アカデミックプログラム［Ｂ講演］ | 15. 有機化学—脂肪族・脂環式化合物，新反応技術：口頭Ｂ講演

2024年3月18日(月) 13:00 ~ 15:40 E1143(11号館 [4階] 1143)

[E1143-1pm] 15. 有機化学—脂肪族・脂環式化合物，新反応技術

座長：安藤 吉勇、美多 剛

日本語
13:00 ~ 13:20

[E1143-1pm-01]
新規ビタミンD誘導体の合成と活性

○伊部 公太[1]、掘田 稜二[1]、中田 春樹、大上 真由、岡本 専太郎[1] (1. 神奈川大)

英語
13:20 ~ 13:40

[E1143-1pm-02]
グリーンものづくり：ファインバブル法によるフェアリー化合物の合成

○Arun Kumar Manna[1]、佐藤 浩平[1]、鳴海 哲夫[1]、間瀬 暢之[1] (1. 静大院)

日本語
13:40 ~ 14:00

[E1143-1pm-03]
H/D同位体性キラル分子の速度論的分割

○内田 竜也[1,2]、中川 雄太[1]、渡 直樹[1] (1. 九大、2. 科学技術振興機構)

14:00 ~ 14:10
休憩

英語
14:10 ~ 14:30

[E1143-1pm-04]
Nickel-Iridium Dual Catalyzed Buchwald-Hartwig-Type Amination Reaction of Aryl Chlorides under Microwave and Visible Light Dual Irradiation

○Abhijit Sen[1], Bukhanko Valerii[1], Heeyoel Baek[1], Aya Ohno[1], Atsuya Muranaka[1], Yoichi M. A. Yamada[1] (1. RIKEN, Center for Sustainable Resource Science)

日本語
14:30 ~ 14:50

[E1143-1pm-05]
量子化学計算に基づくアミンと二酸化炭素からのアルケンの触媒的アミノカルボキシル化：気液フローシステムへの展開

○神名 航[1]、原渕 祐[2,3]、林 裕樹[2,3]、髙野 秀明[2,3]、小塚 智貴[4]、櫻井 大斗[4]、間瀬 暢之[4]、前田 理[2,3,5]、美多 剛[2,3] (1. 北大院総化、2. 北大WPI-ICReDD、3. JST-ERATO、4. 静岡大工、5. 北大院理)

14:50 ~ 15:00
休憩

日本語
15:00 ~ 15:20

[E1143-1pm-06]
独自に合成した多孔性塩基性樹脂による連続フローHenry反応

〇降矢 裕一[1]、石谷 暖郎[1]、小林 修[1] (1. 東京大学)

🏷 日本語
15:20 ~ 15:40
[E1143-1pm-07]

安定化高分子パラジウム触媒を用いた連続フロー式鈴木-宮浦反応の開発

〇Zhang Zhenzhong[1]、大野 綾[1]、山田 陽一[1] (1. 理化学研究所)

日本化学会 第104春季年会 (2024)

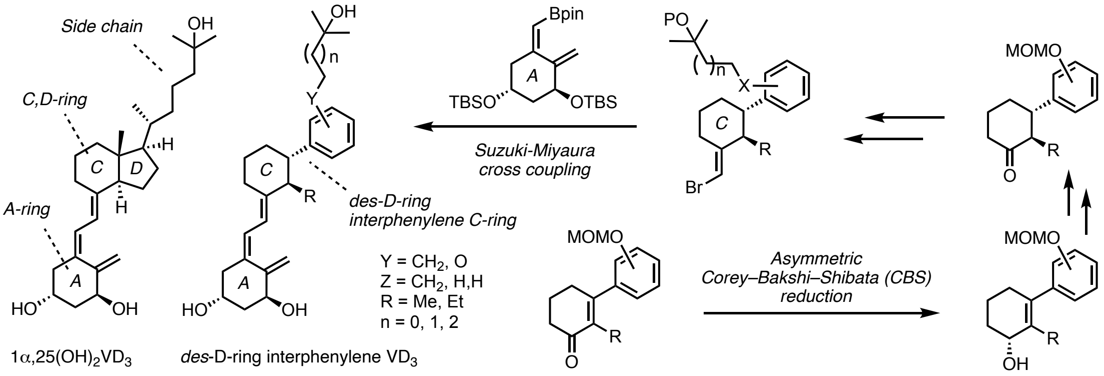
Design, synthesis, and properties of novel vitamin D_3 derivatives

([1]*Department of Frontier Bioscience, Kanagawa University*) ○Kouta Ibe,[1] Ryoji Hotta,[1] Haruki Nakada,[1] Mayu Ohgami,[1] Sentaro Okamoto[1]

Keywords: *des*-D-ring interphenylene vitamin D derivatives; *des*-D-ring interphenylene C-ring unit; A-ring unit; vitamin D receptor

1α,25-dihydroxyvitamin D_3 discovered as a main hormone of calcium and phosphate metabolism, that have a wide range of biological functions including the cell proliferation-differentiation, apoptosis, and the immune systems.[1] However, the therapeutic application of the 1α,25-dihydroxyvitamin D_3 have been limited due to its serious side effects hypercalcemia and hyperphosphatemia. Therefore, the development of more efficient, safer, and topically treatable vitamin D_3 analogues remains an unmet needs. Most of the vitamin D_3 analogues are modified in the side chain and/or A-ring counterparts, only a few having structural modified C,D-ring analogues have been developed. Nevertheless, biological studies on these analogues have been suggested that modified C,D-ring can reduce the calcemic side effects.[2]

Accordingly, we report the design and synthesis of novel C,D-ring modified 1α,25-dihydroxyvitamin D_3 derivatives as a *des*-D-ring interphenylene vitamin D_3, which lack the D-ring and have an interphenylene structure attached to the C-ring. Synthesis of the *des*-D-ring interphenylene C-ring units were carried out using a modified Corey-Bakshi-Shibata (CBS) reduction for key reactions. And its derivatives are then constructed via the Suzuki–Miyaura coupling reaction with the corresponding A-ring unit, and the evaluated on their VDR binding affinity and a reporter-gene assay.[3]



1) G. Jones, S. A. Strugnell, H. F. DeLuca, *Physiol. Rev.*, **1998**, *78*, 1193. 2) G. Eelen, L. Verlinden, R. Bouillon, P. D. Clercq, A. Muñoz, A. Verstuyf, *J. Steroid Biochem. Mol. Biol.*, **2010**, *121*, 417. 3) K. Ibe, H. Nakada, M. Ohgami, T. Yamada, S. Okamoto, *Eur. J. Med. Chem.*, **2022**, *243*, 114795

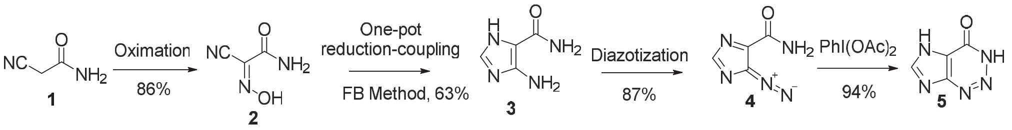
Green Manufacturing: Synthesis of Fairy Chemicals Using Fine Bubble Strategy

(*Graduate School of Science and Technology*, *Shizuoka University)*
○Arun Kumar Manna, Kohei Sato, Tetsuo Narumi, Nobuyuki Mase

Keywords: Green Manufacturing; Fairy Chemicals; Fine Bubble Organic Synthesis; Plant Growth Regulator; Hypervalent Iodine

2-Azahypoxanthine (AHX), 2-aza-8-oxohypoxanthine (AOH), and 1H-imidazole-4-carboxamide (ICA), collectively referred to as fairy chemicals (FCs), which are known for their plant growth-regulating properties. Kawagishi *et al.* have confirmed that these compounds can increase seed production in crops such as rice, wheat, and tomato by over 30-40%.[1] However, large-scale synthesis of these FCs remains underdeveloped due to the absence of efficient chemical synthetic pathways.

In the context of green process developments, we have demonstrated efficient gas-mediated reactions using fine bubbles (FB, <100 μm), which enhance gas concentration in the solution even under ambient pressure because of the long resident time, large surface area, and self-pressurization.[2,3] For AHX synthesis, commercially available 2-cyanoacetamide (**1**) was used as the starting material. Oxime **2** was synthesized using $NaNO_2$ and acetic acid in 86% yield. Compound **3** was obtained through a one-pot reductive coupling reaction employing FB-H_2 as a green reactant, Pt/C as a catalyst, and formamidine acetate as a coupling partner. We explored four distinct FB technologies, with the highest yield of 63% achieved using a multi-stacking element (MSE) FB generator under atmospheric H_2 pressure. Although compound **3** formation depends on various factors, the formed microbubbles (MB, 1-100 μm) concentration plays a major role in the reaction. The big MB covers the catalyst's active site and reduces the catalytic activity.[4] The resulting compound **3** was subjected to diazotization, affording diazene **4** intermediate stable in a solid state at room temperature.[5] After optimization of the subsequent intramolecular cyclization, we found $PhI(OAc)_2$ was effective as a catalyst (0.5 mol%),[6] facilitating the intramolecular cyclization in water within 15 minutes and precipitating the desired product in 94% yield.



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H/D 同位体性キラル分子の速度論的分割

（九大 I2CNER・九大基幹・JST PREST[1]・九大院理[2]）[1]○内田 竜也[1]・中川 雄太[2]・渡 直樹[2]

Optical resolution of H/D isotopic chiral molecule ([1]*International Institute for Carbon Neutral Energy Research, Kyushu University, Faculty of Arts and Science, Kyushu University, JST PREST*, [2]*Graduate School of Science, Kyushu University*) ○ Tatsuya Uchida,[1] Yuta Nakagawa,[2] Naoki Watari[2]

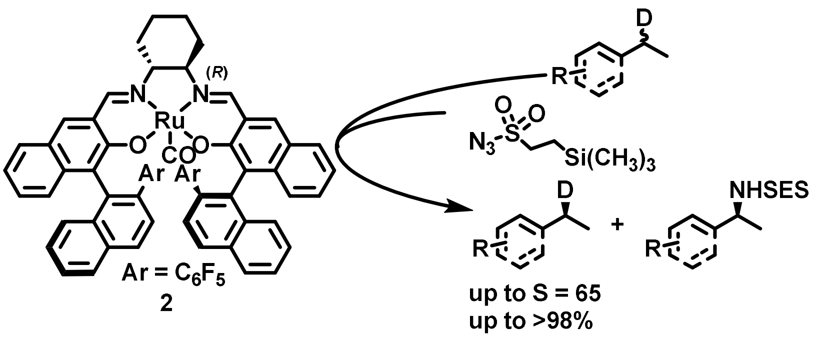
The direct recognition and resolution of H/D isotopic chirality remain challenges in chemistry because there is no difference in size and bond length between each isotopomer. Therefore, isotopic chirality is considered a cryptochiral compound. However, there is a significant difference in the bond dissociation energy between C–H and C–D bonds. Therefore, it was considered that enantiomerically pure H/D isotopic chiral compounds could be obtained through kinetic resolution by using highly enantioselecive C-H functionalization that exhibits a large kinetic isotope effect.

Based on the consideration, we conducted the asymmetric amidation of H/D isotopic racemic compounds bearing stereogenic center as a reactive site, such as benzylic and allylic positions. We found that almost enantiomerically pure H/D isotopic chiral molecule could be obtained via Ru(CO)-salen **2**-catalyzed asymmetric C–H amidation.

Keywords : H/D isotopic chirality; C–H amidation; Asymmetric C–H functionalization; Kinetic Resolution; Ruthenium

水素（H）および重水素（D）のように同位体元素によって構築される同位体性立体中心は、同位体間に大きさや結合長にほとんど差がなく、構造的には単純なメチレンのように振舞うゆえに、H および D からなる立体中心のみで構成される同位体性キラル分子は、現在も分離困難である。しかし、C–H 結合と C–D 結合間には、明確なエネルギー差があり、このエネルギー差をエナンチオマー間で反応速度差に反映させることができれば、H/D 同位体性キラル分子は、速度論的に分割することができ、その光学純度をほぼ純粋なレベルまで向上させることが可能と考えられた。

実際に、高エナンチオ選択的かつ大きな重水素効果を示すルテニウム-サレン錯体を用いた不斉 C–H アミノ化を用いることで、H/D 同位体性キラル分子の速度論的分割に成功し、その不斉収率をほぼ純粋なレベルまで向上させることに成功した。

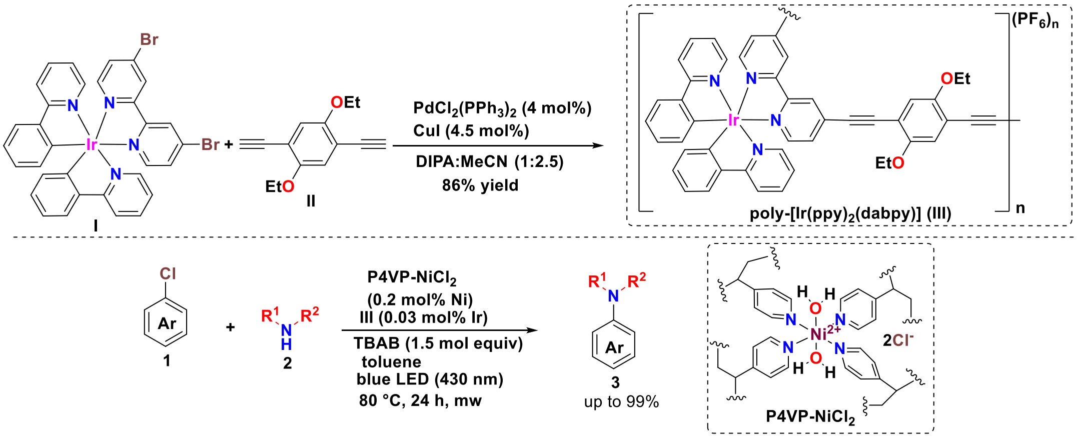


Nickel-Iridium Dual-Catalyzed Buchwald-Hartwig Type Amination Reaction of Aryl Chlorides under Microwave and Visible Light Dual Irradiation

([1]*RIKEN CSRS*) ○Abhijit Sen,[1] Valerii Bukhanko,[1] Heeyoel Baek,[1] Aya Ohno,[1] Atsuya Muranaka,[1] Yoichi, M. A. Yamada[1]

Keywords: Amination; Microwave; Photocatalysis; Heterogeneous catalysis; Nickel catalysis

Nickel-iridium dual-catalyzed Buchwald-Hartwig type C–N bond-forming amination is one of the most important research topics in modern chemistry. Despite being a useful reaction, it is still limited to the reaction of aryl iodides, bromides, and electron-deficient aryl chlorides mainly.[1] This time, we developed a nickel-iridium dual-catalyzed amination of aryl chlorides, independent of the electronic or steric nature.[2] For this purpose, we developed a novel, stable, and reusable polymeric iridium photocatalyst, poly-[Ir(ppy)$_2$(dabpy)] **III**, via the Sonogashira coupling of **I** with **II**. The C–N bond-forming Buchwald-Hartwig type amination of aryl chlorides **1** with amines **2** proceeded with 0.2 mol% of P4VP-NiCl$_2$ and 0.03 mol% of **III**, affording the corresponding amination products in up to 99% yield. Aliphatic (primary, secondary, cyclic, and acyclic) and aromatic amines were tolerable in the reaction. Both nickel and iridium catalysts were recovered and reused 4 times without significant loss of catalytic activity. Microwave and visible light irradiation were essential for this reaction. Multiple biologically active molecules were synthesized, including anti-malaria, anti-HIV, anti-cancer, anti-virus, and anti-bacterial compounds. Complete substrate scope and mechanistic studies will be discussed.



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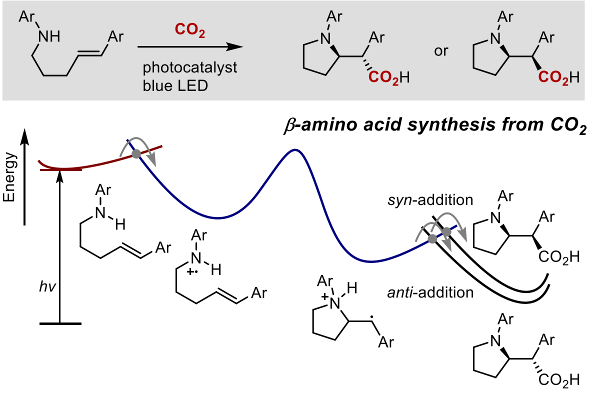
Catalytic Aminocarboxylation of Alkenes from Amines and CO_2: Application to Gas-Liquid Flow System

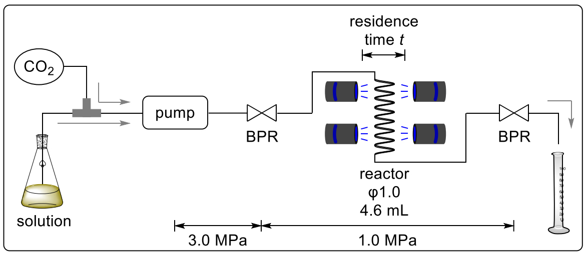
([1]*Grad. School of Chem. Sci. and Eng, Hokkaido Univ.*, [2]*WPI-ICReDD, Hokkaido Univ.*, [3]*JST-ERATO*, [4]*Fac. of Eng., Shizuoka Univ.*, [5]*Fac. of Sci, Hokkaido Univ.*)
○Wataru Kanna[1], Yu Harabuchi[2,3], Hayashi Hiroki[2,3], Hideaki Takano[2,3], Tomoki Kozuka[4], Hiroto Sakurai[4], Nobuyuki Mase[4], Satoshi Maeda[2,3,5], Tsuyoshi Mita[2,3]

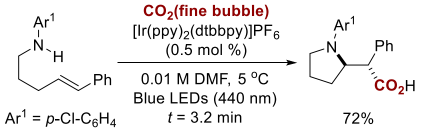
Keywords: *Flow System; β-amino acid; carboxylation; amine; quantum chemical calculations*

β-Amino acids play a crucial role in the design of biologically active compounds, including pharmaceuticals. On the other hand, carbon dioxide (CO_2) stands out as an attractive C1 source in organic synthesis due to its abundant, cost-effective, non-toxic, and renewable nature. In this study, we have developed a synthetic method of β-amino acids via aminocarboxylation of alkenes with aminium radical and CO_2 in the presence of a photoredox catalyst, based on the artificial force induced reaction (AFIR) method.[1] A comprehensive understanding of the reaction mechanism has been achieved through a novel computational method developed within our research group.[2]



Furthermore, we have successfully adapted this synthetic strategy to a gas-liquid flow system. Prior to photoirradiation, the solution of the substrate amino alkane (Ar^1 = *p*-Cl-C_6H_4) and the photocatalyst $[Ir(ppy)_2(dtbbpy)]PF_6$ in DMF was circulated in the reactor without LED irradiation, thereby maximizing CO_2 concentration. Upon initiating the reaction with blue LED lamps, optimal conditions resulted in the production of the target β-amino acid in 72% yield with a residence time *t* of 3.2 min.





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独自に合成した多孔性塩基性樹脂による連続フローHenry 反応

(*東大院理*[1]・*東大院理GSC社会連携講座*[2]) ○降矢裕一[1]・石谷暖郎[2]・小林修[1,2]

Continuous-flow Henry Reactions Using House-made Porous Basic Resins

(School of Science[1] and GSC Social Cooperation Laboratory[2], The Univ. of Tokyo)
○Yuichi FURIYA,[1] Haruro ISHITANI,[2] Shū KOBAYASHI[1,2]

To understand the influence of factors in synthesis of resins on basic catalytic activity of quaternary ammonium hydroxide resins for continuous-flow Henry reactions, we synthesized resins with varying porogen, crosslinker, and functional copolymer ratios. The optimal catalyst, QA-8-105(100), demonstrated higher catalytic ability and turnover number (TON) than commercially available strong basic resins. In order to maximize the production efficiency of the current catalytic flow reaction, a multi-step continuous SV deviation was performed semi-automatically using a HPLC gradient liquid delivery system, and the reaction conditions were efficiently evaluated. The TON reached when the yield decreased by about 10% from the initial yield was 33 for 0.2 M and 53 for 0.9 M. When the flow reaction was performed under an appropriate back pressure, the above TON value reached 70.

Keywords: *Heterogeneous Catalyst, Continuous-flow Reaction, Heterogeneous Base Catalyst, Henry Reaction*

連続フロー条件下で高活性を示す塩基性樹脂を創出するために、多孔化剤、架橋剤、官能基モノマー添加量を系統的に変えた樹脂を合成し、フローヘンリー反応をモデル系として評価した。触媒合成時の上記諸要因を最適化することで得られた新規塩基性樹脂QA-8-105(100)は、フローヘンリー反応において市販の塩基性樹脂A26と同等の官能基量を有し、官能基あたりの触媒作用および触媒リアクターとしての耐久性はA26を大きく上回った。一方、上記の評価は一定供給量に対する収率を基準としているが、連続フロー条件下での不均一系触媒評価には時間生産量やTONを基軸とした評価が重要である。本反応系でのそれらの最大化を目指し、スループットアップ条件に対する触媒性能の評価を行った。実験では、HPLCグラジエントシステムを利用して濃度および送液速度を調整し、時間あたりの供給物質量を8段階で連続的に変化させた。収率変化は、送液条件変更と連動させたオンラインHPLCで効率よく解析した。その結果、高濃度溶液でも十分に高い変換収率が得られることが明らかとなった。次いで、反応器内の触媒活性点量を増やすことで、高生産量と耐久性が両立できる条件を決定することができた。

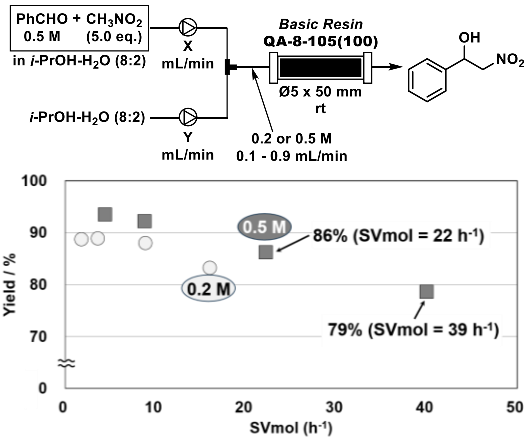


Figure. SVmol-based Evaluation of QA-8-105(100).

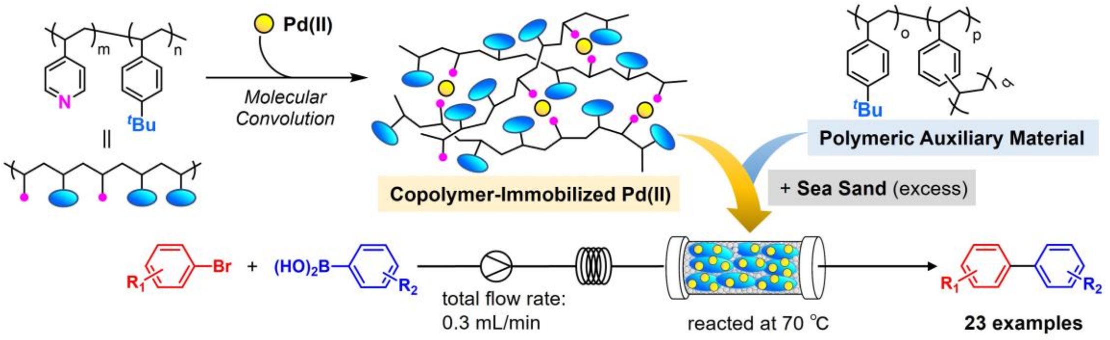
Development of Highly Dispersed and Stabilized Polymeric Pd Catalysts for Continuous Flow Suzuki-Miyaura Coupling

([1]*RIKEN Center for Sustainable Resource Science*, [2]*Department of Life Science Faculty of Life & Environmental Sciences, Teikyo University of Science*) ○Zhenzhong Zhang,[1] Aya Ohno,[1] Hikaru Takaya,[2] Yoichi M. A. Yamada[1]

Keywords: Continuous Flow; Suzuki-Miyaura Coupling; Heterogeneous Palladium Catalysts; Biaryls; XAFS analysis

We developed highly dispersed and stabilized polymeric Pd catalysts for continuous flow Suzuki-Miyaura coupling.[1] A series of copolymers were prepared by polymerizing 4-vinylpyridine with 4-*tert*-butylstyrene, and then Pd(II) species were immobilized via our convolution methodology. In the composite, pyridine units work as the coordination sites for Pd which are sterically separated by bulky *tert*-butyl groups on the polymer chain. This copolymeric Pd catalyst was initially packed with sea sand in a column reactor for the coupling of 4-bromotoluene with phenylboronic acid under continuous flow conditions to optimize the monomer ratio. In addition, cross-linked poly(4-*tert*-butylstyrene) was prepared as a polymeric auxiliary material to disperse further and stabilize the catalyst in the column reactor.

Using this novel catalytic system, a solution of aryl bromides and arylboronic acids in THF/EtOH (5:1, v:v) with an aqueous K_3PO_4 solution flowed over the catalyst at 70 °C with 12–15 min of the residence time. The designed copolymer structure and the cross-linked polymeric auxiliary material effectively dispersed and stabilized the Pd species, enabling the continuous synthesis of a broad spectrum of biaryl products. Liquid-crystalline materials and organic electroluminescent compounds were readily synthesized by the flow system. Furthermore, this catalytic system facilitated a continuous flow process in water as a sole solvent. Two pharmaceutical compounds, felbinac and fenbufen, were synthesized with turnover frequencies of up to 238 h^{-1}. The stability of the catalyst was confirmed through long-term testing in the synthesis of fenbufen in water for 67 h. Subsequently, X-ray absorption spectroscopy studies of the recovered catalyst revealed that almost no Pd aggregation occurred during the reaction.



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