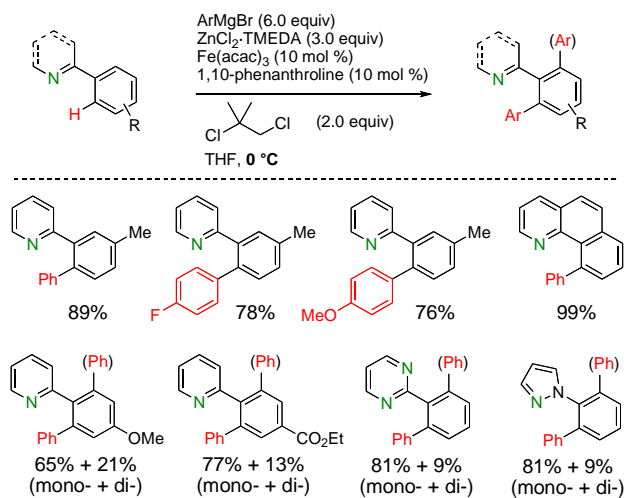


# PHYSICAL ORGANIC CHEMISTRY

## Annual Research Highlights

### (1) “Iron-Catalyzed Direct Arylation Through Directed Aromatic C–H Bond Activation”

In the context of resources depletion and environment awareness, sustainable and atom-efficient synthetic methodologies are the next challenge for the synthetic chemist. Iron is one of the most abundant metals, inexpensive and biocompatible, and therefore it is an ideal metal for clean catalysis. We demonstrated for the first time the use of iron as a catalyst for the direct arylation of aromatic substrates possessing a nitrogen-containing directing group (Fig. 1). Various *in situ*-generated organozinc reagents reacted with 2-phenylpyridine congeners in the presence of an iron salt, a diamine as a ligand, and an organic dihalide as an oxidant, to give the mono- and diarylated products in good yield and under remarkably mild conditions.



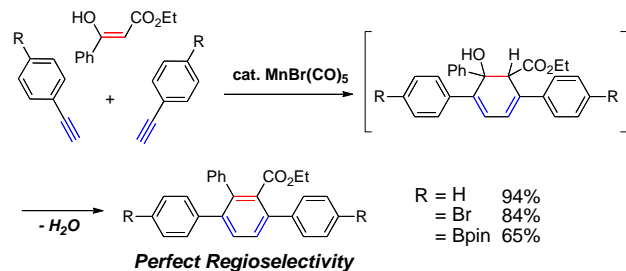
**Fig. 1** Iron-Catalyzed Direct Arylation of Aromatic C–H Bonds.

1.(1)-10) *J. Am. Chem. Soc.*, **130**, 5858 (2008).

### (2) Mn-catalyzed novel approach to multi-substituted benzene derivatives

Benzene synthesis has been main issue in organic synthesis. We have recently developed novel synthetic methodology for benzene synthesis. As shown in Fig. 2, 1,3-dicarbonyl compound and two molecules of alkyne underwent [2 + 2 + 2] cycloaddition in the presence of manganese catalyst and subsequent dehydration to afford tetrasubstituted benzene. Unlike classical Reppe reaction, this reaction achieved excellent regioselectivity: aromatic alkyne afforded the expected *p*-terphenyl compound as a single isomer. Various functional groups such as bromo and boryl functionality tolerated under the present

reaction conditions. This protocol has several synthetically attractive features: the use of non-toxic and naturally abundant manganese as catalyst, high selectivity, and good atom efficiency. This methodology will serve as key step in construction of functional  $\pi$ -materials.

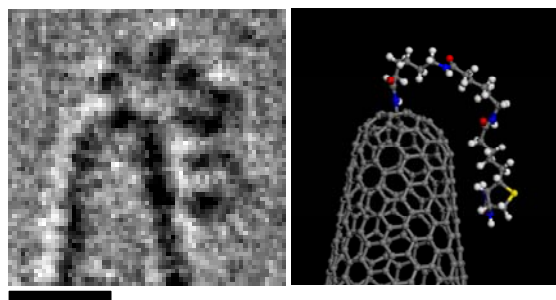


**Fig. 2** Mn-catalyzed [2 + 2 + 2] coupling reaction of 1,3-dicarbonyl compound and alkyne.

1.(1)-12) *J. Am. Chem. Soc.*, **130**, 7792 (2008).

### (3) Imaging of conformational changes of single molecules bonded to a carbon nanotube surface

A chain-like amide molecule bearing a biotin terminus was bonded via an amide linkage to the surface of an aminated carbon nanohorn, a horn-like form of carbon nanotubes, and examined by a transmission electron microscope (TEM). Single molecular images of the amide molecules with 3-nm length were obtained (Fig. 3). An iterative sequence of modeling and simulation allowed us to assign one plausible conformation out of  $> 10^8$  possibilities. Furthermore, the movie images allowed us to study not only the conformation of the molecule but also its time evolution. These results suggest that there is no limitation in molecular size to visualize at a molecular level and this methodology would be applicable for structural and motional analyses of larger molecules such as proteins.



**Fig. 3** A TEM image of triamide-NH conjugate (left) and its molecular modeling structure (right). The scale bar represents 1 nm.

1.(1)-13) *J. Am. Chem. Soc.*, **130**, 7808 (2008).

## 研究ハイライト

### (1) 鉄を用いた炭素-水素結合活性化に基づく芳香族化合物の直接アリール化反応

現在の資源枯渇と環境問題の観点から、環境調和および原子効率の高い合成法の開拓が求められている。鉄は地殻中最も豊富に存在する遷移金属元素であり、または安価および無毒であることから、次世代の環境調和型有機合成の最も適切な元素として注目集めている。今回我々は、鉄触媒による芳香族炭素-水素結合の切断を経る直接アリール化反応の開発に世界初に成功した。触媒量の鉄塩とフェナントリン型配位子及び酸化剤であるジクロロアルカン存在下、アリールピリジン型基質に様々な有機亜鉛試薬を作用させたところ、オルト位の C-H 結合が高效率でアリール化された (図 1)。既存の炭素-水素結合活性化反応と違って、本反応は 0 °C という極めて温和な反応条件で進行することも特徴である。

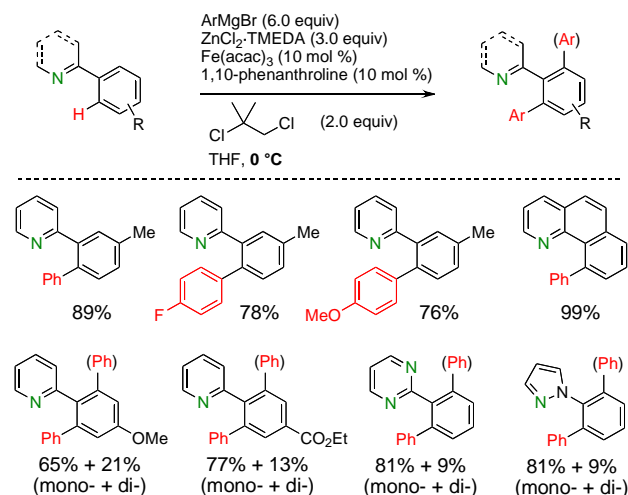


図 1 鉄触媒による芳香族 C-H 結合の直接アリール化反応

1.(1)-10) *J. Am. Chem. Soc.*, **130**, 5858 (2008).

### (2) マンガン触媒による新規多置換ベンゼン合成法の開発

置換ベンゼン合成法の開発は有機合成化学における重要な課題としてこれまで多くの研究者により精力的になされてきた。今回我々は画期的なベンゼン合成法を確立した (図 2)。すなわち、マンガン触媒存在下、1,3-ジカルボニル化合物とアルキン 2 分子から [2 + 2 + 2]付加環化反応が進行し、引き続き脱水反応により四置換ベンゼンを与えることを見いだした。本手法は、古典的な Reppe 反応では困難であった高い位置選択性を実現したほか、臭素、ボロン酸エステルなどの官能基が共存できるなど、高い化学選択

性も有する。また、毒性が低く天然に豊富に存在するマンガン触媒を用いる点、原子効率の高さ等も特徴である。本手法は機能性  $\pi$  共役分子の構築にも役立つと期待される。

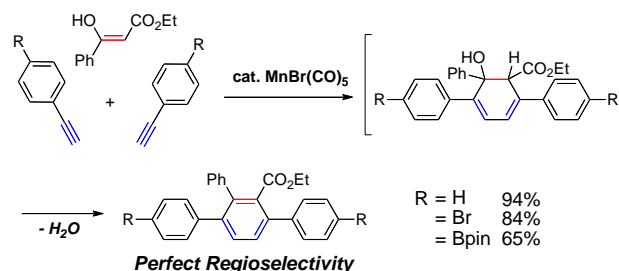


図 2 マンガン触媒による 1,3-ジカルボニル化合物とアルキンとの [2 + 2 + 2] カップリング反応

1.(1)-12) *J. Am. Chem. Soc.*, **130**, 7792 (2008).

### (3) カーボンナノチューブに結合した単一鎖状分子の電子顕微鏡観察

カーボンナノチューブの一種であるカーボンナノホーン上に、ビオチンを末端に有する鎖状アミド分子を結合し、透過型電子顕微鏡で観察を行ったところ、ナノホーンの先端に結合した長さ約 3 nm のアミドの単分子像が得られた (図 3)。また、得られた画像のコントラスト解析を行うことにより、アミド分子に対してその立体配座を決めることができた。さらに、アミド分子の配座変換の様子を数分にわたる動画として記録することにも成功した。今回の発見は単分子観察可能な分子のサイズに実質的な制限がないことを示すものであり、本手法を今後タンパク質などの巨大分子の構造解析および動態分析に応用することも可能であると考えられる。

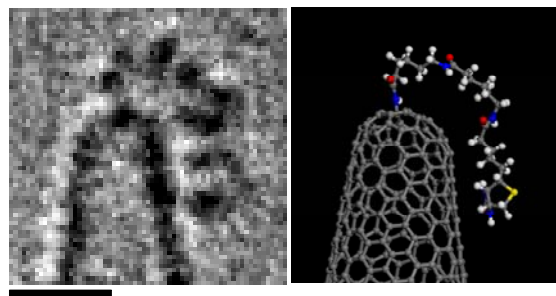


図 3 カーボンナノチューブ表面に結合したアミド分子の透過型電子顕微鏡像およびその分子モデル。スケールバーは 1 nm を表す。

1.(1)-13) *J. Am. Chem. Soc.*, **130**, 7808 (2008).

## 1. 原著論文

### (1) Refereed Journals

- 1) Water-Soluble Fullerene Vesicle Alleviates Angiotensin II Induced Oxidative Stress in Human Umbilical Venous Endothelial Cells, R. Maeda, E. Noiri, H. Isobe, T. Honma, T. Tanaka, K. Negishi, K. Doi, T. Fujita, and E. Nakamura, *Hypertens. Res.*, **31**, 141-151 (2008).
- 2) Synthesis of  $C_5$ -symmetric Functionalized [60]Fullerenes by Copper-mediated Five-fold Addition of Reformatsky Reagents, T. Nakae, Y. Matsuo and E. Nakamura, *Org. Lett.*, **10**, 621-623 (2008).
- 3) A Ruthenium Bridge in Fullerene–Ferrocene Arrays. Synthesis of  $Ru(C_{60}Me_5)R(CO)_2$  ( $R = C_6H_4Fc$  and  $C\equiv CFc$ ) and Their Charge-Transfer Properties, Y. Matsuo, K. Matsuo, T. Nanao, R. Marczak, S. S. Gayathri, D. M. Guldi and E. Nakamura, *Chem. Asian J.*, **3**, 841-848 (2008).
- 4) Modular Synthesis of Functionalized Benzosiloles by Tin-mediated Cyclization of (*o*-Alkynylphenyl)silane, L. Ilies, H. Tsuji, Y. Sato and E. Nakamura, *J. Am. Chem. Soc.*, **130**, 4240-4241 (2008).
- 5) Construction of Chiral Quaternary Carbon Center by Indium-Catalyzed Asymmetric  $\alpha$ -Alkenylation of  $\beta$ -Ketoesters, T. Fujimoto, K. Endo, H. Tsuji, M. Nakamura and E. Nakamura, *J. Am. Chem. Soc.*, **130**, 4492-4496 (2008).
- 6) Addition of Tetrahydrofuran to [60]Fullerene through C-H Bond Activation Induced by Aryl Zinc Reagent, Y. Matsuo, Y. Zhang and E. Nakamura, *Org. Lett.* **10**, 1251-1254 (2008).
- 7) Stereoselective Synthesis of Trisubstituted *E*-Iodoalkenes by Indium-catalyzed *syn*-Addition of 1,3-Dicarbonyl Compounds to 1-Iodoalkynes, H. Tsuji, T. Fujimoto, K. Endo, M. Nakamura and E. Nakamura, *Org. Lett.*, **10**, 1219-1221 (2008).
- 8) Mechanism of the Nucleophilic Substitution of Acyl Electrophiles using Lithium Organocuprates, N. Yoshikai, R. Iida and E. Nakamura, *Adv. Synth. Catal.*, **350**, 1063-1072 (2008) (A. Pfaltz Special Issue).
- 9) Photocurrent Generating Properties of Organometallic Fullerene Molecules on Electrode, Y. Matsuo, K. Kanaizuka, K. Matsuo, Y.-W. Zhong, T. Nakae, and E. Nakamura, *J. Am. Chem. Soc.*, **130**, 5016-5017 (2008).
- 10) Iron-Catalyzed Direct Arylation through Directed C-H Bond Activation, J. Norinder, A. Matsumoto, N. Yoshikai and E. Nakamura, *J. Am. Chem. Soc.*, **130**, 5858-5859 (2008).
- 11) Modular Synthesis of Benzo[b]phosphole Derivatives via BuLi-mediated Cyclization of (*o*-Alkynylphenyl)phosphine, H. Tsuji, K. Sato, L. Ilies, Y. Itoh, Y. Sato and E. Nakamura, *Org. Lett.* **10**, 2263-2265 (2008).
- 12) Manganese-Catalyzed Benzene Synthesis by [2+2+2] Coupling of 1,3-Dicarbonyl Compound and Terminal Acetylene, H. Tsuji, K. Yamagata, T. Fujimoto and E. Nakamura, *J. Am. Chem. Soc.* **130**, 7792-7793 (2008).
- 13) Imaging of Conformational Change of Biotinylated Triamide Molecules Covalently Bonded to Carbon Nanotube Surface, E. Nakamura, M. Koshino, Y. Niimi, K. Harano, Y. Nakamura and H. Isobe, *J. Am. Chem. Soc.*, **130**, 7808-7809 (2008).
- 14) Synthesis of Metal Fullerene Complexes by the Use of Fullerene Halides, Y. Matsuo, Y. Kuninobu, A. Muramatsu, M. Sawamura and E. Nakamura, *Organometallics*, **27**, 3403-3409 (2008).
- 15) Triazole-linked Analogue of Deoxyribonucleic Acid ( $^{TL}$ DNA): Design, Synthesis and Double Strand Formation with Natural DNA, H. Isobe, T. Fujino, M. Guillot-Nieckowski, E. Nakamura, *Org. Lett.*, **10**, 3729-3732 (2008).
- 16) Group 6 Metal Complexes of the  $\eta^5$ -Pentamethyl[60]fullerene, Y. Matsuo, A. Iwashita and E. Nakamura, *Organometallics*, **27**, 4611-4617 (2008).

- 17) Penta(pyrenyl)[60]fullerenes. Pyrene–Pyrene and [60]Fullerene–Pyrene Interactions in Crystal and in Solution, Y. Matsuo, K. Morita and E. Nakamura, *Chem. Asian J.*, **3**, 1350-1357 (2008).
- 18) Light Emission of [10]Cyclophenacene through Energy Transfer from Neighboring Carbazolyphenyl Dendrons, X. Zhang, Y. Matsuo, and E. Nakamura, *Org. Lett.*, **10**, 4145-4147 (2008).
- 19) Origin of the Regio- and Stereoselectivity of Allylic Substitution of Organocopper Reagents, N. Yoshikai, S.-L. Zhang, and E. Nakamura, *J. Am. Chem. Soc.*, **130**, 12862-12863 (2008).
- 20) Imaging the Passage of a Single Hydrocarbon Chain through a Nanopore, M. Koshino, N. Solin, T. Tanaka, H. Isobe and E. Nakamura, *Nat. Nanotechnol.*, **3**, 595-597 (2008).
- 21) Mono- and Penta-Addition of Enol Silyl Ethers to [60]Fullerene, E. Nakamura, S. Mouri, Y. Nakamura, K. Harano, and H. Isobe, *Org. Lett.*, **10**, 4923-4926 (2008).
- 22) Ligand Exchange as the First Irreversible Step in the Nickel-Catalyzed Cross-Coupling Reaction of Grignard Reagents, N. Yoshikai, H. Matsuda, and E. Nakamura, *J. Am. Chem. Soc.*, **130**, 15258-15259 (2008).
- 23) Regioselective Synthesis of 1,4-Di(organo)[60]fullerenes through DMF-assisted Monoaddition of Silylmethyl Grignard Reagents and Subsequent Alkylation Reaction, Y. Matsuo, A. Iwashita, Y. Abe, C.-Z. Li, K. Matsuo, M. Hashiguchi, and E. Nakamura, *J. Am. Chem. Soc.*, **130**, 15429-15436 (2008).
- 24) Diastereoselective Addition of Zincated Hydrazones to Alkenylboronates and Stereospecific Trapping of Boron/Zinc Bimetallic Intermediates by Carbon Electrophiles, T. Hatakeyama, M. Nakamura, and E. Nakamura, *J. Am. Chem. Soc.*, **130**, 15688-15701 (2008).
- 25) Uniquely Shaped Double-Decker Buckyferrocenes - Distinct Electron Donor-Acceptor Interactions, M. Renata, M. Wielopolski, S. S. Gayathri, D. Guldi, Y. Matsuo, K. Matsuo, K. Tahara and E. Nakamura, *J. Am. Chem. Soc.*, **130**, 16207-16215 (2008).
- 26) Efficient Formation of Ring Structures Utilizing Multisite Activation by Indium Catalysis, Y. Itoh, H. Tsuji, K. Yamagata, K. Endo, I. Tanaka, M. Nakamura, and E. Nakamura, *J. Am. Chem. Soc.*, **130**, 17161-17167 (2008).

## (2) その他

### 2. 総説・解説

- 1) Selective Multi-addition of Organocopper Reagents to Fullerenes, Y. Matsuo and E. Nakamura, *Chem. Rev.*, **108**, 3016-3028 (2008).
- 2) 百聞は一見に如かず –有機分子 1 分子の動きを見る, 中村栄一, 現代化学, No. 422, pp16–22 (2008).

### 3. 著書

### 4. その他

- 1) Chemical & Engineering News (2008年6月23日) "Electron Microscopy For Chemists"
- 2) 化学工業日報 (2008年9月16日) 「世界初直接観察に成功, 分子のナノサイズ細孔通過」
- 3) 朝日新聞 (2008年9月19日) 「形変え動く分子観察」
- 4) 科学新聞 (2008年9月19日) 「ナノサイズの穴を通る分子の動き」
- 5) Chemical & Engineering News (2008年9月22日) "Imaging Molecular Escapes"
- 6) nanowerk (2008年9月22日) 「Nanotechnology escape artists squeezing through a hole in the wall」
- 7) Asia Materials (2008年10月2日) "Molecular snap-shots"