

PHYSICAL ORGANIC CHEMISTRY

Annual Research Highlights

(1) “Development of New Synthetic Route to Substituted Benzofurans and Indoles Based on Intramolecular Cyclization Reaction”

Benzoheteroles are fundamental building block of bioactive agent as well as organic electronic material, and the exploration of versatile synthetic method has been highly desired. We have developed a new synthetic route to substituted benzofurans and indoles on the basis of intramolecular cyclization reactions. Thus, heating of zinc *o*-alkynylphenoxide and *o*-alkynylanilide undergo intramolecular cyclization to quantitatively afford 3-zincio benzofuran and indole, respectively. The resulting zincio intermediates are versatile reagents which can be subjected to further derivatization with various electrophiles to afford various substituted benzofurans and indoles (Fig. 1).

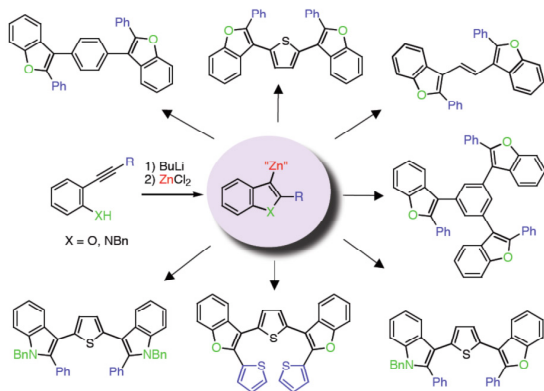


Fig. 1 Divergent synthesis based on 3-zincio benzoheteroles.

1.(1)-1) *Angew. Chem. Int. Ed.*, **45**, 944 (2006)

1.(1)-14) *Org. Lett.*, **8**, 2803 (2006)

(2) “Synthesis, Purification, Structure Determination, and Cytotoxicity of Water-Soluble, Transition-Metal-Free Carbon Nanotube”

Risk assessment of carbon materials, inter alia, carbon nanotubes has surfaced as an important subject of nanomaterials research, which has however been hampered by the lack of characterization of sample materials. In this study, we have prepared water-soluble and metal-free carbon nanotube aggregate and evaluated its cytotoxic effect.

We first prepared water-soluble carbon nanohorn aggregates by the reaction with sodium amide (Eq. 1, Fig. 2a). After the structure determination of obtained amino nanohorn aggregates, we evaluated the toxic effect on the mammalian cells and found that the amino nanohorn aggregates did not show significant cytotoxicity (Fig. 2b). Taking advantage of good solubility, we could first determine all the properties which are suspected to affect living things. Our water-soluble carbon nanotube aggregates may serve as standards for risk assessment of

carbon nanoparticles.

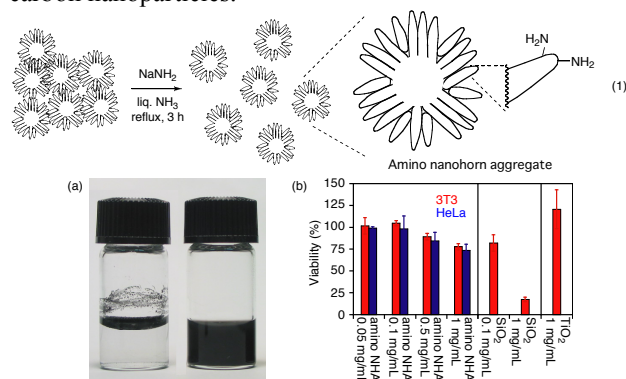


Fig. 2 (a) Picture of intact (left) and chemically treated water-soluble (right) carbon nanohorn aggregates in water. (b) Viability of cells dosed with amino nanohorn aggregates (amino NHA). Quartz particles and TiO₂ particles are used as control.

1.(1)-16) *Angew. Chem. Int. Ed.*, **45**, 6676 (2006)

(3) “Development of Novel Multidentate Ligand for Copper-catalyzed Enantioselective Conjugate Addition”

Copper-catalyzed conjugate addition of organometallic reagent is among very useful methods for carbon-carbon bond formation. Nevertheless, the development of the enantioselective variant has been hampered by its mechanistic complexity, and has generally required many trials and errors. On the basis of our previous studies on the mechanism of organocuprate conjugate addition, we designed a novel chiral multidentate ligand and succeeded in its application to highly enantioselective conjugate addition.

A multidentate ligand **L**, which has a donor atom to copper (P), one to zinc (N), and one bridging both metals (O), was designed. The ligand **L** was easily synthesized from the corresponding amino acid, and applied to the conjugate addition. The alanine-derived ligand immediately ($R = \text{Me}$) turned out to give an excellent enantioselectivity in the conjugate addition to an acyclic enone. Thus, conjugate addition to a variety of acyclic substrates proceeded in high enantioselectivity (> 98% ee). The ligand in fact provided best selectivities among hundreds of previously reported ones. A modeling study with density functional calculations suggested that a copper/zinc bimetallic species formed on the ligand allows facile face selection and activation of the substrate.

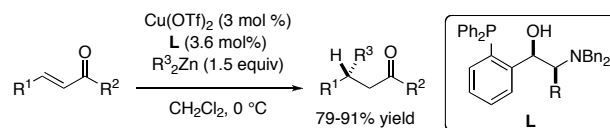


Fig. 3 Copper-catalyzed enantioselective conjugate addition.

1.(1)-18) *Org. Lett.*, **8**, 4153 (2006)

研究ハイライト

(1) 分子内環化反応による置換ベンゾフラン・インドール誘導体の新規合成法

ベンゾヘテロール類は生理活性物質や有機電子材料の基本骨格をなすものであり、その自在合成および修飾法の開発が望まれていた。我々は、オルト位にアルキニル基を有するフェノールおよびアニリンから発生させた亜鉛アルコキシドおよび亜鉛アニリドを、トルエン中で加熱することでアルキン部位への分子内付加環化反応が進行し、対応する3-亜鉛化ベンゾフランおよびインドールが形成されることを見出した。これら新規有機金属活性種から、パラジウム触媒を用いたクロスカップリング反応、あるいは亜鉛を銅等の他の金属へトランスメタル化した後各種求電子試薬との反応を行うことで、様々な新規ベンゾフランおよびインドール誘導体が合成可能になった (図1)。

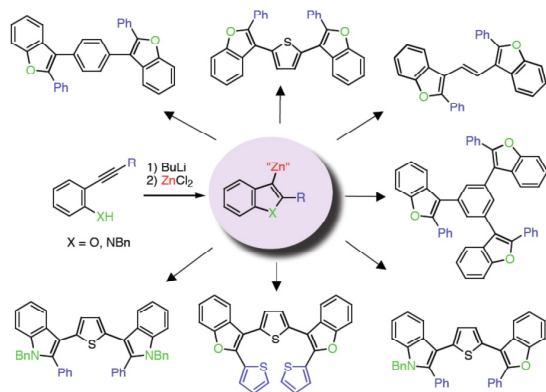


図1 3-亜鉛化ベンゾヘテロール：新規有機金属活性種の合成と誘導化

1.(1)-1) *Angew. Chem. Int. Ed.*, **45**, 944 (2006)

1.(1)-14) *Org. Lett.*, **8**, 2803 (2006)

(2) 遷移金属を含まない水溶性カーボンナノチューブの合成、構造決定と細胞毒性

カーボンナノチューブをはじめとするナノカーบอนは環境や生体への悪影響が懸念されていたが、これまで安全評価に用いられたナノカーบอนは複雑な混合物であったため有毒であるか無毒であるかはっきりとした結論はでていなかった。我々は、カーボンナノチューブのひとつであるカーボンナノホーンにアミノ基を導入する手法を開発し、金属微粒子を含まない水溶性カーボンナノホーンを合成した (式1, 図2a)。この水溶性カーボンナノホーンを用いて細胞毒性試験を行ったところ、ナノカーบอนには強い毒性がないことを明らかにした (図2b)。今回

合成した水溶性カーボンナノホーンは今後ナノカーบอนの安全評価の「標準物質」として応用が期待される。

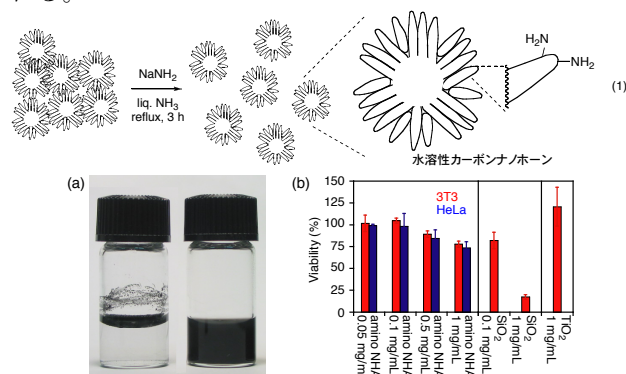


図2 (a) 化学処理する前(左)と処理した後(右)のカーボンナノホーン, (b) 水溶性カーボンナノホーン (amino NHA) を投与した細胞の生存率。石英粒子は有毒な、二酸化チタン粒子は無毒な粒子の参照物質。

1.(1)-16) *Angew. Chem. Int. Ed.*, **45**, 6676 (2006)

(3) 多座配位子の合理設計に基づく銅触媒不斉共役付加反応の開発

銅触媒による有機典型金属化合物の共役付加反応は重要な炭素-炭素結合生成反応の一つである。しかし、その反応機構は十分には明らかにされておらず、不斉触媒化は試行錯誤に大きく依存してきた。我々は、これまで行ってきた有機銅反応に関する反応機構研究に基づいて新規な光学活性多座配位子を設計し、これを用いて有機亜鉛試薬の高立体選択的共役付加反応を実現した。

銅、亜鉛それぞれに対する配位部位およびそれらを架橋する部位を有する配位子として、アミノ酸由来の配位子 **L** を設計合成し、不斉共役付加反応へと適用した。その結果、アラニン由来の配位子 (R = Me) が、直鎖の α,β -不飽和カルボニル化合物へのジアルキル亜鉛の共役付加において一様に高い立体選択性 (> 98% ee) を示すことを見いだした。事実、本配位子は過去に開発された数百に及ぶ配位子のなかで最も高い立体選択性を与える。密度汎関数法計算によるモデリングから、配位子 **L** を足場として形成される銅・亜鉛複核錯体が基質の面選択および活性化に有効に作用していることが示唆された。

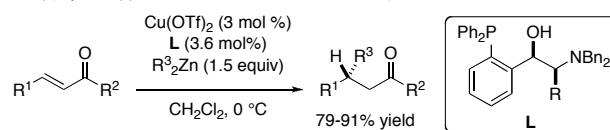


図3 銅触媒による不斉共役付加反応

1.(1)-18) *Org. Lett.*, **8**, 4153 (2006).

1. 原著論文

(1) Refereed Journals

- 1) M. Nakamura, L. Ilies, S. Otsubo and E. Nakamura, "3-Zincobenzofuran and Indole: Versatile Tools for Construction of Conjugated Structures Containing Multiple Benzoheterole Units", *Angew. Chem. Int. Ed.*, **45**, 944-947 (2006).
- 2) H. Isobe, W. Nakanishi, N. Tomita, S. Jinno, H. Okayama and E. Nakamura, "Non-viral Gene Delivery by Tetraamino Fullerene", *Mol. Pharm.*, **3**, 124-134 (2006).
- 3) J. Miyawaki, M. Yudasaka, H. Imai, H. Yorimitsu, H. Isobe, E. Nakamura and S. Iijima, "In vivo Magnetic Resonance Imaging of Single-Walled Carbon Nanohorns by Labeling with Magnetite Nanoparticles", *Adv. Mater.*, **18**, 1010-1014 (2006).
- 3) Y.-W. Zhong, Y. Matsuo and E. Nakamura, "Convergent Synthesis of Polyfunctionalized Fullerene by Regioselective Five-Fold Addition of a Functionalized Organocopper Reagent to C₆₀", *Org. Lett.*, **8**, 1463-1466 (2006).
- 4) Y. Matsuo and E. Nakamura, "Synthesis of Trialkyl[60]fullerene C₆₀(CH₂SiMe₃)₃H and Its Potassium and Rhodium(I) Complexes", *Inorg. Chim. Acta*, (Gerard van Koten special issue) **359**, 1979-1982 (2006).
- 5) J. Miyawaki, M. Yudasaka, H. Imai, H. Yorimitsu, H. Isobe, E. Nakamura and S. Iijima, "Synthesis of Ultrafine Gd₂O₃ Nanoparticles inside Single-Wall Carbon Nanohorns", *J. Phys. Chem., B* **110**, 5179-5181 (2006).
- 6) J. Norinder, J.-E. Bäckvall, N. Yoshikai and E. Nakamura, "Unusual Homo-Coupling in the Reaction of Diorganocuprates with an Allylic Halide", *Organometallics*, **25**, 2129-2132 (2006).
- 7) Y. Matsuo, K. Tahara and E. Nakamura, "Synthesis and Electrochemistry of Double-decker Buckyferrocenes", *J. Am. Chem. Soc.*, **128**, 7154-7155 (2006).
- 8) Y. Matsuo, Y. Mitani, Y.-W. Zhong and E. Nakamura, "Remote Chirality Transfer within a Coordination Sphere by the Use of a Ligand Possessing a Concave Cavity", *Organometallics*, **25**, 2826-2832 (2006).
- 9) D. M. Guldi, G. M. A. Rahman, R. Marczak, Y. Matsuo, M. Yamanaka and E. Nakamura, "Sharing Orbitals: Ultrafast Excited State Deactivation with Different Outcomes in Bucky Ferrocenes and Ruthenocenes", *J. Am. Chem. Soc.*, **128**, 9420-9427 (2006).
- 10) N. Yoshikai, M. Yamanaka, I. Ojima, K. Morokuma and E. Nakamura, "Bimetallic Synergism in Alkyne Silylformylation Catalyzed by Cobalt-Rhodium Mixed Metal Cluster", *Organometallics*, **25**, 3867-3875 (2006).
- 11) H. Isobe, W. Nakanishi, N. Tomita, S. Jinno, H. Okayama and E. Nakamura, "Gene Delivery by Aminofullerene: Structural Requirements for Efficient Transfection", *Chem. Asian J.*, **1**, 167-175 (2006).
- 12) N. Yoshikai, T. Yamashita and E. Nakamura, "Mechanism of Remote Conjugate Addition of Lithium Organocuprates to Polyconjugated Carbonyl Compounds", *Chem. Asian J.*, **1**, 322-330 (2006).
- 13) S. Sato, T. Fujino, H. Isobe and E. Nakamura, "Diels-Alder Reaction of Cyclopentadienone Acetal with Pyrrole and Indole", *Bull. Chem. Soc. Jpn.*, **79**, 1288-1292 (2006). ("Selected Paper of the Month")
- 14) M. Nakamura, L. Ilies, S. Otsubo and E. Nakamura, "2,3-Disubstituted Benzofuran and Indole by Copper-Mediated C-C Bond Extension Reaction of 3-Zincobenzoheterole", *Org. Lett.*, **8**, 2803-2805 (2006).
- 15) Y. Matsuo, A. Muramatsu, Y. Kamikawa, T. Kato and E. Nakamura, "Synthesis, Structural, Electrochemical and Stacking Properties of Conical Molecules Possessing Buckyferrocene on Apex", *J. Am. Chem. Soc.*, **128**, 9586-9587 (2006).
- 16) H. Isobe, T. Tanaka, R. Maeda, E. Noiri, N. Solin, M. Yudasaka, S. Iijima and E. Nakamura, "Preparation, Purification, Characterization, and Cytotoxicity of Water-soluble, Transition-metal Free Carbon Nanotube Aggregate", *Angew. Chem. Int. Ed.*, **45**, 6676-6680 (2006).
- 17) Y. Matsuo, A. Iwashita and E. Nakamura, "Coupling of Alkylarene and Pentamethyl[60]fullerene by Iridium-Catalyzed Benzylic C-H Bond Activation", *Chem. Lett.*, **35**, 858-859 (2006).
- 18) A. Hajra, N. Yoshikai and E. Nakamura, "Aminohydroxyphosphine Ligand for Copper-Catalyzed Enantioselective Conjugate Addition of Organozinc Reagents", *Org. Lett.*, **8**, 4153-4155 (2006).

- 19) Y. Matsuo, A. Muramatsu, A. Koide and E. Nakamura, "Synthesis of 6,9,12,15,18-pentamethyl-1,6,9,12,15,18-hexahydro ($C_{60}-I_h$)[5,6]fullerene", *Org. Synth.*, **83**, 80-87 (2006).

2. 総説・解説

- 1) フラーレン C_{60} の生体関連機能, 磯部寛之, 中村栄一, 「ウイルスを用いない遺伝子導入法の方法論, 技術, 方法論の新たな展開 (遺伝子医学 MOOK 5号)」, メディカルドゥ 1章10節, pp79-83 (2006).
- 2) PET のための超高速有機合成 - 1/ 酸素 - 15 標識糖の超高速合成とその応用 時間との究極の戦い / 依光英樹, 村上佳裕, 西村伸太郎, 中村栄一, 化学と生物, Vol143, 731-733 (2005).
- 3) 環状 π 電子共役系・シクロフェナセンの合成と構造研究 / 松尾 豊, 中村栄一, 日本結晶学会誌, Vol148, 227-282 (2006).