Multicomponent Reactions Among Alkyl Isocyanides, *sp* reactants, and *sp*^{2} Carbon Cages

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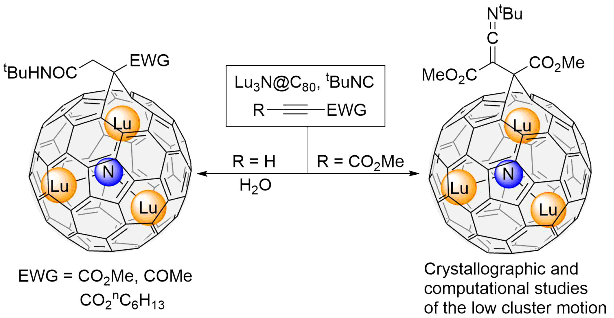

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Abstract We explored the reactivity and substrate scope of the reactions among an alkyl isocyanide, an *sp*-hybridized reactant (i.e. alkyne or allene), and a carbon cage, as a new approach to functionalize fullerenes and metallofullerenes. This account summarizes the key findings in our recent published work, and some original data for the reaction involving an isocyanide, allenes, and metallofullerene $Lu_3N@C_{80}$.

Key words isocyanide, cluster motion, endohedral, fullerenes, multicomponent reaction

1. Introduction

Endohedral metallofullerenes (EMFs) have many intriguing properties due to their unique structures with metal atoms or clusters encapsulated inside a fullerene carbon cage.[1] The successful encapsulation of rare-earth[1] and actinide metal ions[2] provide an isolated and protected environment for the metal species, which lead to broad range of applications, including single molecular magnets,[3] spin-quantum computing,[4] artificial photosynthesis,[5] dynamic nuclear polarization,[6] magnetic resonance imaging (MRI) contrast agents,[7] and therapeutic agents.[8]

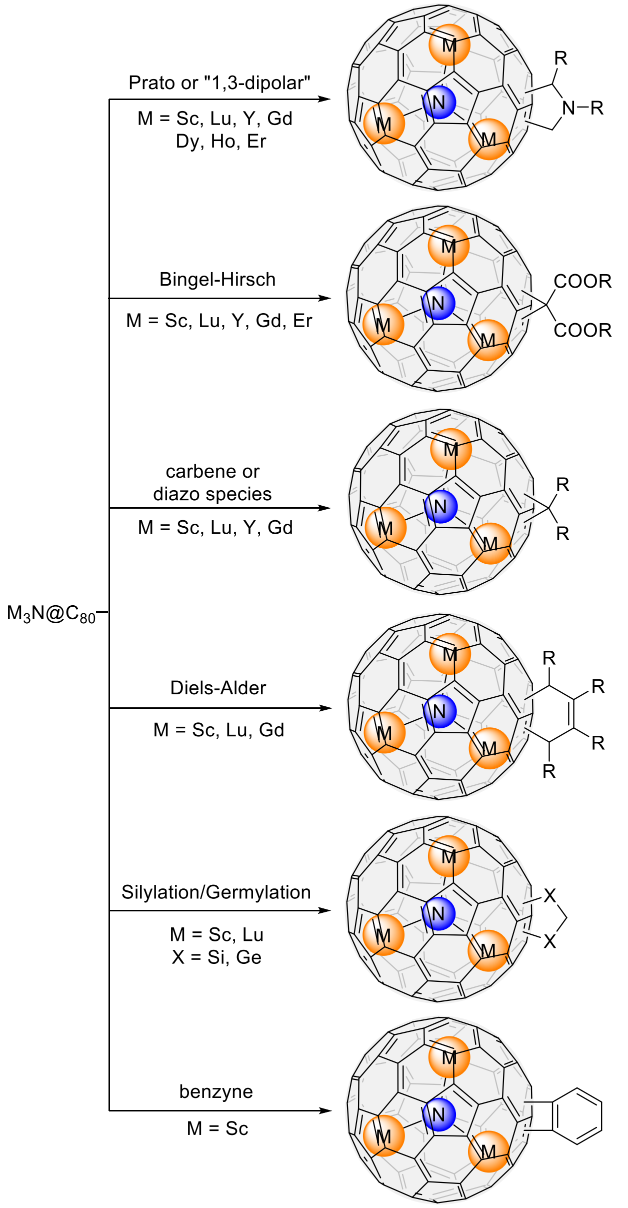
A subgroup of EMFs, the nitride clusterfullerenes (NCFs), or the so-called trimetallic nitride template (TNT) EMFs,[9] are significantly stabilized by the six electrons transferred from the endohedral cluster M_3N to the cage.[10] The species with highest symmetry and most production yield in the NCF family, $M_3N@I_h$-C_{80} (M = Sc, Y, lanthanides, "@" denotes encapsulation, I_h refers to the point group symmetry of the cage and is written in italic by convention),[11] are particularly stable which poses challenges on their chemical functionalization.

The exohedral functionalization of EMFs generally increases the solubility and allows for structural building for desired materials functions.[1a] The chemical reactivity of EMFs is very different from empty cage fullerenes due to the electron transfer from the encapsulated atoms to the carbon cages, which makes them generally more inert as electron acceptors.[12] Only a small percentage of reactions reported for empty fullerenes[1b] has been successfully applied to EMFs. Among these less reactive EMFs, NCFs sharing a closed shell structure with up to six electrons transferred from the metal cluster towards the fullerene cage, show a consequential decrease of reactivity that makes their chemical modification challenging.[10, 13] The reported NCF $M_3N@C_{80}$ reactions (Scheme 1) mainly include Prato reactions,[14] Bingel–Hirsch reactions,[15] carbene[16] or diazo additions,[17] Diels–Alder reactions,[18] silylation and germylation,[19] benzyne additions,[20] radical additions,[21] reactions with azides,[22] reactions with special 1,3-dipoles,[23] coordination,[24] dimerization[25] and EMF anion-induced reactions.[26] Overall, chemical methods to modify $M_3N@I_h$-C_{80}, especially those are not adopted from a well-established C_{60} reaction, are still in high demand.

2. Isocyanide-induced fullerene/EMF reactions with substituted alkynes

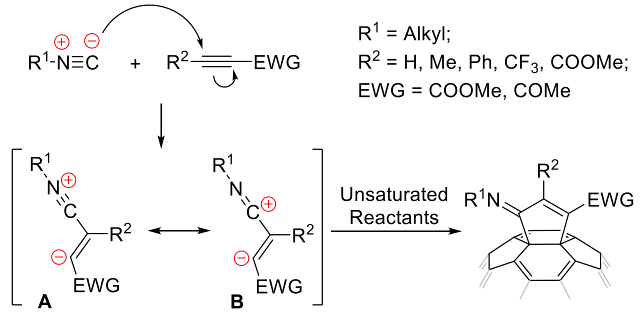
As cycloadditions dominate the successful reactions on NCFs, one strategy to develop new reactions is to find reactive species that can react with alkenes, similar to the diene in a Diels-Alder reaction or the 1,3-dipole in a Prato reaction. In our recent work,[27, 28] we had our eye on *sp*-hybridized carbon reactants linked to an electron-withdrawing group (EWG), which react with alkyl isocyanide to generate reactive dipolar species, to be captured by a third, alkenyl reactant. These multicomponent reactions have been widely used to construct cyclic structures in organic synthesis using alkynes[29] and allenes.[30] When an alkyl isocyanide reacts with an alkyne, they are expected to form a reactive species, represented by two resonance forms A and B, shown in Scheme 2. When they react with fullerenes or EMFs, the most straightforward prediction for the cycloaddition product should be a [3+2] addition from **A** or **B** (Scheme 2). However, the sole example of such reactions on fullerene species, reported in

2005, among *t*-butyl isocyanide (^{t}BuNC), a special alkyne dimethyl acetylenedicarboxylate (DMAD), and empty cage C$_{60}$, was reported to give two fullerene derivatives: [3+2] cycloadduct, and a [2+2] cycloadduct,[31] with the latter very surprising to our understanding. We carefully examined the report, and found that the structural elucidation of the products lacked crystallographic proof, while the spectroscopic characterization of the [2+2] product was rather ambiguous. Therefore, we explored the utility of the isocyanide-induced reactions with various *sp*-hybridzed substrates, on fullerene C$_{60}$[28] and EMF Lu$_3$N@I_h-C$_{80}$[27] concurrently. In the notably stable family of M$_3$N@I_h-C$_{80}$, Lu and Sc are the more inert members,[32] which means if the reactions on Lu$_3$N@C$_{80}$ were successful, they are likely to work on other EMFs as well.



Scheme 1 Typical cycloaddition reactions of TNT-EMFs. In the scheme, all products are drawn in a general form without specifying the bonds at the reaction sites (i.e., [5,6] vs [6,6] bond, open vs close cage).

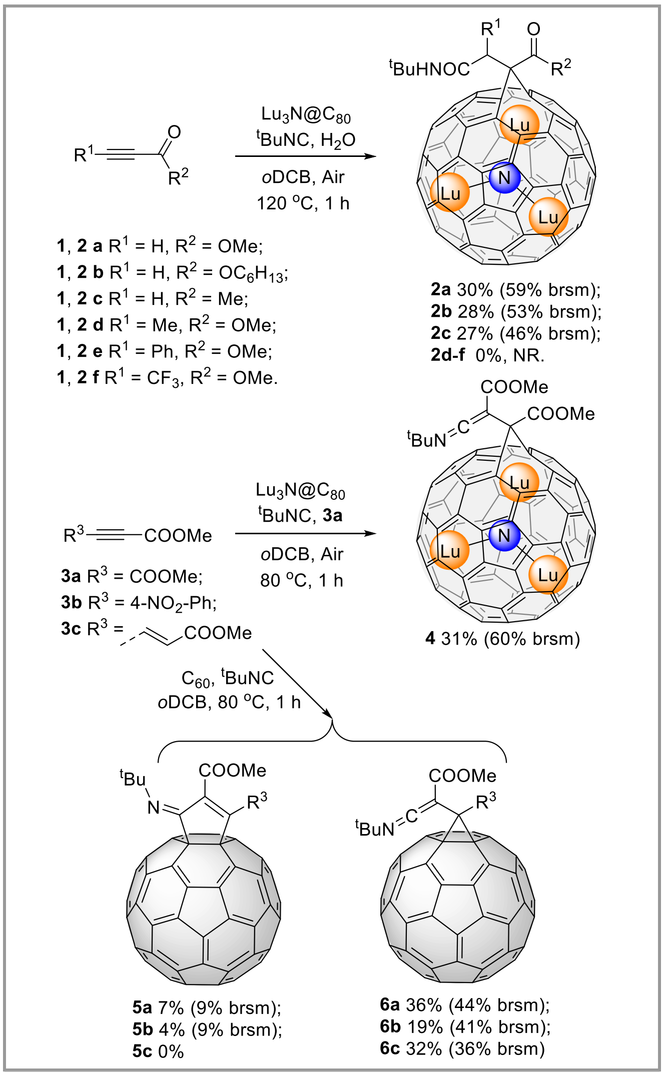
Unexpectedly, from all the C$_{60}$ and Lu$_3$N@C$_{80}$ reactions with alkyl isocyanides and alkynes, the major product was neither [2+2] nor [3+2] products. Instead, they are resulted from a cyclopropanation process, as both were confirmed by crystallography. With the aid of density functional theory (DFT) calculations, we found the reaction mechanism on Lu$_3$N@C$_{80}$ is a stepwise attack, similar to a Bingel-Hirsch reaction,[15a] and we conjecture the mechanism for the C$_{60}$ reactions were the same. There are key differences in the EMF and empty fullerene derivatives though. First, EMF reactions gave almost exclusively cyclopropyl products, while C$_{60}$ reactions gave cyclopropyl and [3+2] products. Second, the Lu$_3$N@C$_{80}$ cyclopropyl derivatives rearranged into open-cage metallofulleroids, whereas the C$_{60}$ cyclopropyl derivatives remained as close-cage methanofullerenes. For many of the cyclopropyl products, spontaneous hydration occurred in quantitative yields, but the DMAD reactions yielded stable ketenimine products without hydration.



Scheme 2 Reactive species formed from an alkyl isocyanide and alkynes linking an electron-withdrawing group

There are also important differences in the reactivity and substrate scope. We started with the multicomponent reaction among Lu$_3$N@C$_{80}$, ^{t}BuNC and an EWG-bearing terminal alkyne, with the EWG being a carbonyl or an ester group (**1a-c** in Scheme 3).[27] All three generated a dominate product in decent yields. Then, keeping an ester EWG, we changed the terminal alkynes to internal alkynes, none of the **1d-f** worked, and the only exception was the symmetric internal alkyne DMAD. For C$_{60}$, however, terminal or internal alkynes **1a-f** all failed, and only DMAD yielded two products, as previously reported,[31] except the once-considered [2+2] products were actually methanofullerenes (Scheme 3). On the other hand, when we further explored the substrate scope for C$_{60}$, we found that two other internal alkynes also reacted (Scheme 3), with either an allylic or a 4-nitrophenyl group. Our results suggested that for C$_{60}$ reactions, electron-withdrawing resonance effects on the triple bond were critical.

An intriguing feature of product **4** is that the endohedral Lu$_3$N cluster was fully ordered in crystal studies at 120 K. Monitoring the cluster in the crystal of **4** at different temperatures (120, 250, 298 K) indicate that the cluster motion started at higher temperature compared to most M$_3$N@C$_{80}$ monoderivatives and may not have fully free cluster motion even at room temperature. This is very different from **2a** and **2c**, which have highly disordered clusters at 120 K, with very similar structures. We had to consider the possibility that the differences in the size and shape of the organic appendants, caused by the extra ester group in **4** vs the hydration step in **2a**, **2c**, led to the difference. Indeed, careful examination of the crystal profiles revealed that the molecules of **4** pack tighter than **2a** and **2c** in solid state, with shorter distance between the EMF cage and the carbonyl oxygen atoms on the appendant from an adjacent molecule. The interaction was studied by DFT calculations using the PBE functional. The rotational energy barrier of the Lu_3N cluster around the Lu1-N axis were similar for **2a** and **4** (2.5 kcal/mol), when only single molecule was considered. However, when the appendant of the neighboring molecule, which is present in the crystal packing of **4** but absent in **2a** and **2c**, is considered in the computation, the barrier for the rotation significantly increased to 6–7 kcal/mol. Car-Parrinello molecular dynamics (CPMD) simulations confirms that the cluster motion in **4** is controlled externally by the appendant, especially the two carbonyl O atoms of the dicarboxylate, of another neighboring molecule. The DFT finding enabled the understanding of the origin of the interaction that dictated the lack of cluster rotation in **4**, which was further corroborated with CPMD simulations showing that one Lu atom is actually interacting alternatively back and forth with the two carbonyl oxygen atoms of the dicarboxylate (Figure 1).



Scheme 3 The multi-component reactions among ${}^tBuNC$, substituted alkynes, and $Lu_3N@C_{80}$ or C_{60}. brsm = based on recovered starting material; NR = No reaction.

Temperature-dependent cluster rotation modulated by non-covalent interactions have been demonstrated for unfunctionalized NCFs theoretically and experimentally.[33] In functionalized NCFs, fully ordered clusters were mostly achieved via direct and strong interactions between the functional group and the cage (e.g. multi-additions, or formal charge on the ligand and cage, etc.) [16b, 21c, 24, 34] Our work demonstrated that weak intermolecular interactions between the organic ligands and the NCF cage can also restrict the cluster motion in the solid state of synthetically straightforward monoadducts, which provides a new direction of materials design for magnetic and quantum applications.

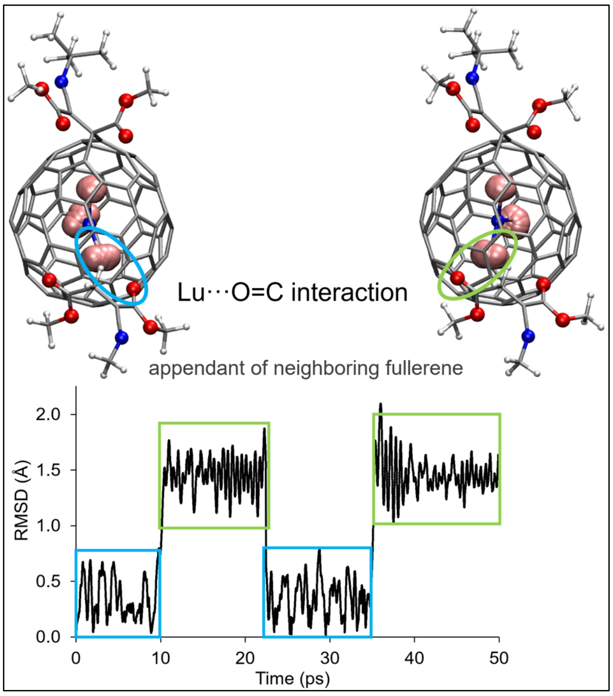


Figure 1 Root mean square deviation (RMSD) along the 50 ps trajectory of the Car–Parrinello simulation of product **4** interacting with the appendant of a neighboring molecule in the solid state. One Lu atom is interacting back and forth with each of the two carbonyl oxygen atoms of the dicarboxylate.

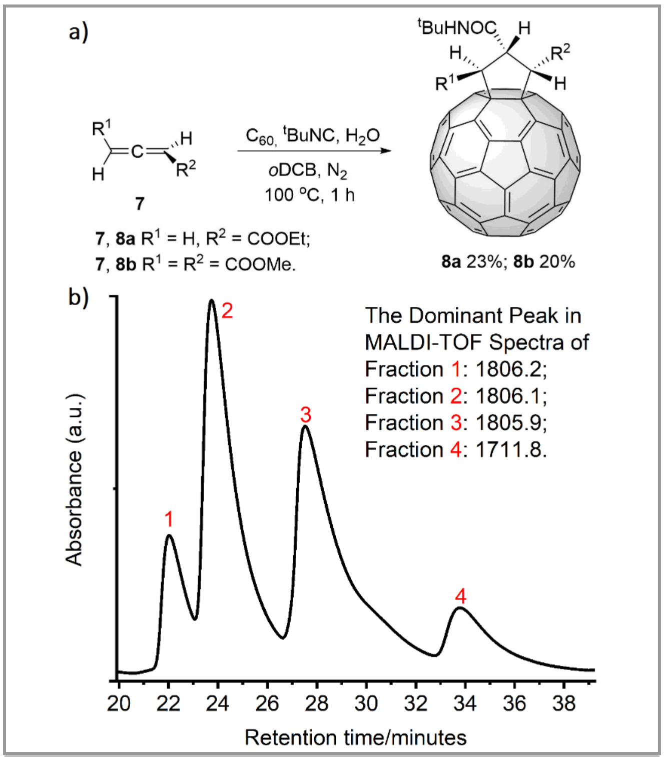


Figure 2 a) Four-component reactions of C_{60}, ${}^tBuNC$, **7** and H_2O. b) HPLC spectrum (2 mL/minute, toluene, 5PYE) of the products isolated via silica gel

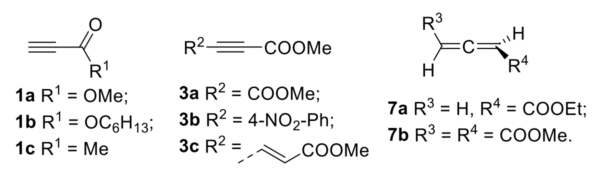
column from the multicomponent reaction of Lu$_3$N@C$_{80}$, ^{t}BuNC and **7a**.

3. Isocyanide-induced fullerene/EMF reactions with substituted allenes

Allenes represent another form of *sp* carbon atoms, which are also used with alkyl isocyanides to create cyclic structure in organic synthesis via multi-component reactions (Figure 2a).[30] Replacing the triple bond with cumulated double bonds, ethyl buta-2, 3-dienoate **7a** and dimethyl 2, 3-pentadienedioate **7b**, the allenoate counterpart of **1a** and DMAD, were attempted in the multicomponent reactions, which yielded **8a** and **8b** from four-component reactions among ^{t}BuNC, allenoate, C$_{60}$ and one molecule of water.[28]

Not reported in our papers,[27, 28] similar reactions were performed on Lu$_3$N@C$_{80}$. The reaction involving **7a**, ^{t}BuNC and Lu$_3$N@C$_{80}$ gives only one product spot on TLC (although the combined conversion rate is rather low), which was isolated via flash chromatography and then studied with HPLC on 5PYE column (Figure 2b). There are four major peaks on the HPLC spectrum, which have been isolated from each other and tested by MALDI-TOF MS respectively. Peaks 1-3 share the similar MS value 1806, equal to the sum of one molecule of Lu$_3$N@C$_{80}$, one molecule of ^{t}BuNC and two molecules of **7a**, while peak 4 gives clear molecular ions 1712 corresponding to a mass of three reactants plus one molecule of water. The existence of the major peaks 1-3 on HPLC spectrum reveals that the addition pattern of the reaction is clearly different from that of the C$_{60}$. Due to the poor selectivity and low conversion of Lu$_3$N@C$_{80}$ starting material, which did not improve via varying reaction conditions, we chose to not scale up this reaction. It was hypothesized that the poor selectivity might be caused by the asymmetry of **7a**, so symmetric substrate **7b** was attempted in such reaction, but no reaction occured despite of our optimization effort. We include this result not only to report this preliminary finding, but also to alert readers (especially young researchers) about a common situation in the field of EMF functionalizion: a lot of times reactions occur, but due to the limitations in converstion (yield), selectivity, solubility, or sometimes, the challenges in crystalization, these results may take a long time to publish, or do not get published.

Table 1 Different reactivities of Lu$_3$N@C$_{80}$ and C$_{60}$[a]



1a R^1 = OMe;
1b R^1 = OC$_6$H$_{13}$;
1c R^1 = Me

3a R^2 = COOMe;
3b R^2 = 4-NO$_2$-Ph;
3c R^2 = COOMe

7a R^3 = H, R^4 = COOEt;
7b R^3 = R^4 = COOMe.

Substrates	Lu$_3$N@C$_{80}$	C$_{60}$
1a-c	[6,6]-Open metallo-fulleroids **2a-c**	No isolable products
3a	[6,6]-Open ketenimine metallofulleroid **4**	[6,6]-Closed [3+2] cycloadduct **5a** and ketenimine methanofullerene **6a**
3b	No reaction	[6,6]-Closed [3+2] cycloadduct **5b** and ketenimine methanofullerene **6b**
3c	[6,6]-Open ketenimine metallofulleroid[a]	[6,6]-Closed ketenimine methanofullerene **6c**
7a	Low conversion and poor selectivity	[6,6]-Closed cyclopentanofullerene **8a**
7b	No reaction	[6,6]-Closed cyclopentanofullerene **8b**

[a] The reaction involving **3c** and Lu$_3$N@C$_{80}$ gives similar product as **6c** based on primary characterization data including MALDI-TOF MS and NMR spectra without single crystal data.

In conclusion, isocyanide-induced multicomponent reactions involving *sp*-hybridized alkynes and allenes have been investigated on Lu$_3$N@C$_{80}$ and C$_{60}$. Endohedral fullerene-Lu$_3$N@C$_{80}$ and empty fullerene-C$_{60}$ show different reactivities, as summarized in Table 1. Notably, metallofulleroid **4** showed restricted cluster motion caused by the close interaction with the exohedral organic appendant of a neighbor molecule. These multi-component annulation reactions can be explored with other carbon cages, such as C$_{70}$ and the other endohedral fullerenes.

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Biosketches

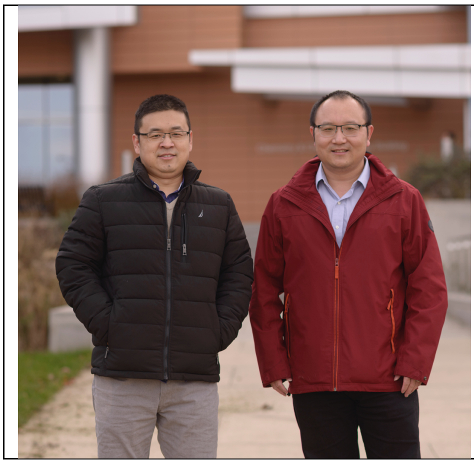

Photo of Yanbang Li (left) and Jianyuan Zhang (right), in front of the building of the Department of Chemistry and Chemical Biology at Rutgers University.

After graduation with B Sc. from Beijing Normal University, Jianyuan ("Jason") Zhang joined the group of Prof. Harry C. Dorn to study endohedral metallofullerenes, and obtained his Ph.D in Dec. 2013. Then he joined Prof. Alex K.-Y. Jen's team at the University of Washington to explore the application of fullerenes, metallofullerenes, and conjugated polymers in organic optoelectronic materials. In Sep. 2015, he started a new endeavor with Prof. Robert J. Macfarlane at the Massachusetts Institute of Technology on polymer coated nanoparticles. In Sep. 2017, Jianyuan started his independent research at Rutgers University as an assistant professor. His current research interests include metallofullerene reactions, and their applications as biomedical, energy and quantum materials, and other nanostructures such as carbon nanodots and inorganic nanoparticles.