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Snapshots of some topics of interest of recent notable advances in chemistry

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Construction of "Cyborg Erythrocytes" Containing Calcium Carbonate Nanoparticles for Removal of Extracellular Lead Ions

A novel strategy based on "cyborg cells" is described. The constructed "cyborg erythrocytes" are achieved through the in situ reaction of exogenous calcium and carbonate ions to provide calcium carbonate nanodots inside erythrocytes. These nanodots endow erythrocytes with new properties without adverse effects. The in vitro and in vivo results reveal that the "cyborg erythrocytes" can remove 80% of lead ions in blood poisoning model and reduce its level in the kidney and lever.

The "cybrog cells" defined as living cells with built-in nanoscaffolds, which integrate the biological function of the cell with the functionality of the nanomaterials affording new functions. Taking advantage of erythrocytes as important cells for oxygen transportation, and featured by long circulating half-life, membrane selective permeability, flexibility and stability, big cell cavities and high surface-to-volume ratio, Lu team constructed "cyborg erythrocytes" through the in situ reaction of exogenous calcium and carbonate ions to generate calcium carbonate nanodots (NDs) inside erythrocytes. The intracellular NDs combined with proteins and are stealth under the cover of erythrocytes, which can restrict the migration of NDs and avoid the unexpected accumulation of NDs in the body, improving their biosafety.

$CaCO_3$ nanoscaffolds were synthesized through two-step sequential permeation of Ca^{2+} and CO_3^{2-} into erythrocytes. The distribution of $CaCo_3$ NDs in "cyborg erythrocytes", and the interaction between Ca^{2+} and the endogenous hemoglobin (Hb) as well as $CaCO_3$ NDs and Hb were assessed and the results revealed that The $CaCO_3$ NDs are well dispersed in the erythrocytes with a size of about 3.90 nm, and the interactions between both of Ca^{2+} and $CaCO_3$ with Hb take place. The interaction between $CaCO_3$ NDs with Hb restricts the migration and accumulation of NDs in the body. Furthermore, the properties of functionalized erythrocytes proved secure from any detectable change.

The intracellular stealth $CaCO_3$ nanoscaffolds could endow erythrocytes with new functions different from their native ones. Through the membrane transport of Pb^{2+} and the subsequent precipitation transformation from $CaCO_3$ to $PbCO_3$ (Figure), the as-prepared functionalized erythrocytes could efficiently remove 80% of lead ions in a blood poisoning model in vitro and reduce the Pb^{2+} accumulation in kidney and liver of mice in vivo, which can be excreted by urine from the mice.

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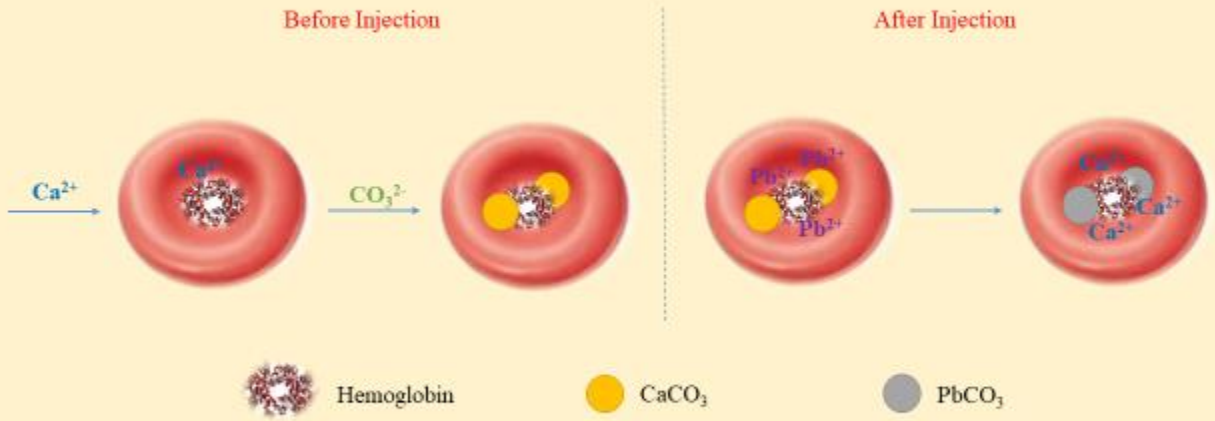

Figure. Schematic illustration for the construction mechanism of the functionalized erythrocytes and the reduction of Pb^{2+} accumulation in kidney and liver of mice

This novel strategy based oh “cyborg cells” may pave the way to construct a new class of bio-molecular compounds with outstanding advantages.

Review

X. Ru, Y. Guo, Z. Bai, X. Xie, X. Ma, L. Zhu, K. Wang, F. Wang, L. Yang, J. Lu, *Nature Comm.*, **2019**, *2*, 105.

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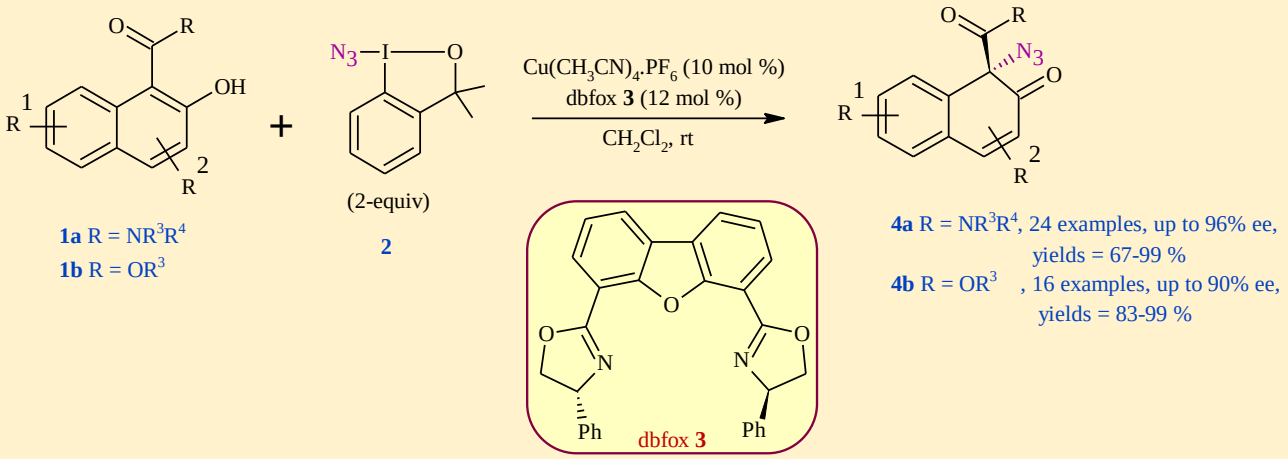
Copper-mediated Enantioselective Dearomative Azidation of *β*-naphthols

A new methodology is described for asymmetric dearomative azidation of *β*-naphthols using N_3-transfer reagent in the presence of a combination of copper salt as a catalyst with dbfox as a stereo-directing ligand to provide the corresponding products in high yields with moderate to excellent enantioselectivities under mild reaction conditions.

Organic azides play a key role in a variety of reactions. They can be easily transferred into nitrogen-containing structural motifs through “click” reaction, *aza*-Wittig reaction, Staudinger reduction, and Schmit rearrangement. In addition, they serve as powerful precursor for reactive species such as nitrenes and nitrenium ions.

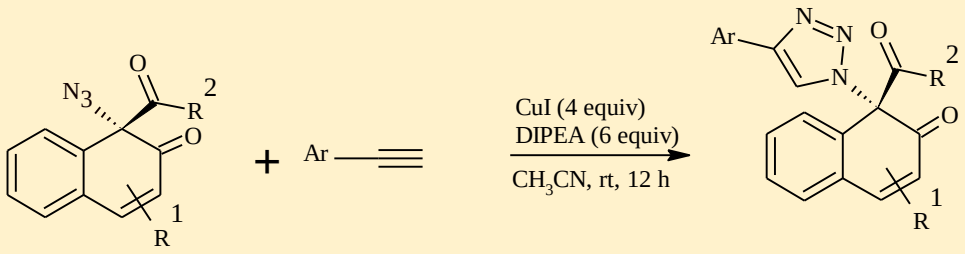
In view of the importance of chiral azides as well as naphthalenone derivatives, which they are important structural motifs of different biologically active natural products and therapeutic reagents, Wang and co-workers reported the first example of copper-catalyzed asymmetric dearomative azidation of *β*-naphthols for the synthesis enantioenriched *α*-azide *β*-naphthalenones.

In this procedure, a variety of the substituents on the core of 2-hydroxy-*N*,*N*-diisopropyl-1-naphthamide **1a** as well as 2-hydroxy-1-naphthoates **1b** were reacted with T-shaped iodine (III) compounds **2** in the presence of a combination of copper salt (Cu(CH3CN)$_4$.PF$_6$) as a catalyst with 4,4-dibenzofurandiyl-2,2'-bisoxazoline (dbfox) ligand **3** as a stereo-directing ligand in dichloromethane at room temperature to provide the corresponding products **4a & 4b** in excellent yields and good enantioselectivities (Scheme 1).



Scheme 1. Synthesis of 2-hydroxy-1-naphthamides and 2-hydroxy-1-naphthoates.

The utility of this procedure was further investigated through the conversion of azide products into the corresponding 1,2,3-triazoles using Cu-catalyzed azide-alkyne cycloaddition (Scheme 2). The obtained triazoles were in good yields and enantiosecetivities.



Scheme 2. Further Transformations of the Azide Products.

The method exhibits a good tolerance of diverse functional groups.

Review

C-J. Wang, J. Sun, W. Zhou, J. Xue, B-T. Ren, G-Y. Zhang, Y-L. Mei, Q-H. Deng, *Org. Lett*., **2019**, *21*, 7315−7319.

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A New Azetidine Scaffold for Colony Stimulating Factor-1 Receptor (CSF-1R) Type II Inhibitors

Based on a docking model, a new azetidine scaffold for colony stimulating factor-1 receptor (CSF-1R) Type II inhibitors is described. The azetidine compounds showed great therapeutic potential.

Colony-stimulating factor-1 receptor (CSF-1R) is a cell-surface protein encoded, in humans, by *CSF1R* gene, and acts as the receptor for colony stimulating factor 1, a cytokine which controls the production, differentiation, and function of macrophages. It binds to macrophage colony-stimulating factor (CSF-1) and interleukin-34 (IL-34). These bindings activate the receptor kinase through a process of oligomerization and trans-phosphorylation leading to stimulate the survival, proliferation, and differentiation of mononuclear phagocyte system at progenitor cells in bone marrow, through the various intermediate stages of differentiation, to the mature macrophage.

Based on the co-crystal structure of GW2580, as one of the most selective CSF-1R Type II inhibitor (Figure 1) which binds to the DFG (Asp-Phe-Gly)-out state protein, Ikegashire and co-workers reported a new class of azetidine compounds as CSF-1R Type II inhibitors.

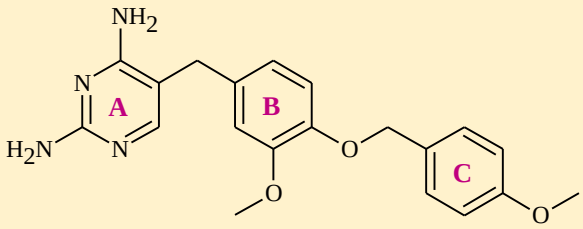
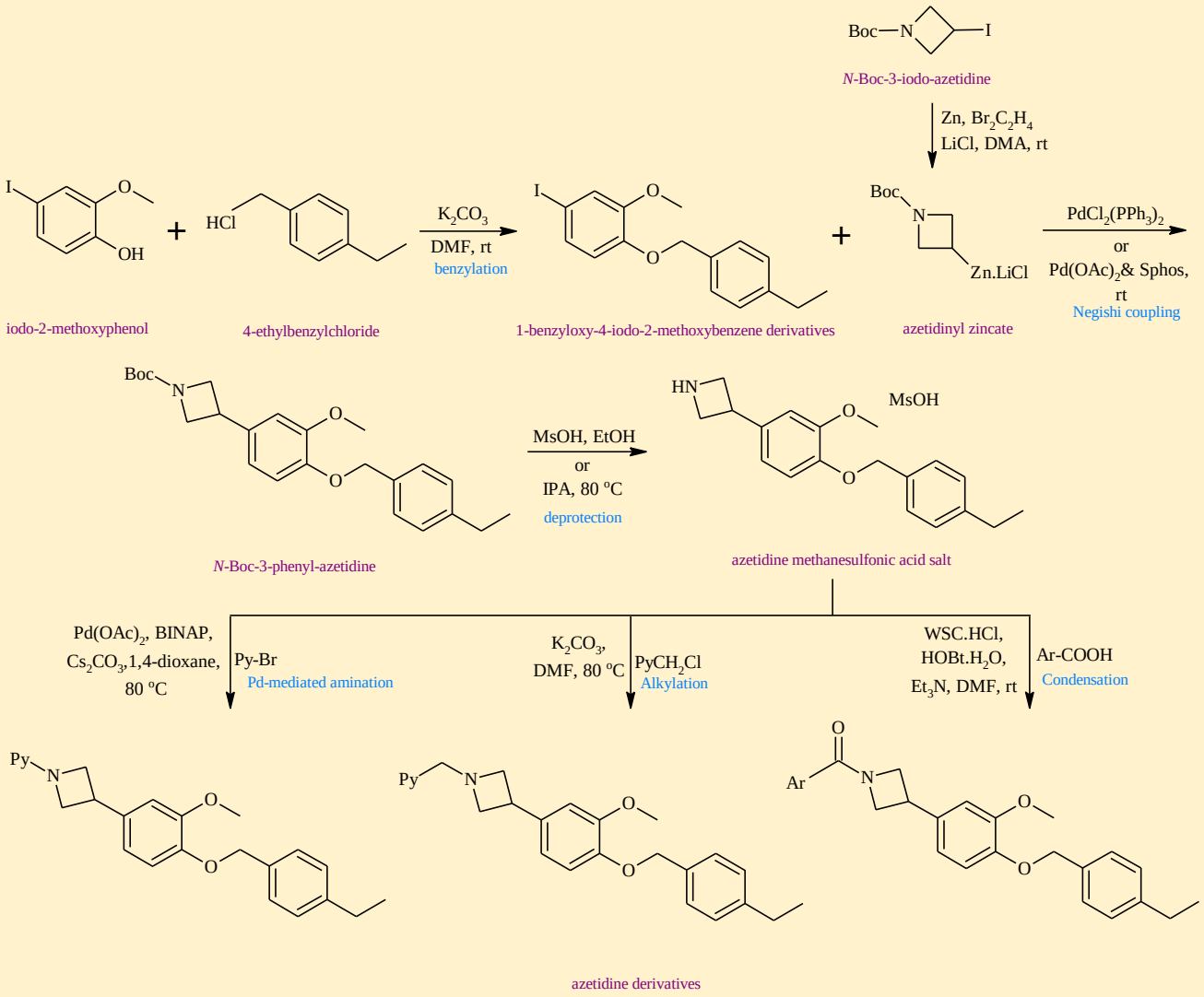


Figure 1. The structure of GW2580.

The co-crystal structure of GW2580 with CSF-1R showed that: (i) ring A binds to the hinge region of the kinase protein with four hydrogen bonds; (ii) rings A and B form an L-shape conformation through methylene; (iii) the two oxygen atoms of the methoxy and benzyloxy groups on ring B make the bidentate hydrogen bonding network to the backbone amide NH of the protein; and (iv) ring C occupy the hydrophobic pocket in the DFG-out state.

The employed strategy is based on the alteration of the hinge binding substructure to enhance the activity, while maintaining the bidentate hydrogen bonds. The synthesis of these azetidine compounds was achieved as shown in Scheme 1.



Scheme 1. Preparation of azetidine compounds. Sphos = dicyclohexyl-(2′,6′-dimethoxy-[1,1′-biphenyl]-2-yl)phosphine,

Among the crystal structures of these compounds in complex with CSF-1R, a crystal structure is obtained, which is considered as a clinical candidate.

Review

K. Ikegashira, T. Ikenogami, T. Yamasaki, Y. Hase, T. Yamaguchi, K. Inagaki, S. Doi, T. Adachi, Y. Koga, H. Hashimoto, *Bioorg. Med. Chem. Lett.*, **2019**, *29*, 115–118.

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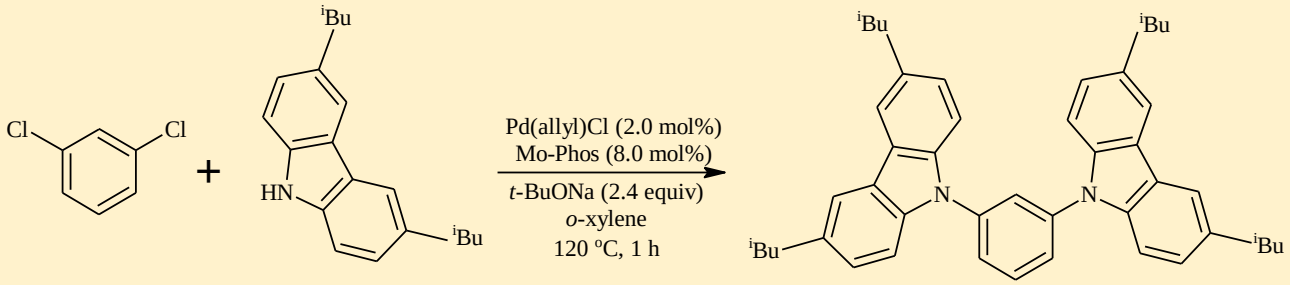
An Oxidizing System Induce Double Intramolecular C-H/C-H Coupling

An oxidizing system of Pd(II)-Ag(I) has been employed to induce double intramolecular C-H/C-H coupling of 1,3- and 1,4-bis(3,6-di-*tert*-butyl-9*H*-carbazol-9-yl)benzenes to provide the corresponding highly π-extended polycyclic compounds. While a singly cyclized product has been isolated from 1,2-bis(3,6-di-*tert*-butyl-9*H*-carbazol-9-yl)benzene.

Nitrogen-containing planar and non-planar polycyclic condensed aromatic compounds including heterocyclic moiety are considered as an important source of electron donors. Therefore, the synthesis and properties of this class of compounds have been a significant research objective.

In this regard, Miura team reported synthetic procedures for oxidative cyclization of 1,3-, 1,4- and 1,2-bis(9H-carbazol-9-yl)benzenes bearing *tert*-butyl substituents on the 3- and 6-positions of each carbazole moiety.

The synthesis of 1,3-bis(carbazolyl)benzene **1** was achieved using a catalyst system of Pd(allyl)Cl_2/Mo-Phos (Scheme 1). While its pyridine analogue **2** was obtained in the presence of CuI, t-BuOLi, and N-methyl-imidazole. The intramolecular C-H/C-H coupling reactions of **1** and **2** were accomplished in the presence of $Pd(TFA)_2$ to afford the corresponding condensed compounds **3** & **4** respectively.



1,3-dichlorobenzene

3,6-di(tert-butyl)carbazole

1

1,3-bis(carbazolyl)benzene derivative
73% yield

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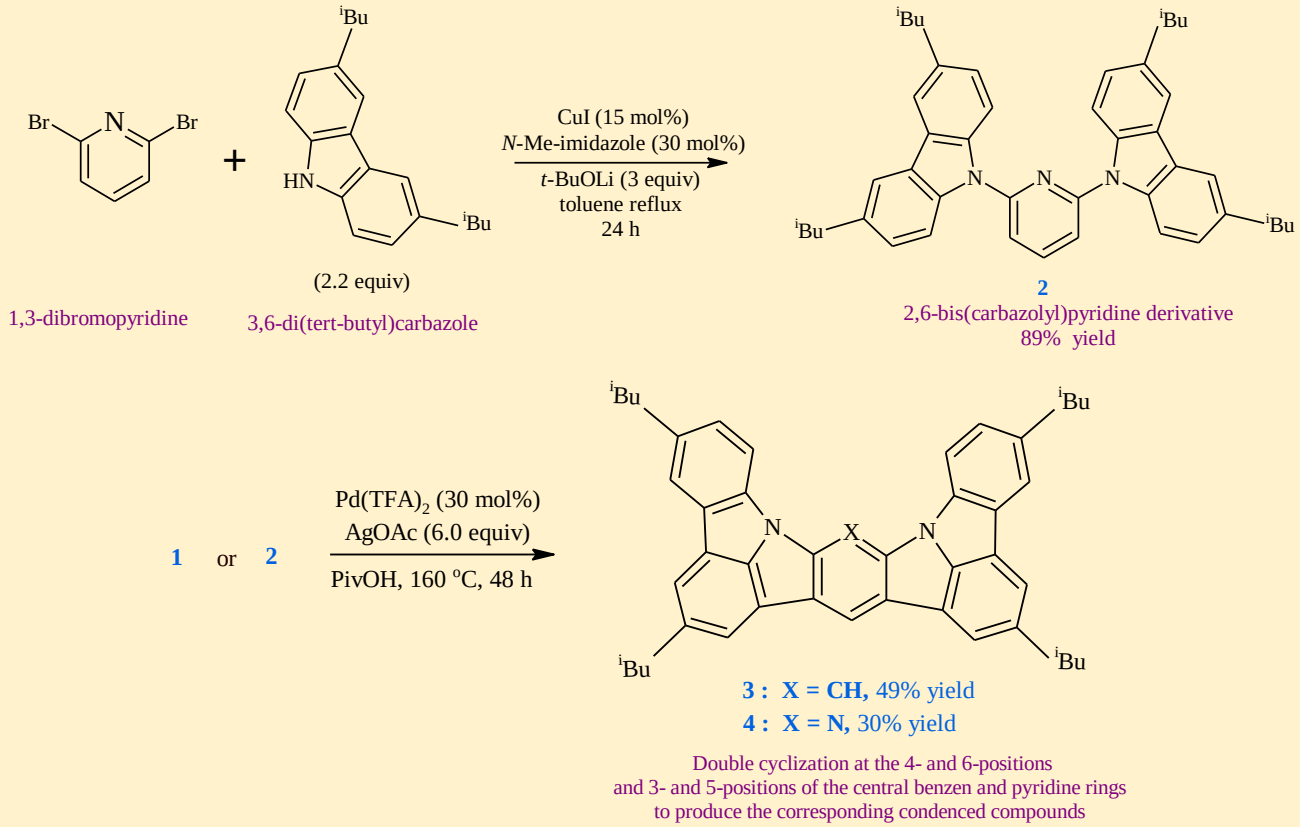
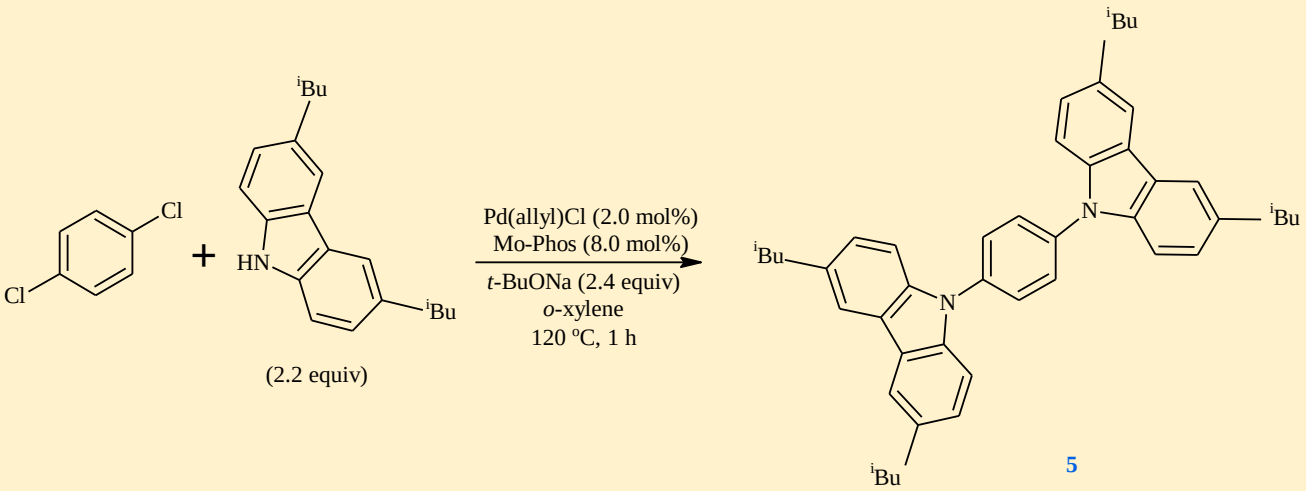
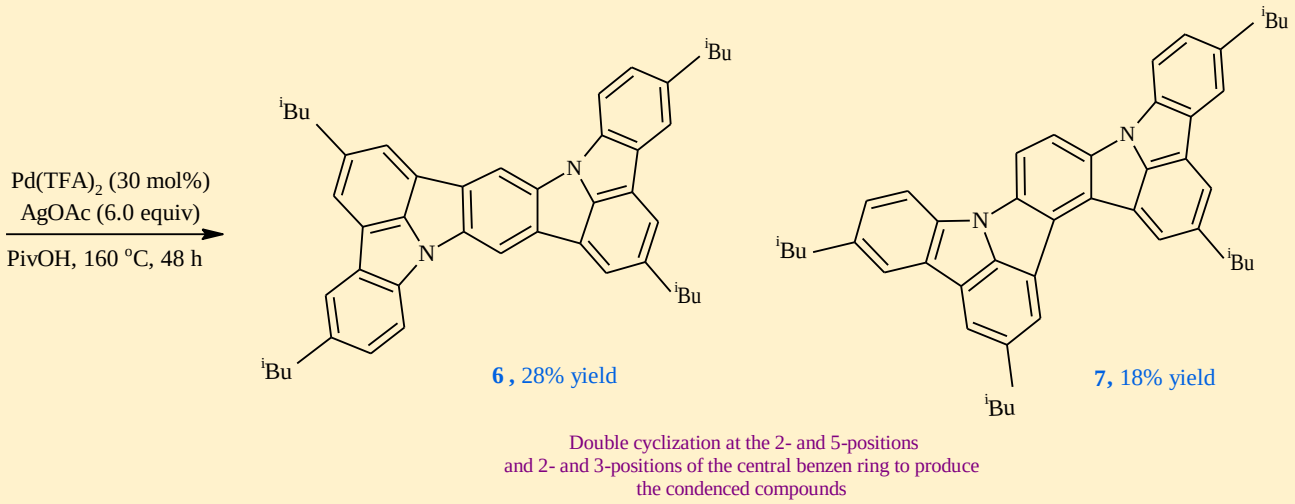


Scheme 1. Preparation of the condensed compounds 3 and 4. Mo-Phos = di-*tert*-butyl(2,2-diphenyl-1-methyl-1-cyclopropyl)-phosphine.

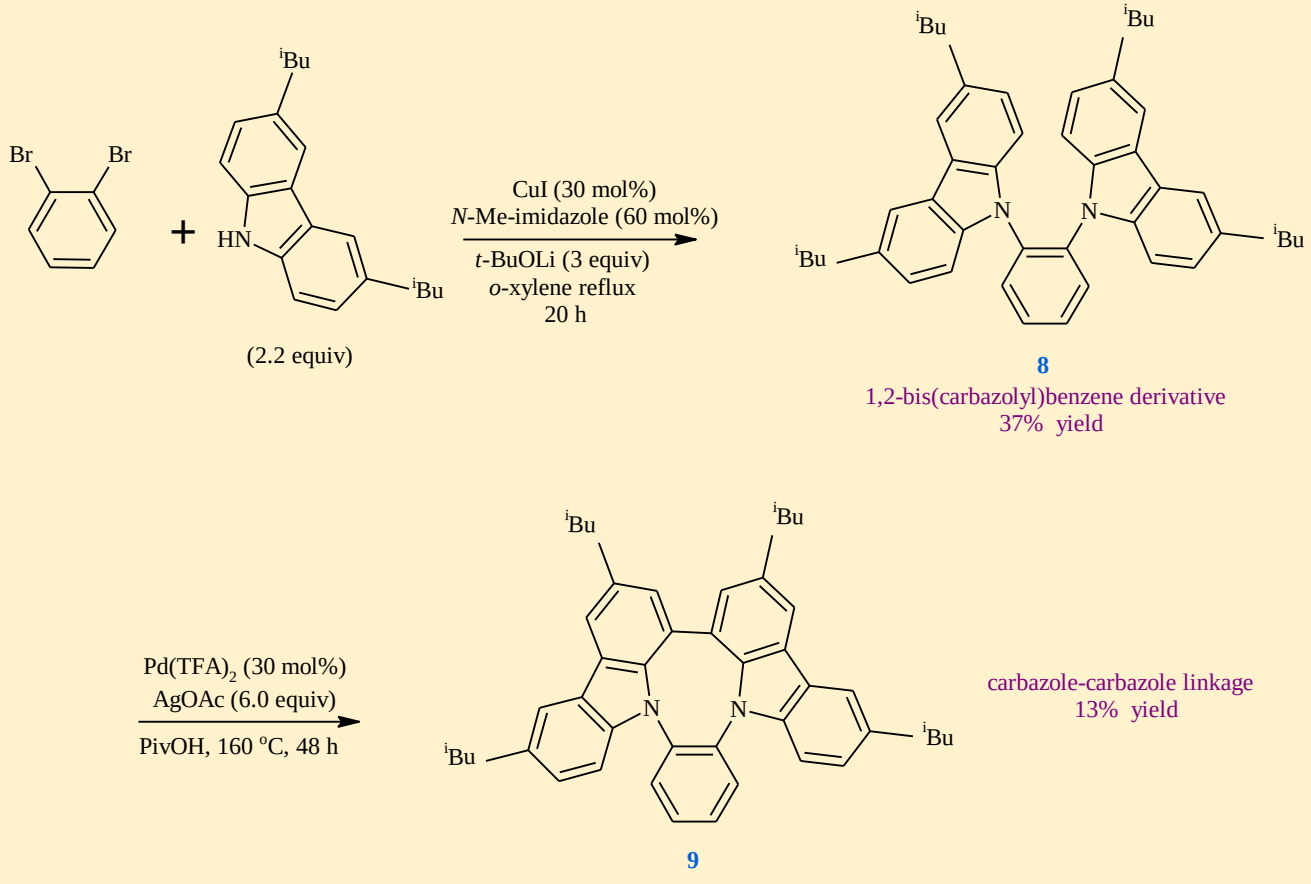
The double cyclization of the 1,4-bis(carbazolyl)benzene **5** proceeded in two possible ways at the 2- and 5-positions and the 2- and 3-positions of the central benzene ring to provide compounds **6** and **7,** respectively (Scheme 2).





Scheme 2. Preparation of compounds 6 and 7.

The preparation of the 1,2-bis(carbazolyl)benzene **8** was achieved by the copper-promoted method (Scheme 3). The proximity of two carbazole rings in **8** may be the major reason for the formation of **9**.



Scheme 3. Preparation of compound 9.

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The cardinal optoelectronic properties revealed that compound **6** is the most electron-donating due to the effective of π-conjugation, while compound **4** is the least oxidizable. The products are soluble and tractable, while having high melting points mostly higher than 300 °C. They exhibit violet to blue fluorescence with good quantum yields and are also expected to be utilizable as electron donors.

Review

T. Taniguchi, Y. Itai, Y. Nishii, N. Tohnai, M. Miura, *Chem. Lett.*, **2019**, *48*, 1160–1163.

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Antimicrobial Additives for Use in Water-based Latex Paints

Polymeric *N*-halamine latex emulsions are highlighted, which showed potent antimicrobial activities against a range of bacteria, drug-resistance species, fungi, mold, and viruses upon addition of small amount of them into commercial water-based latex paints as antimicrobial additives. These polymeric *N*-halamines were prepared by emulsion polymerization of *N*-halamine monomer [*N*-chloro-2,2,6,6-tetramethyl-4-piperidinyl methacrylate (Cl-TMPM)].

To protect the building materials from damage caused by mold action, antimicrobial paints can be used to inhibit or inactivate such action. Mold can sensitize and produce allergic responses in allergic individuals, and can also cause serious fungal infections for individuals with impaired immune systems. Antimicrobial paints are used to control/ inhibit the wide spreading of healthcare-associated infections (HAIs), which are associated with multi-drug-resistant pathogens. Therefore, there is a need to provide potent antimicrobial paints with biocidal functions against bacteria (including the drug-resistant species), mold, fungi, and viruses.

In this context, Cao and Sun developed polymeric *N*-halamine latex emulsions for used in antimicrobial paints. Such class of *N*-halamine contains one or more nitrogen-halogen covalent bonds, that are formed by chlorination of imide, amide, or amine groups.

The preparation of *N*-halamine monomer, *N*-chloro-2,2,6,6-tetramethyl-4-piperidinyl methacrylate (Cl-TMPM), was accomplished via chlorination of TMPM with a solution of dichlorisocyanurate sodium (DCCNa) in $CHCl_3$ (Scheme). The monomer could be polymerized using a semicontinuous emulsion polymerization technique, in which dioctyl sulfosuccinate sodium (DSS) and TX-100 were used as emulsifiers and ammonium persulfate ($(NH_4)_2S_2O_8$) as initiator. The monomer pre-emulsion was dropped into the dispersion of the seed particles at rate of 0.1 ml/min for 3 h and the system was maintained at 70 ^oC for 30 min. under constant stirring followed by cooling at room temperature to form stable, water-based, latex emulsions.

The product could be directly added into commercial water-based latex paints as antimicrobial additives providing potent antimicrobial activities against *Staphylococcus aureus,* methicillin-resistant *S. aureus,* vancomycin-resistant enterococcus, *Escherichia coli, Candida tropicalis,* MS2 virus, and *Stachybotrys chartarum* spore.

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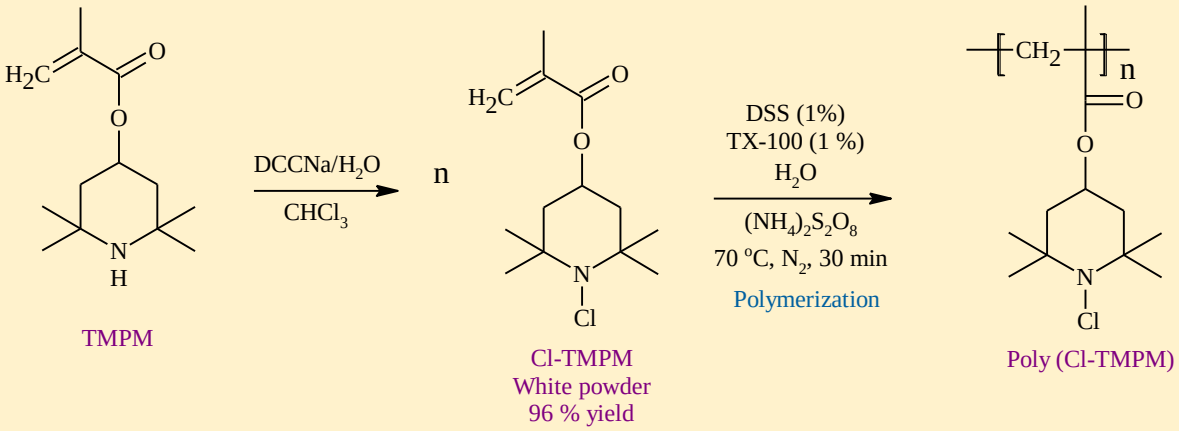

Scheme. Preparation of Cl-TMPM monomer and poly(Cl-TMPM) emulsion through polymerization.

Their functions were long-lasting for more than 1 year under normal in-use conditions, easily monitorable by a simple potassium iodine/starch test, and readily rechargeable if the functions were accidently lost as a result of challenging conditions such as heavy soil, flooding, etc.

Review

Z. Cao, Y. Sun, *Appl. Materials & Int.*, **2009**, *1*, 494-504.