ダイオキシンの処理に有望である。Device 2 が本反応に有効であることが見出され、飽和ギ酸ナトリウム水溶液存在下、5 mMの塩化アリのルが反応温度50 °C、滞留時間8秒で定量的で脱塩素化されることが示された。また、アルデヒド、ケトン、アミド基を有する基質を用いた場合でも、選択的に脱塩素化が進行する事が見出された。さらに電子顕微鏡などの測定により、触媒活性種がパラジウムナノ粒子であると考察されている。

第7章では全体の総括、結論が述べられている。

以上のように、マイクロリアクターの層流界面に触媒膜を初めて調製することにより瞬間的な有機変換反応が実現された。一連の成果は査読付きの国際学術誌 *Chemical Communications* および *Chemistry European Journal* に報告され、*Chemical Communications* では Hot Article に選出されるなど国際的にも高い評価を受けた。本論文は、独創的なコンセプトによる分子科学の新機軸が提示され、国際的に高い水準の研究であると判断された。よって、審査委員会は本論文が博士（理学）の学位論文に値するものであると全員一致で結論付けた。