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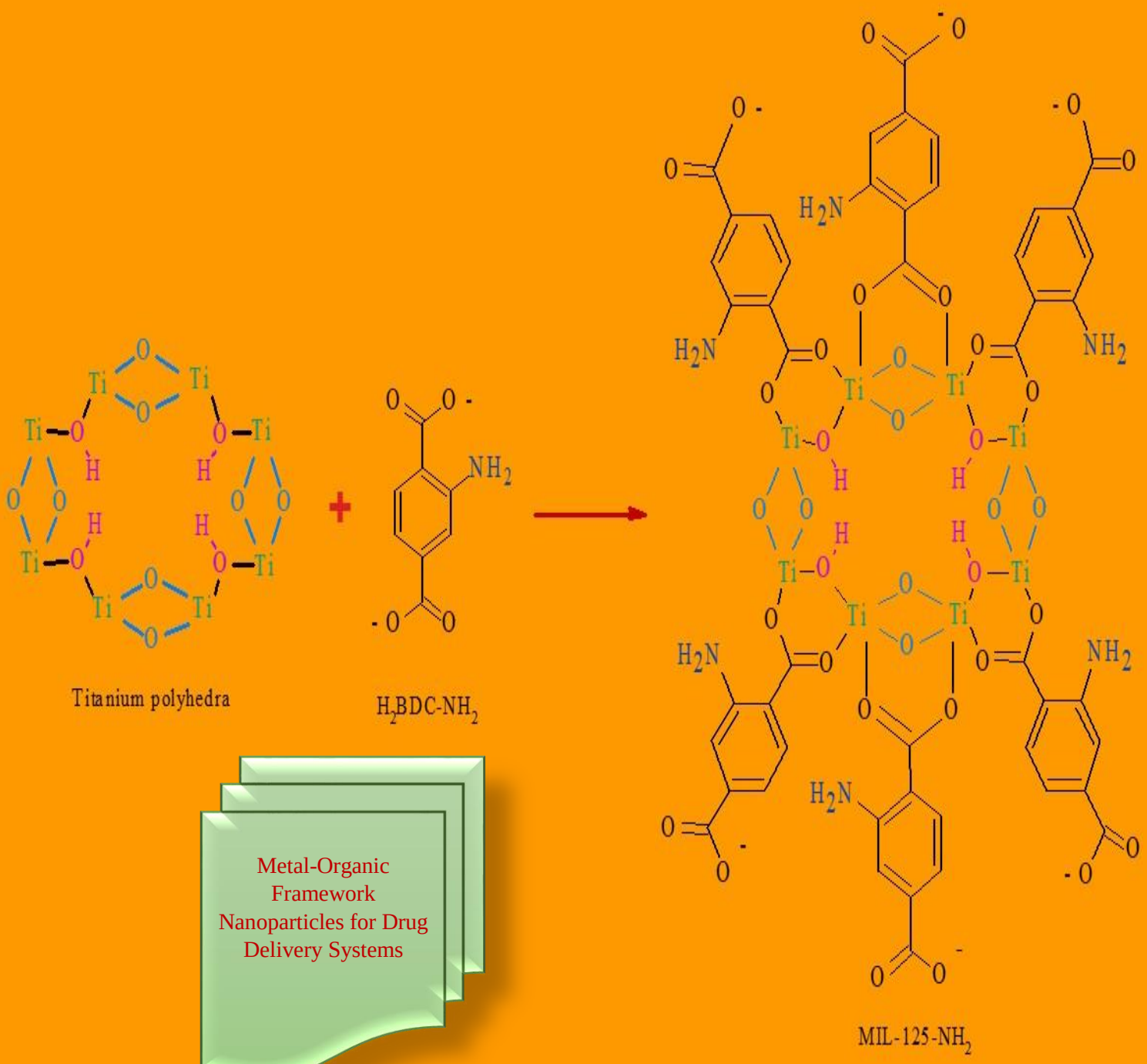

Metal-Organic Framework Nanoparticles for Drug Delivery Systems

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Metal-Organic Framework Nanoparticles for Drug Delivery Systems

Atef S. Iskander

Metal-organic framework nanoparticles (nano-MOFs) offer many opportunities for applications in a wide variety of fields, in particularly, biomedical fields. Their remarkable intrinsic properties enable possible applications as delivery vehicles for therapeutic agents and bioactive gases. This article highlights how nano-MOFs can be used as drug carriers.

Introduction

Metal-Organic Frameworks (MOFs), also known as Porous Coordination Polymers (PCPs), are an emerging class of porous crystalline materials. They are composed of metal ion or metal ion clusters connected by organic linkers through strong coordination bonds. These porous materials exhibit characteristic features such as ultrahigh regular porosity – with pore sizes 0.4 – 6 nm, high surface area, easily tunable hybrid composition, and thermal, chemical and mechanical stability. By varying the choice of metal ion and shape and terminal functionality of organic linker, diversity of MFOs topologies and structures can be achieved. Such versatility has led to numerous applications, including catalysis[1], gas storage[2], gas separations[3], and biomedical applications[4]. In particular, down-sizing MOFs to nanoscale confers them with different properties to those of the bulk counterparts, enabling to develop new therapeutic and diagnostic applications. MOF nanoparticles (nano-MOFs) have several promising applications in biological and medical landscapes such as drug delivery, biomimetic catalysis, and enantioseparation. This article will illustrate some potential applications of MOF nano-carriers as a new type of platform for drug delivery.

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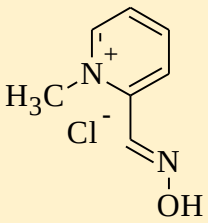
Potential applications of MOF nano-carriers

Bio nano-MOFs are of interest as drug delivery hosts due to their high drug loading capacities; excellent biodegradability; and controlled as well as prolonged releases, associated with their exceptional porosity and chemical flexibility. Their hydrophilic-hydrophobic internal microenvironment is adaptable to host a wide variety of active molecules. Moreover, they are compatible with intravenous administration. All these aspects make them highly interesting to develop smart nano-carriers capable of bypassing extra- and intracellular barriers. Some of recent developments are discussed as specific examples of such versatility of nano-MOFs.

Delivery of therapeutic agents

The incorporation of the nerve agent antidote, 2-[(hydroxyimino) methyl]-1-methyl-pyridinium chloride (2-PAM or pralidoxime) **1** into the microporous titanium aminoterephthalate MIL-125-NH_2 (MIL: Material of Institut Lavoisier) has been reported.[5] The particular focus is on the treatment of organophosphate (OP) poisoning as a result of its ability to inhibit acetylcholinesterase (AChE) by forming a covalent bond with a serine residue in the active site of the enzyme leading to a rapidly hydrolysis of the neurotransmitter acetylcholine (ACh) in cholinergic synapses in peripheral as well as in central nervous tissues. Such inhibition of AChE by OPs causes accumulation of ACh in the synapses and overstimulation of ACh receptors, resulting in severe symptoms such as convulsions, flaccid muscle paralysis, and seizures. The synthesis of nano-carrier MIL-125-NH_2 was achieved by solvothermal as well as by microwave-assisted solvothermal methodologies (Scheme). MIL-125-NH_2 was isolated as monodispersed nanoparticles (~ 220 nm) which are compatible with intravenous administration. These colloidally stable MIL-125-NH_2 solutions were able to effectively encapsulate the nerve agent antidote 2-PAM into the MOF NP pores via π-stacking and hydrogen bond interactions using a simple impregnation method. Moreover, both MOF NP and 2-PAM@MIL-125-NH_2 exhibited high colloidal stability in vitro during 24 h.



2-PAM

1

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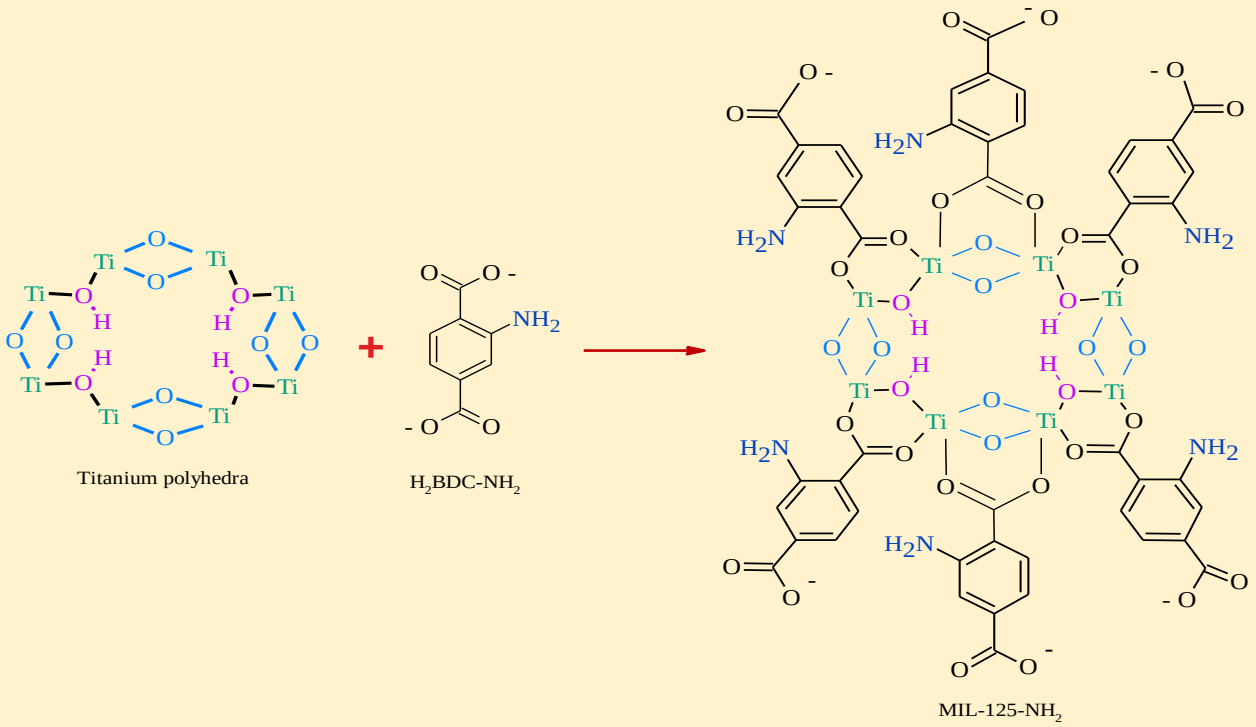

Scheme: synthesis of MIL-125-NH2; $H_2BDC\text{-}NH_2$ = 2-aminoterephthalic acid; MIL = Material of Institut Lavoisier

The encapsulation of two antibiotics with different solubility, tetracycline hydrochloride (TC) and doxycycline monohydrate (DOX), were achieved separately in nano-MIL-100(Fe)[6], which is composed of a polycrystalline powder of iron and benzene tricarboxylic acid. Both of DOX@MIL-100(Fe) and TC@MIL-100(Fe) showed no burst effect, which indicated that the drugs are well dispersed into the pores of nano-MIL-100(Fe). The carrier showed a mediating effect on these antibiotics. The release of DOX in PBS was increased by 25% more than that of conventional methods, whereas TC showed slower release due to the formation of stronger bonds with the carrier. The slower kinetics of TC lead to 96% of the drug being released after 48 h in acidic medium, which is much higher than previous reports. Such sustained release of antibiotics into the body would be desirable for treatment of infections that need more time to cure.

Another interesting approach is based on the loading of MOF nanoparticles with multiple drugs followed by coating these drug carriers with a lipid shell acting as a temporary seal for the

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encapsulated drugs, and allowing control of interactions with intracellular fluids. In this regard, liposome-coated iron fumarate nano-MOF (Lip-MIL-88A) was synthesized via the fusion method for the purpose of combination therapy.[7] The cell experimental results revealed that Lip-MIL-88A nanoparticles could readily take up a significant amount of therapeutic agents (20 wt %) and showed a significant intracellular release without leakage of their cargo (e.g. SBHA, irinotecan and floxuridine) after three to four days of incubation. There delivery carriers, which allow loading with both single and multiple drugs at the same time, make them an interesting candidate for use in combination therapy and could as such contribute to improve cancer chemotherapy.

Delivery of bioactive gases

Nano-MOFs have also been of great interest for delivery of gases. For instance, nitric oxide (NO) is a key molecule in the cardiovascular system and helps keep blood vessels healthy and regulate blood pressure. Furthermore, it has also been found to be essential in many other bodily systems (such as the immune system and the nervous system, including the brain) and in many chronic conditions and diseases (such as chronic inflammation, erectile dysfunction, and cancer). Owing to the physical and chemical characteristics of NO its release from a material is a method of generating local (rather than systemic) effects, which also has the advantage of reducing undesired side effects. In this regard, nano-MOFs are promising porous materials for gas separation and storage, due to their exceptional adsorption capacity and selectivity. Some of MOFs show considerable structural flexibility in response to various stimuli. For example, the nano-carrier, $Cu_2(OH)(C_8H_3O_7S)(H_2O).2H_2O$, showed exceptional low-pressure selectivity towards nitric oxide, *i.e.* adsorb only NO and no other gases.[8] In addition, it features great flexibility which can be controlled by addition of a supplementary coordinating molecule resulting in increasing the thermal stability of the solid to match its utility for direct imaging with electron microscopy.

The NH_2-MIL-125(Ti)-hemoglobin nano-conjugate was synthesized by a covalent post-modification stratey.[9] It showed its ability to retain the gas-binding capacity of hemoglobin which could be potentially used as an oxygen carrier.

Conclusions

There are many characteristic features make nano-MOFs so attractive for drug delivery systems. They are highly regular channel structures, controllable pore sizes and pore volumes,

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guest responding flexible pores, and designable pore surface functionality, which produce efficient pores and excellent porous functionalities. These features reflect their availability for large loadings of biological molecules including multiple drugs or biogases, which can be entrapped within their pores. In addition, the high available functionality of either metal sites or functional groups on the organic linkers leads to control accurately the guest-host interaction. Besides, their release into the environment can be tuned effectively.

In view of these significant advantages of nano-MOFs as drug carriers, many challenges with biomedical applications still remain such as their biosafety, bio-distribution and efficacy in *vitro* and/or in *vivo*. Such challenges need further development to meet the requirement of real biomedical applications. Nevertheless, nano-MOFs will become an excellent strategy for biological and medical applications.

References

1) J.S. Seo, D. Whang, H. Lee, S.I. Jun, J. Oh, Y.J. Jeon, K.A. Kim, *Nature*, **2000**, *404*, 982.
2) A.R. Millward, O.M. Yaghi, *J. Am. Chem. Soc.*, **2005**, *127*, 17998-17999.
3) S. Ma, D. Sun, X.S. Wang, H.C.A. Zhou, *Angew. Chem. Int. Ed.*, **2007**, *46*, 2458-2462.
4) D. Liu, Z.G. Ren, H.X. Li, J. –P. Lang, N.Y. Li, B.F. Abrahams, *Angew. Chem. Commun.* **2010**, *52*, 4767-4770.
5) S. M. F. Vilela, P. Salcedo-Abraira, I. Colinet, F. Salles, M. C. de Koning, M. J. A. Joosen , Ch. Serre, P. Horcajada, *Nanomaterials*, **2017**, *7*, 321.
6) S. D. Taherzade, J. Soleimannejad, A. Tarlani, *Nanomaterials*, **2017**, *7*, 215.
7) B. Illes, S. Wuttke, H. Engelke, *Nanomaterials*, **2017**, *7*, 351.
8) B. Xiao, P. J. Byrne, P. S. Wheatley, D. S. Wragg, X. B. Zhao, A. J. Fletcher, K. M. Thomas, L. Peters, J. S. O. Evans, J. E. Warren, W. Z. Zhou, R. E. Morris, *Nat. Chem.*, **2009**, *1*, 289–294.
9) W. Wang, L. Wang, Y. Huang, Z. Xie, X. Jing, *Chem. Asian J.*, **2016**, *11*, 750–756.

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

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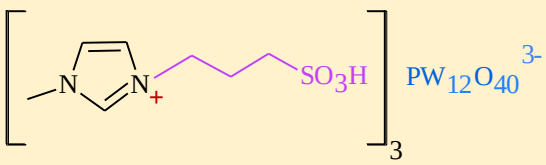
Reaction-Induced Self-Separation Catalysts for Esterification

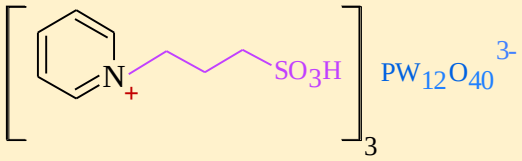
A series of heteropolyanion-based ionic liquids compounds containing organic cations demonstrated their ability to serve as reaction-induced self-separation catalysts for various esterification reactions.

The esterification processes have a broad range of utility in chemical and pharmaceutical industries. They are mostly achieved by acid catalysts or heterogeneous catalysts which suffer from drawbacks ranging from corrosive, difficult separation and recovery, the tendency to deactivation till operation loss and high transfer resistance. Although various homogeneous and heterogeneous catalysts are just fine for some applications, they are far from ideal for highly efficient and reusable catalysts.

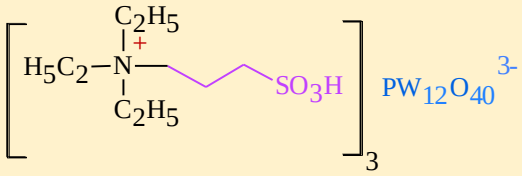
In this context, Wang and co-workers reported an approach for a series of nonconventional catalysts for various esterification reactions which are composed of propane sulfonate (PS) functionalized organic cations and heteropolyanions (Figure).



$(MIMPS)_3PW_{12}O_{40}$



$(PyPS)_3PW_{12}O_{40}$



$(TEAPS)_3PW_{12}O_{40}$

MIM = methylimidazolium, PS = propane sulfonate, TEA = triethylammonium, Py = pyridinium

Figure: A series of heteropolyacids salts containing organic cations.

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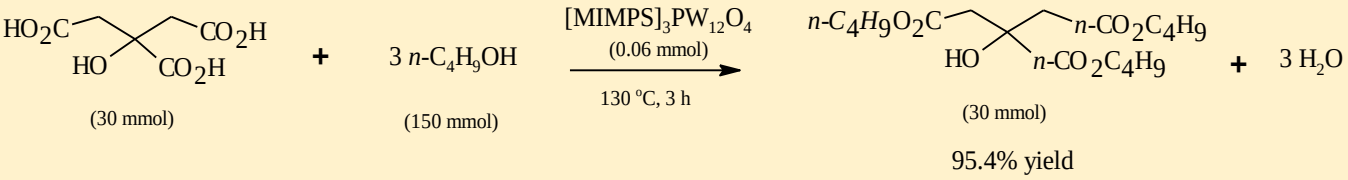
They took advantage of ionic liquids (ILs) as green reaction media, to synthesize heteropolyanion-based ILs containing PS group that provides the acid site responsible for the high catalytic activity, whereas heteropolyanions endow the IL catalyst with high melting points (> 100 ^{o}C), which is responsible for the reaction induced phase separation.

For example, the esterification of citric acid with *n*-butanol was accomplished using $[MIMPS]_3PW_{12}O_{40}$ as the catalyst to give tributyl citrate in 95.4% yield and a selectivity of 98% (Scheme).



Scheme: Esterification reaction over the $[MIMPS]_3PW_{12}O_{40}$ catalyst.

The good solubility in the polycarboxylic acid or polyol, nonmiscibility with ester product, and high melting points of heteropolyanion-based IL catalysts result in the switching from homogeneous to heterogeneous catalysis, which makes the recovery and catalytic reuse, for up to four times with a slight deactivation of the recovered catalyst, very convenient.

Review

Y. Leng, J. Wang, D. Zhu, X. Ren, H. Ge, L. Shen, *Angew. Chem. Int. Ed.*, **2009**, *48*, 168 – 171.

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The Third Generation of Fluorinating Agents

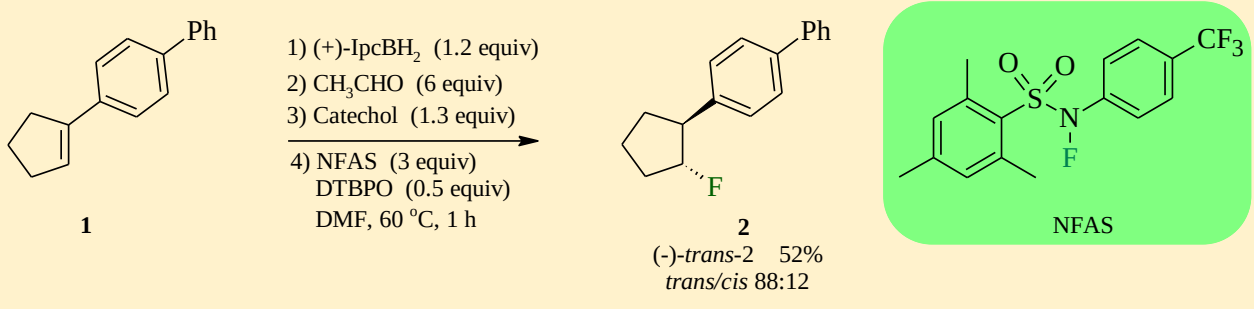
N-fluoro-*N*-arylsulfonamides (NFASs) were developed as a new class of fluorinating reagents. They are demonstrated by a metal-free radical hydro-fluorination of alkenes including an efficient remote C–H fluorination via a 1,5-hydrogen atom transfer.

The synthetic applications of the first generation of radical fluorination reagents were limited by their hazardous nature such as F_2, hypofluorites (ROF), and XeF_2, whereas the limitation of the second generation was related to their strongly electrophilic nature such as *N*-fluorobenzenesulfonimide (NFSI), Selectfluor®, and N-fluoropyridinum salts (NFPY).

Renaud and co-workers developed a new class of fluorinating reagents, *N*-fluoro-*N*-arylsulfonamides (NFASs), which are suitable for radical fluorination under mild conditions. They are favored than those of the second generation by their lower N-F bond dissociation energies (30-45 kJ mol^{-1}) which facilitate the radical processes.

Hydrofluorination of non-terminal alkenes

A one-pot enantioselective hydrofluorination of **1** was performed (Scheme 1). This one-pot procedure includes a hydroboration of the alkene with monoisopinocampheylborane [(+)-IpcBH$_2$], conversion to the diethyl boronate, transesterification to the *B*-alkylcatecholborane and a final radical fluorination. The fluoride **2** was isolated in 52% yield and 91:9 enantiomeric ratio.



1

2
(-)-*trans*-2 52%
trans/cis 88:12

Scheme 1 Preparation of the enantioenriched fluoride (–)-trans-**2** from alkene **1** using (+)-isopinocampheylborane [(+)-IpcBH$_2$] in the hydroboration step, DTBPO = di-*tert*-butyl peroxyoxalate (as an initiator).

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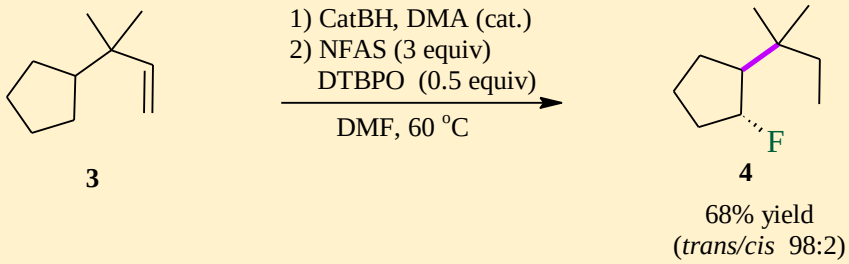
Remote Fluorination

The radical hydrofluorination process can be employed for efficient remote fluorination via 1,5-hydrogen atom transfer. The hydrofluorination of the terminal alkene **3** afforded the fluoride **4** in 68% yield with excellent diastereoselectivity (Scheme 2). The lower nucleophilicity of primary alkyl radical slows the direct fluorination and favors hydrogen atom abstraction processes leading to remote fluorination of unactivated C–H bonds.



3 **4**

68% yield
(*trans/cis* 98:2)

Scheme 2 Hydrofluorination of terminal alkenes.

NFASs have the potential to deeply transform the field of radical fluorination by enabling powerful transformations under milder conditions than the former generations of fluorinating agents.

Review

D. Meyer, H. Jangra, F. Walther, H. Zipse, Ph. Renaud, *NAT. COMMUNICATIONS*, **2018**, 9:4888.

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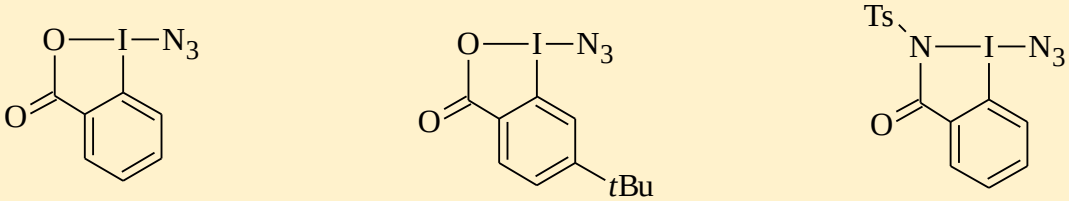
Safer Cyclic Hypervalent Iodine Reagents as Azide Sources

*t*Bu-azidobenziodoxolone (*t*BuABX) and azidobenziodazolone (ABZ) were described as safer cyclic hypervalent iodine reagents for azidation.

The Zhdankin reagent **1**, azidobenziodoxolone (ABX) (Figure), is an excellent azide source whether under thermal, photoredox, or metal-mediated activation, but it has high thermal potential hazard. In this regard, Waser and co-workers introduced two derivatives, *t*Bu-ABX **2** and azido-benziodazolone (ABZ) **3** (Figure), with a better safety profile in comparison with the Zhdankin reagent, in particular, ABZ. An azidative ring-expansion of alkene-silylated cyclobutanol derivatives was accomplished using these reagents. The best results were obtained with ABZ **3** to afford azidated cyclopentanones in 90% yield (Scheme).

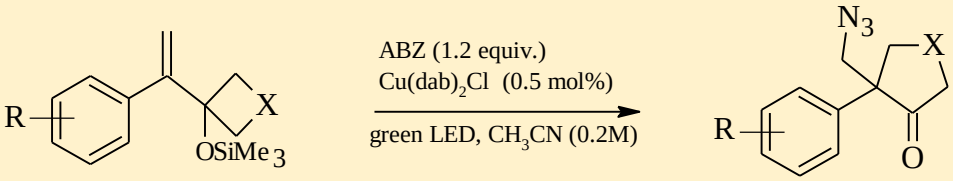


1
ABX

2
*t*Bu-ABX

3
ABZ

Figure. cyclic hypervalent iodine reagents as azide sources.



(0.5 mmol)

R = H, X = CH_2

Scheme. The ring expansion reaction.

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They came to the conclusion that ABZ was as efficient as the Zhdankin reagent in a new photoredox-mediated ring expansion process as well as in established radical- or metal-mediated azidations.

Review

S. Alazet, J. Preindl, R. Simonet-Davin, S. Nicolai, A. Nanchen, Th. Meyer, J. Waser, *J. Org. Chem.*, **2018**, *83*, 12334−12356.