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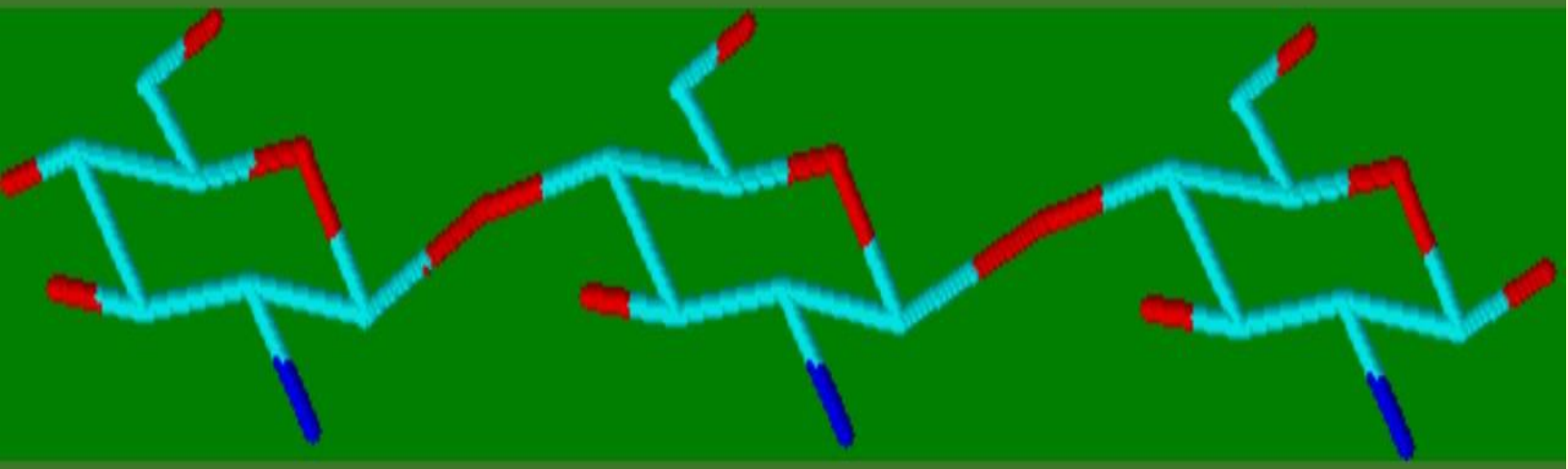

Biodegradable Nanocomposites

Snapshots of Scientific Literature Review:

- Modification of Cellulose Nanocrystals
- Aminofluorination of Alkenes
- Detection of Residual Palladium
- Polycyclic Quinazolines

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Biodegradable Nanocomposites for Biomedical Applications

Atef S. Iskander

Biodegradable nanocomposites are characterized by their outstanding properties including nano-sized dimensions, biodegradability, biocompatibility, nontoxicity, and easy modification. Thus, they can be widely used in a variety of areas such as biomedical applications, tissue engineered scaffolds, cancer therapy, and clinical bioanalytical diagnostics and therapeutics. This article focuses on a few basic aspects of biodegradable nanocomposites, design challenges and some examples of their biomedical applications. Finally, a general outlook on future opportunities and challenges is highlighted.

INTRODUCTION

Biodegradable nanocomposites have attracted a great deal of interest in the field of medical science due to their appealing intrinsic properties. These biodegradable materials are used as a viable carrier for site specific delivery of drugs, vaccines, and other biomolecules in a controllable way; tissue engineered scaffolds; cancer therapy; and clinical bioanalytical diagnostics and therapeutics.[1,2] Polymers based biodegradable nanoparticles are polymeric colloidal materials containing hydrolysable linkages along their chain, e.g. amide, enamine, ester, urea, and urethane linkages, which are susceptible to biodegradation by hydrolytic enzymes. These polymer nanoparticles are characterized by their nano-sized dimensions (in the 1 – 100 nm rang), high surface area, biodegradability, less or nontoxicity, low density, and easy modification.[3-5] They are classified according to their origin into two groups: natural and synthetic polymers. Their natural polymers include polysaccharides such as cellulose and chitosan; proteins such as gelatin and collagen; and carbohydrate polymers produced by natural

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or genetically modified organisms such as poly(3-hydroxybutyrate) (PHB). Whereas the synthetic polymers are produced from oil and include aliphatic polyesters such as poly(ε-caprolactone) (PCL); poly(butylene succinate) (PBS); and poly(vinyl alcohol) (PVA). Polymer nanocomposites refer to multiphase materials consisting of a polymer matrix and nanofillers. They exhibit appealing unique properties, due to the nanometric size effect, which make them easier to penetrate physiological barriers and transport a therapeutic agent of interest within the circulatory systems of a host and release the active substance to the target site with a convenient rate.[7] Such therapeutic agent can be embedded or encapsulated with their polymeric matrix or adsorbed or conjugated on the surface.[6] Within this article, I discuss a few basic aspects of biodegradable nanocomposites, design challenges and some examples of their biomedical applications. Finally, a general outlook on future opportunities and challenges is highlighted.

PREPARATION OF BIODEGRADABLE NANOCOMPOSITES

Processing techniques have a great influence on the properties of the final products. Therefore, the applied techniques should take into account the nature and properties of polymer matrix, and the desired final properties of the nanocomposites. Indeed, various methods are adopted for the synthesis of biodegradable nanocomposites for biomedical applications that should be ideally controllable regarding shape, size, biodegradable, biocompatible, nontoxic, inexpensive, and high product yield. Figure 1 summarizes the most common synthetic processes of nanocomposites.

The most important criterion in the preparation of high-performance polymer/therapeutic agent nanocomposites is the dispersibility of therapeutic agent in polymer matrix. Most of the therapeutic agents can homogenously disperse in water and are usually obtained as aqueous suspensions. Therefore, water is the optimal medium for preparation of nanocomposites. In this sense, solvent evaporation technique is the most extensively synthetic method employed for the preparation of a wide variety of biodegradable polymeric nanocomposites.

Solvent evaporation technique

In this technique, a polymer organic solution is first mixed with drug aqueous suspension to obtain homogenous dispersion, which is then emulsified using an appropriate surfactant/emulsifying agent; subsequently, the nanocomposites with the drug incorporated into polymer matrix are obtained by evaporation of the solvent.

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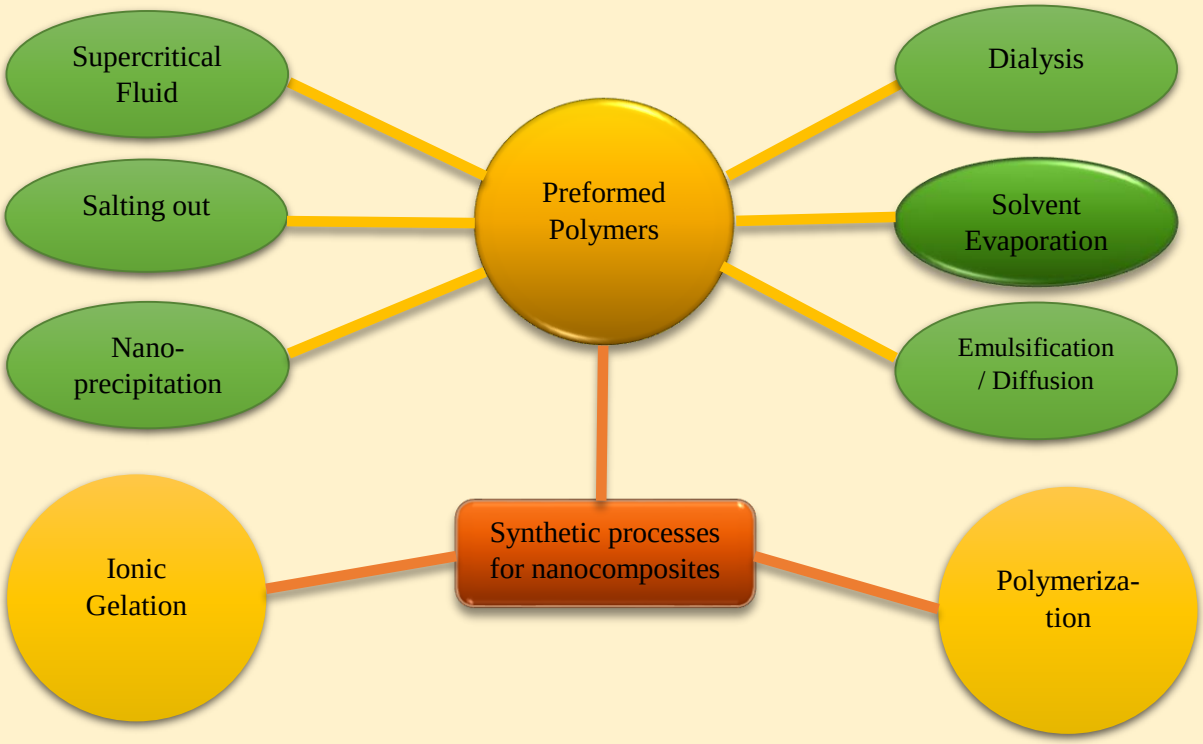

Figure 1. The most common processes for synthesis of polymer nanocomposites.

BIODEGRADABLE NANOPARTICLES

The nature of polymeric nanoparticles (NPs) is very important as it determines their electrostatic interaction with bioactive compounds. Therefore, a brief overview on the most widely used biodegradable polymer matrixes should be presented (Figure 2).

Poly(lactic acid) (PLA)

PLA is a biocompatible and biodegradable polymer. PLA nanoparticles can be prepared by

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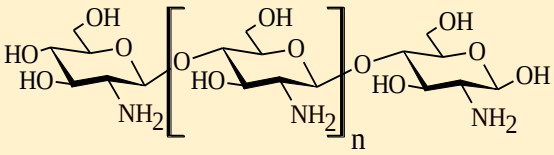
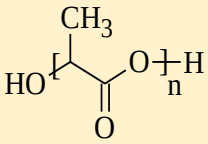
different synthetic path ways including direct poly-condensation in an azeotropic solution and salting out procedure. The salting out method is more favorable because it minimizes stress to protein encapsulants.

Poly(Ɛ-caprolactone) (PCL)

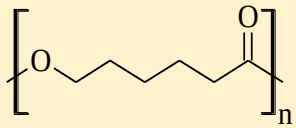
PCL is a biocompatible and biodegradable polymer. Its biodegradability can be enhanced by copolymerization. It is a relatively hydrophobic material with low glass transition temperature, T_g = - 60 ºC, and a crystalline structure that melts at 59-64 ºC, depending on the molecular weight. The rate of degradation is rather slow (2-4 years) which made it good candidate for producing long-term implantable devices. Moreover, PCL has very high permeability and used in many drugs. In addition, it can be used as scaffolds for tissue engineering due to its excellent biocompatibility.



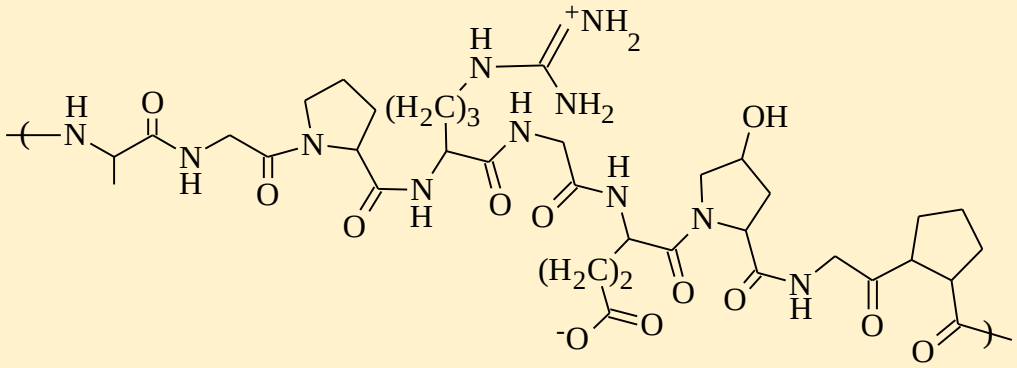
Chitosan



Poly(lactic acid)



Poly(Ɛ-caprolactone)



Gelatin

Figure 2. Chemical structures of the most widely used biodegradable polymer matrixes.

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Chitin and Chitosan

Chitin is a naturally occurring polysaccharide and is synthesized via a biosynthetic way by living organisms. Chitosan, as the most important derivative of chitin, can be prepared by deacetylation of chitin. Both of them have many excellent properties including biocompatibility, biodegradability, nontoxicity, and easy modification conferred by the large amount of surface hydroxyl groups. In addition, they can be widely used in reinforcing polymer nanocomposites.[8] The amorphous domains of chitin can be removed under certain conditions such as acidolysis to give rise to nanosized crystalline particles (chitin whiskers). Whereas the rate of degradation of chitosan inversely depends on the degree of acetylation and crystallinity of the polymer. The highly deacetylated form exhibits the lowest degradation rates and may last several months *in vivo.*

Collagen and Gelatin

Collagen is a hydrophilic protein and undergoes enzymatic degradation within the body to yield the corresponding amino acids. Thermal and chemical dissociation of collagen polypeptide chains forms gelatin. Gelatin nanoparticles are very efficient in delivery and controlled release of the drugs. Their mechanical properties such as swelling behavior as well as thermal properties depend on the degree of cross-linking between cationic and anionic groups of their constituents. Such properties can be manipulated to prepare the desired type of nanoparticles.

DESIGN CHALLENGES

One of the challenges faced the utility of nanocomposites *via* intravenous route was their rapid removal by the phagocytic cells. Moreover, the loading of bioactive agents and encapsulation formed another challenges. Recently, many strategies have been adapted to overcome those problems.

Surface Modification

The phagocytic system is one of the body's innate defenses that filters and eliminate any harmful objects including nanocomposites from the blood stream. In order to escape such recognition as foreign particles, nanocomposites necessitated to modify their surface to achieve their desired target *in vivo.* It has been shown that nanocomposites with hydrophilic surface have the ability to escape from being phagocytosed. The most preferred method of surface

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modification is the adsorption or grafting of poly-ethylene glycol (PEG) to the surface of nanocomposites.[9,10] There are other hydrophilic polymers such as polysorbate 80, polysorbate 20, polysaccharides such as dextran and different types of co-polymers that can be used to coat nanocomposites. However, the nature and intensity of the surface charge of nanocomposites is very important as it determines their interaction with the biological environment as well as their electrostatic interaction with bioactive compounds.

Bioactive compounds loading and Encapsulation

The high loading capacity for bioactive compounds is the optimal goal in nanocomposites engineering. Such loading can be accomplished by incorporating the bioactive compound at the time of nanocomposites production; or by adsorption the compound after the formation of the nanoparticles. The adsorption method can be achieved by incubating the nanoparticles in a concentrated bioactive compound solution. The encapsulation process can be accomplished using either of those techniques. The amount of compounds bound to the nanoparticles and the type of interaction between them depend on the chemical structure of both the compound and the polymer as well as the conditions of compound loading.

BIOMEDICAL APPLICATIONS OF BIODEGRADABLE NANOCOMPOSITES

Targeting delivery of anticancer drugs

Tumor cells express many molecules on their surface that distinguish them from normal cells. Using nanoparticles as a drug carrier for tumor targeting provides substantial advantages in terms of increasing efficacy and reducing side effects. They have potential for the delivery of therapeutic agents into intimate contact with diseased tissues in a controlled way. Beside specificity, other advantages may be protection against premature inactivation, decreased toxicity and the flexibility administration. The strategies for design of nanocarriers targeting tumor cells can be achieved with either direct targeting or the pretargeting approach. In direct targeting approach, the tumor cells receive the nanocarriers that covalently coupled with the targeting ligands, expressing a homologous receptor on their surfaces. Such ligand-receptor interaction ensures that the nanocarriers bearing the active substance become attached specifically to the tumor cells. In this regard, the molecular recognition processes such as ligand-receptor specificity or antigen-antibody interaction plays an important role in achieving such ‘active targeting’. In the pretargeting method, the targeting ligand is administered prior to the administration of therapeutic agent.

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Oral delivery

Oral delivery of therapeutic agents using biodegradable nanoparticles can offer significant advantages over the conventional drug delivery in terms of high stability, high specificity, high active substance loading capacity, ability for controlled release, possibility to use in different access way of administration and the capability to deliver both hydrophilic and hydrophobic compounds. Virtually any bioactive ingredient can be encapsulated. For instance, the preparation of core-shell nanocomposites for delivery of riboflavin can be achieved by crosslinking chitosan with sodium tripolyphosphate (TPP), followed by coating the nano-gel-particles with either native or denatured 3-lactoglobulin.[11]

Tissue engineering

Nanocomposites have a fast field of application in regenerative medicine. Regenerative medicine, that is, the tailored, clinically-oriented reconstruction of damaged tissue, benefits from biocompatible scaffolds on which stem cells can grow and differentiate, either under preliminary *ex vivo* conditions for further grafting into the injured organ, or as a result of direct *in vivo* implants. For example, magnetic nanoparticles are being used as powerful applications in tissue engineering due to the ability to control the location of these particles using magnets, and to induce a high concentration in a given tissue or organ. Magnetic nanoparticles contain a magnetic core (e.g. Fe_3O_4) and coated with a polymeric layer that minimizes hydrophobic interactions, enhancing colloid dispersion and biocompatibility.[12]

CONCLUSIONS AND OUTLOOK

Nanocomposites have already been applied as drug delivery systems with great success. They provide massive advantages concerning delivery of therapeutics and /or diagnostic agents to the target sites. However, there are many technical challenges in developing some techniques such as virus-like systems for intracellular systems, control of sensitive therapeutic agents, architecting of biomimetic polymers, and nanochips for nanoparticle release. Thus, great endeavors are necessary to make those areas more prosperous and fruitful.

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

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Modification of Cellulose Nanocrystals by Surface Grafting with Silane and Polyacrylate

The synergy of silane and polyacrylate on the surface of cellulose nanocrystals is described. The modified cellulose nanocrystals exhibited improved hydrophobicity and high thermal stability without disturbing their morphologies, which enhanced their suitability to serve as reinforcements in plastic nanocomposites.

Cellulose nanocrystals (CNCs) have outstanding properties including biodegradability, renewability, high specific strength and modulus. Their applications in industry are limited due to their intrinsic hydrophilicity and reduced thermal stability as a result of incorporation of sulfate half-ester groups during their hydrolysis with sulfuric acid.

To overcome these limitations, Jiang and Wang and their co-workers reported a new strategy which based on the grafting reactive double bonds on the surface of CNCs as an initiating site *via* one-step reaction which can nucleate the polymer grafting of CNCs. They employed methacryloxypropyl-trimethoxysilane (MPS) as an intermediate to graft poly(*n*-butylacrylate) (PBA) on the CNCs surface (Figure).

The Synthetic Procedure

Frist, MPS was grafted on the CNCs surface through pre-hydrolysis of silan (stirring MPS in ethanol for 1 h), then the temperature was increased to 60 ^{o}C, followed by the addition of CNCs and allowed the reaction to proceed for 3 h at 60 ^{o}C. The formed suspension was filtered, collected, and dried at 60 ^{o}C for 24 h. The dried powders were heated at 110 ^{o}C for 2 h to promote the self-crosslinking and covalent interaction of silane with CNCs.

The synthetic pathway of CNC-PBA was achieved *via* stirring a mixture of CNCs, potassium persulfate (KPS), and *n*-butyl-acrylate in H_2O/DMF (1:1) for 30 min. under a N_2 atmosphere. Then, the temperature was raised to 65 ^{o}C, and the reaction was performed for 1 h.

Finally, CNC-MPS-PBA was synthesized through the reaction between CNC-MPS and BA according to the same synthetic procedure of CNC-PBA.

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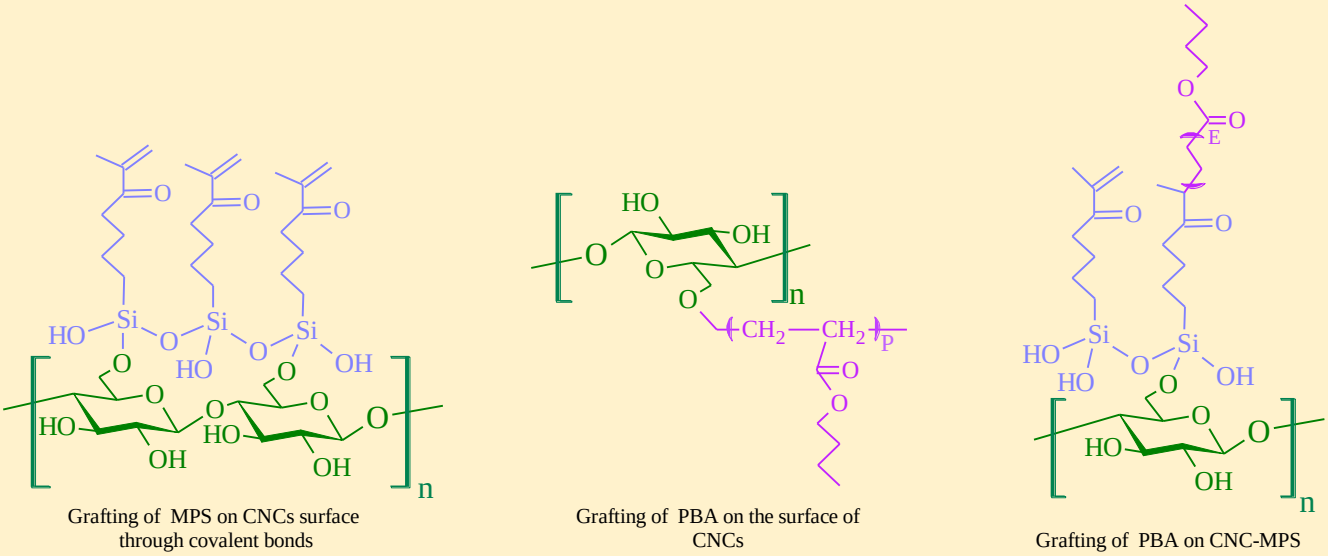

Figure: Schematic illustration of the interaction modes of CNCs with silane and polyacrylate.

Review

Y. Yin, C. Lou, M.A. Hubbe, X. Tian, X. Jiang, H. Wang, W. Gao, *Chem. Lett.*, **2018**, *47*, 1272-1275.

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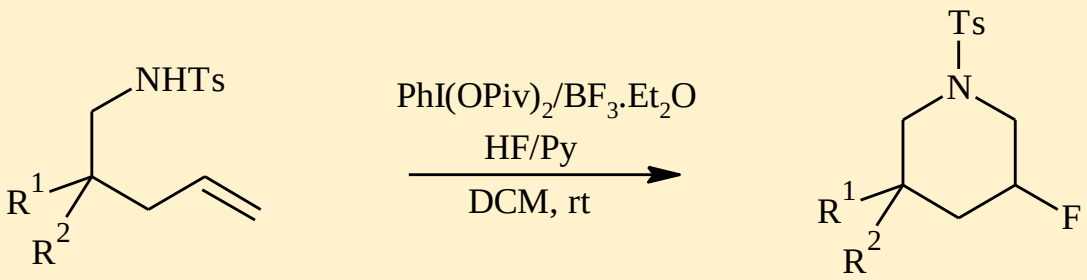
Metal-free Intramolecular Aminofluorination of Unactivated Alkenes

An efficient, highly regionselective and stereoselective metal-free method for the synthesis of fluorine containing cyclic amines is described.

Organoflurines are very important compounds in the synthesis of pharmaceuticals, agrochemicals and materials. In this regard, an interesting method for constructing Carbon-fluorine bond is highlighted.

Meng and Li and their co-workers reported a novel BF_3-OEt_2-catalyzed metal-free method for the intramolecular aminofluorination of unactivated alkenes, in which they employed hydrogen fluoride-pyridine (acting as the fluorine source) in the presence of $PhI(OPiv)_2$. (Scheme 1). The method is highly regioselective and stereoselective and has a broad synthetic scope.



Scheme 1. Intramolecular aminopivaloylation of alkenes.

Mechanistically, they proposed two possible pathways (a) & (b) (Scheme 2). In view of the high stereoselctivity of the products, they believed that pathway (b) is more likely than pathway (a).

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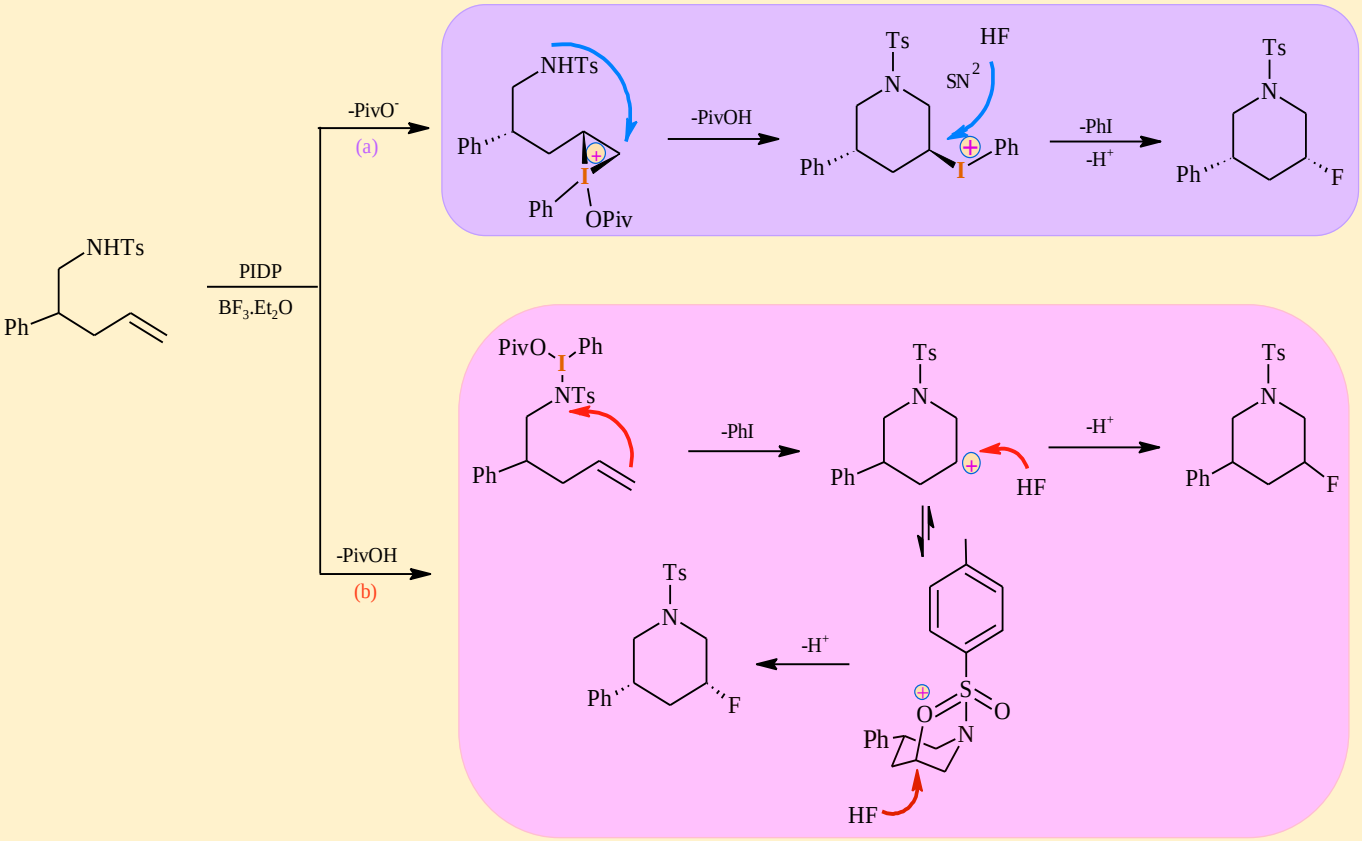

Scheme 2. Possible mechanism of $PhI(OPiv)_2/BF_3.OEt_2$ mediated aminofluorination of alkenes.

Review

Q. Wang, W. Zhong, X. Wei, M. Ning, X. Meng, Z. Li, *Org. Biomol. Chem.*, **2012,** *10*, 8566-8569.

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Quick Detection of Residual Palladium in Pharmaceutical Process Research

A fast and inexpensive high-throughput approach for detection of residual palladium (Pd) in pharmaceutical process research samples is highlighted.

The increasing use of palladium catalysis in the synthesis of active pharmaceutical ingredients (APIs) and pharmaceutical intermediates has motivated the development of a rapid and efficient detection method for the estimation of residual Pd levels in pharmaceutical process development.

In this sense, Welch and co-workers reported a fast and inexpensive high-throughput method which relied on the strategy of Koid group for fluorometric palladium determination that based on Pd^{o}-catalyzed Tsuji-Trost deallylation of allyl Pittsburgh Green Ether (APE) to produce a highly fluorescent product (Figure).

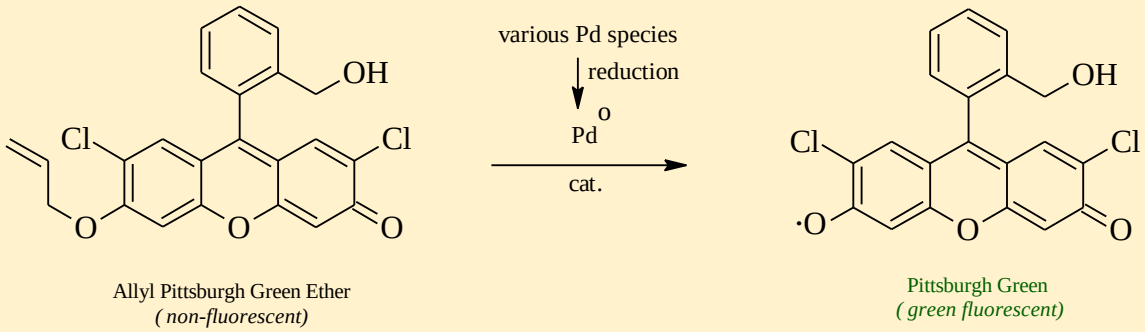

Figure The Koide group method for fluorometric palladium determination.

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They demonstrated that a single reagent cocktail consisting of tri(2-furyl) phosphine (TFP); allyl Pittsburgh green ether (APE) and butylated hydroxytoluene (BHT) in DMSO/pH 7 phosphate buffer has the ability to quantify palladium effectively in a variety of 'real world' samples, including mixed oxidation-state samples containing strong Pd ligands. Quantitation of palladium can be performed using either visual examination or measurement of fluorescence at 525 nm (λ_{ex} = 497 nm) or UV-vis absorbance at 515 nm. The use of a fluorescence plat reader allows rapid high-throughput analysis.

For samples that have particularly challenging palladium removal problems, they found that an appropriate pretreatment of those samples with *aqua regia* improves the accuracy. Moreover, pretreatment with sodium borohydride ($NaBH_4$) significantly improves the accuracy of the APE method for measuring residual palladium.

The method showed excellent sensitivity and linearity with palladium standers, and a reasonably good accuracy (80 – 110% of actual values). This fluorescence assay has the potential for on-the-spot palladium estimation to support laboratory or pilot-plant investigations of palladium removal.

Review

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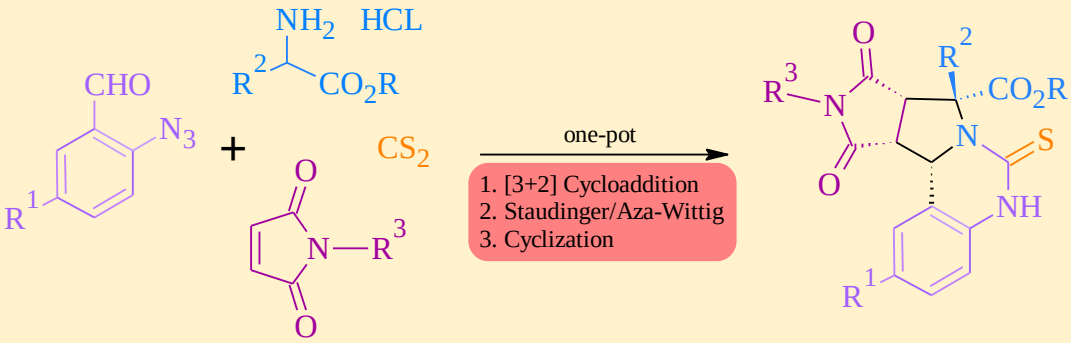
Synthesis of Polycyclic Quinazolines Derivatives

A synthetic strategy for synthesis of one-pot dihydroquinazolinethione-based polycyclic system was developed using diastereoselective [3 + 2] cycloaddition of azomethine ylides; Staudinger-aza-Wittig reaction; and Cyclization.

The synthesis of highly substituted quinazolines has been the focus of much attention, as these structural motifs are widely present in many natural products and pharmaceutically useful agents.

Zhang *et al.* reported a one-pot and diastereo-selective synthesis of quinazoline-2(1*H*)-thione-containing polycyclic compounds (Scheme). They took advantage of [3+2] cycloaddition of azomethine ylides to electron-deficient alkenes for constructing substituted pyrrolidines. Further, the synthetic strategy was developed using Staudinger-aza-Wittig reaction with azides for the generation of iminophosphoranes, followed by the formation of isothiocyanates. Cyclization of amines to isothiocyanates afforded, efficiently, dihydroquinazolinethiones.



Scheme: Diastereoselective synthesis of dihydroquinazolinethiones.

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Review

W. Zhang, X. Zhang, X. Ma, W. Zhang, *Tetrahedron Lett.*,**2018**, *59*, 3845-3847.