**Artificial Nacre-like Bionanocomposite Films from the Self-Assembly of Chitosan–Montmorillonite Hybrid Building Blocks**

Hong-Bin Yao, Zhi-Hua Tan, Hai-Yu Fang, and Shu-Hong Yu*

In the last decade, there has been a trend in chemistry to reduce the human impact on the environment. Special attention has been paid to the replacement of conventional petroleum-based plastics by materials based on biopolymers. However, the mechanical and thermal properties and functionalities of these biopolymers have to be enhanced to be competitive with the petroleum-based plastics from the viewpoint of practical applications. One of the most promising solutions to overcome these drawbacks is the elaboration of bionanocomposites, namely the dispersion of nanosized filler into a biopolymer matrix.

Because of their functional properties, bionanocomposites as green nanocomposites based on biopolymers and layered silicates (clays) have received intensive attention in materials science. Chitosan and montmorillonite (MTM), an abundant polysaccharide and a natural clay respectively, have been widely used as the constituents of bionanocomposites. The intercalation of chitosan into MTM and the dispersion of MTM nanosheets in the chitosan matrix have been systematically investigated. Bionanocomposites based on chitosan intercalation into MTM can be used as a sensor applied in the potentiometric determination of several anions. Bionanocomposite films formed through the dispersion of MTM nanosheets in the chitosan matrix have shown enhancement of the mechanical and thermal properties compared with the pure chitosan film. Unfortunately, the enhancement of the tensile strength and thermal stability of the chitosan–MTM bionanocomposite film is still low far from the expectations in industry.

Systematic studies are carried out in materials science on natural materials with the objective of duplicating their properties in artificial materials. Natural nanocomposites provide prime design models of lightweight, strong, stiff, and tough materials due to the hierarchical organization of the micro and nanostructures. One attractive biological model for artificial material design is nacre (mother-of-pearl). The microscopic architecture of nacre has been classically illustrated as a "brick-and-mortar" arrangement that plays an important role in the amazing mechanical properties of the nacre. This arrangement is constituted of highly aligned inorganic aragonite platelets surrounded by a protein matrix, which serves as a glue between the platelets.

Recently, the microstructure of the nacre has been mimicked by several innovative techniques to fabricate the artificial nacre-like materials with high mechanical performance. For example, layer-by-layer (LBL) deposition combining with cross-linking yielded poly(vinyl alcohol)/MTM nacre-like nanocomposites with a tensile strength of up to 400 MPa. The ice-crystal templates of the microscopic layers were designed to form a brick-and-mortar microstructured Al₂O₃/poly(methyl methacrylate) composite that is 300 times tougher than its constituents. The assembly of Al₂O₃ platelets on the air/water interface and subsequent spin-coating was developed into the fabrication of lamellar Al₂O₃/chitosan hybrid films with high flaw tolerance and ductility. The self-assembly of nanoclays with polymers coating by a paper-making method resulted in the nacre-mimetic films and nacre-like structural MTM–polyimide nanocomposites were fabricated by centrifugation deposition-assisted assembly. Our group has also fabricated nacre-like chitosan-layered double hydroxide hybrid films with a tensile strength of up to 160 MPa by sequential dipping coating and the LBL technique. The concept of mimicking nacre and recently developed innovative techniques inspired us to fabricate the highly sustainable artificial nacre-like chitosan–MTM bionanocomposite film with high performance to seek a promising material for the replacement of conventional petroleum-based plastics.

Herein, we introduce a novel approach to fabricate artificial nacre-like chitosan–MTM bionanocomposite films by self-assembly of chitosan–MTM hybrid building blocks (Scheme 1). The chitosan molecules are very easily coated onto exfoliated MTM nanosheets to yield the hybrid building blocks by strong electrostatic and hydrogen-bonding interactions. These hybrid building blocks can be dispersed in distilled water and then aligned to a nacre-like lamellar microstructure by vacuum-filtration or water-evaporation-induced self-assembly because of the role that the orientation of the nanosheets and linking of the chitosan play. The fabrication process is simple, fast, time-saving, and easily scaled up compared with the LBL ice-crystal-template and other techniques.
At the first stage, the chitosan-MTM hybrid building blocks were prepared through mixing an aqueous suspension of exfoliated MTM nanosheets and an aqueous solution of chitosan. The resulting mixture was stirred for 12 h to allow the chitosan molecules to fully adsorb onto the surface of the MTM nanosheets. TEM images (Figure 1a,b) confirm the sheet-like morphologies of both the MTM and chitosan-MTM, implying that chitosan-MTM is an ideal building block for fabricating lamellar microstructures.

The surface morphologies and the thickness of the MTM nanosheets before and after the adsorption of the chitosan molecules were characterized by AFM (Figure 1c,d; Supporting Information, Figures S1, S3). The surface of the MTM nanosheets changed from smooth to rough and the average thickness increased from 0.97 to 1.98 nm, indicating that a total of about 1 nm-thick chitosan layers adsorbed on both sides of MTM nanosheets, which was confirmed by the TGA (Supporting Information, Figure S3). The adsorption of the chitosan molecules on the MTM nanosheets was also demonstrated by the FTIR spectra (Supporting Information).

Figure S4: The adsorptions at 1556 and 1414 cm⁻¹ can be designated as δCH₂ and νCH₃, respectively. The MTM nanosheets with a chitosan coating were isolated by the centrifugation, washed with deionized water twice to remove unabsorbed chitosan, and finally collected as a glue-like substance. The obtained glue showed a strong adhesion and it can be painted on a glass slide (Figure 1e). Interestingly, the chitosan-MTM patterns on the glass slide disappeared (Figure 1f) under water due to the swelling. After the glass slide dried in the surrounding environment, the patterns would reappear as the original (Figure 1g), indicating the adhesive properties of the hybrid building blocks even under the water.

The MTM nanosheets with chitosan coatings can be redispersed into deionized water, resulting in a milky white colloidal suspension after stirring and ultrasonication. The chitosan-MTM hybrid can then be easily used to fabricate the films with nacre-like lamellar microstructures by vacuum-filtration- or water-evaporation-induced self-assembly. Photographs of the obtained chitosan-MTM bio-nanocomposite films are shown in Figure 2, inset. These films are flexible, glossy, and their surfaces are very smooth. The evaporation-induced film is more transparent than the film obtained by vacuum filtration owing to it being less thick. The microstructures of the fabricated films were observed by an SEM image in Figure 2. The chitosan-MTM hybrid building blocks are stacked together to form a densely oriented lamellar microstructure, which is reminiscent of the brick-and-mortar structure of nacre. Small-angle PXRD patterns also indicate the well-defined lamellar microstructures with a d spacing of 2.6 nm (Supporting Information, Figure S5). SEM images of the surfaces of the films reveal that the microstructures of the surface are flat, with only some nanoscale roughness (Supporting Information, Figure S6) that is slightly less in vacuum-filtration-induced composite films. The content of chitosan in these nacre-like bio-nanocomposite films was determined as 24 wt% by organic elemental analysis (Supporting Informa-
tensile strength of both the well-aligned artificial nacre-like films and conventional film. The mechanical performance of the well-aligned artificial nacre-like film is better than that of the film made by conventionally simply mixing the constituents. The Young’s modulus and ultimate tensile strength of the well-aligned artificial nacre-like films are respectively 3–5-fold and 2–3-fold higher than that of the conventional film.

An atomic modeling (Figure 3b) was used to investigate the mechanical properties at the molecular scale. The modeling shows that the geometry of SiO2 tetrahedrons on the surface of the MTM is conducive to cooperative hydrogen bonding. On the chain of the chitosan molecules, there are many OH and NH2 groups, which are likely to form the hydrogen bonding with SiO2 tetrahedrons on the surface of the MTM when the chitosan chains are close to the surface of MTM under the electrostatic attraction. On the other hand, the stereochemistry of the six rings in the chitosan chain is an obstacle to the hydrogen bonding formation of some OH and NH2 groups with SiO2 tetrahedra. Moreover, we did not observe Al–O–C bond formation in the FT-IR spectra: PVA molecules can form Al–O–C bonds, as reported by Kotov et al. Thus, it is reasonable that the chitosan–MTM films can not achieve mechanical strengths that are as high as PVA–MTM films. However, the hydrogen bonding and the lamellar structure can contribute to a higher mechanical performance compared with the conventional chitosan–MTM films.

The well-aligned lamellar microstructures also lead to a good light transmittance of the films. Because of the high orientation of the chitosan–MTM hybrid building blocks, which greatly decreases the light scattering between the nanosheets, the obtained chitosan–MTM films were more transparent than conventional chitosan–MTM films in which the MTM nanosheets are randomly dispersed. The transmittance spectra (Figure 3c) show about 60–80% transparency across the visible spectrum of light for the evaporation-induced chitosan–MTM film, in contrast to only 2–3% for the conventional film. Interestingly, when the chitosan–MTM films were swollen by water, their transparency was further enhanced, in contrast to a small increase for that of conventional films. There are two main reasons leading to the enhancement of transmittance of nacre-like films, which almost completely disappeared in water (Figure 3d). One reason is the common physical phenomenon that when water fills the space, the light scattering occurring at the interfaces would decrease because the refractive index of water is more similar to that of the solid material than that of air. We used weighting paper as the contrast sample to show how this effect occurred on the increase of transmittance of the film (Fig-
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Figure 3d), and transmittance spectra indicate that such an increase is limited (Figure 3e). The other reason is that the lamellar microstructures of the nacre-like films lead to the increase of transparence. After water swelling, the chitosan molecules between the MTM nanosheets stretched to optimize the lamellar microstructures, which largely decreased the light scattering between the MTM nanosheet interfaces (Figure 3e). The optimization of lamellar microstructures contributed to a 20-30% increase of transparence across the visible spectrum for the vacuum-filtration-induced chitosan-MTM film.

LBL assembled lamellar structural polyelectrolyte-clay coatings on fabric have shown high efficient fire retardancy.[49] The fire retardancy of the vacuum-filtration-induced chitosan-MTM film was tested because of its considerable thickness (see video provided in the Supporting Information). When exposed to the flame of blast burner, the film initially burnt very briefly owing to the small amount of the chitosan adsorbed on the MTM nanosheets, and the film gradually became black, which was partly induced by carbonization of the chitosan. After burning out the chitosan, the MTM nanosheets do not support any burning and remain inert under prolonged exposure to the flame (Figure 4b, inset).

![SEM images of the nacre-like chitosan-MTM bio-nano composite film after burning: a) the surface of the film, b) the inside structure of the film. Insert in (b) shows the film being exposed to the flame.](image)

Furthermore, burning the film never lead to any dripping of hot fluids such as for plastic films, and the shape of the film was maintained even with constant exposure to the flame of a blast burner. The microstructures of the film after burning were checked by SEM, and the images showed that a flame-protective cuticle of tightly condensed nanoclay formed (Figure 4a) and the nacre-like lamellar microstructures were still maintained inside the film (Figure 4b).

In summary, hybrid building blocks with a thin layer of chitosan coating on the MTM nanosheets can be conveniently prepared and self-assembled to form chitosan-MTM bio-nano composite films by vacuum filtration or water evaporation. The MTM-chitosan hybrid nanosheets were characterized by the AFM, FTIR, and TGA; these methods indicate that about 1 non-thick total chitosan molecules were adsorbed on both sides of MTM nanosheets. The obtained biocomposite films have a nacre-like brick-and-mortar microstructure, which leads to their high performances in mechanical properties, light transmittance, and fire resistant properties. The Young’s modulus and ultimate tensile strength of the well-aligned artificial nacre-like films are 3-5-fold and 2-3-fold higher than that of films fabricated by conventional methods. The chitosan-MTM film has 60-80% transparency across the visible spectrum, compared to 2-3% of that of the conventional films. The chitosan-MTM films can maintain their self-supported shapes under the constant exposure to flame of blast burner. The present facile fabrication process is expected to allow the design and preparation of different biomimetic nanocomposites with unique functionalities with improved performances.

Experimental Section

Chitosan and glacial acetic acid were purchased from Sinopharm Chemical Reagent Co. Ltd. Sodium montmorillonite (Na-MTM) nanosheets were offered by Zhejiang Fengsheng Clay Co. Ltd. Chemicals were analytical grade and used as received without further purification.

Preparation of chitosan-MTM hybrid nanosheets: A dispersion of Na-MTM in deionized water (0.5 wt%) was stirred thoroughly for one week and then centrifuged at 3000 rpm for 10 min to remove unexfoliated Na-MTM. Chitosan (2 wt%) was dissolved in an aqueous solution of 2 wt% glacial acetic acid at 40°C and stirred for 24 h.

The same volume of the exfoliated Na-MTM solution and chitosan solution (2 wt%) were mixed under the constant stirring for 24 h to guarantee the full adsorption of chitosan on MTM nanosheets. The chitosan-coated MTM hybrid nanosheets were collected by centrifugation at 9000 rpm for 10 min, washed by deionized water twice to remove the unabsorbed chitosan, and finally collected as a gel-like substance.

Nacre-like chitosan-MTM biocomposite films were fabricated by two different self-assembly procedures: A desired amount of chitosan-MTM gel was dispersed into deionized water (20 mL) under ultrasonication. 1) Vacuum filtration-induced self-assembly: The obtained suspension was vacuum filtered to form nacre-like chitosan-MTM biocomposite film on the cellulose acetate filtration paper, with pore size of 0.2 μm, and then dried in a 60°C oven. Free-standing films were obtained by dissolving the cellulose acetate filtration paper in acetic acid. 2) Water-evaporation-induced self-assembly: The obtained suspension was poured into the Petri dish and kept in the 60°C oven to evaporate to form nacre-like chitosan-MTM biocomposite film on the bottom of the Petri dish. Free-standing films were obtained by directly peeling off from the bottom of the Petri dish.

Fabrication of conventional film: In a typical procedure, Na-MTM (3 g) was dispersed into chitosan solution (2 wt%, 50 mL) under constant stirring for 24 h and the suspension was set for several hours. The suspension (20 mL) was then poured into the Petri dish and kept in a 60°C oven to evaporate and form the chitosan-MTM biocomposite film on the bottom of the Petri dish. The free-standing film was peeled off from the bottom of the Petri dish.

X-ray powder diffraction (PXRD) patterns were obtained with a Japan Rigaku Dmax-A reflection-mode X-ray diffractometer equipped with graphite-monochromated Cu Kα radiation (λ = 1.54178 Å). Transmission electron microscope (TEM) images were taken with a Hitachi H-7650 transmission electron microscope at an accelerating voltage of 120 kV. Atomic force microscope (AFM) images were carried out by Veeco di Nanova. A freshly cleaved mica slide was used as the substrate for the AFM measurement and one drop of the dilute solution of sample (0.5 wt%) was dropped on the substrate and dried naturally for the AFM characterization. Scanning electron microscope (SEM) images were taken with a Zeiss Supra 40 scanning electron microscope at an acceleration voltage of 5 kV. The UV-Vis transmission spectra of the films were collected on a Shimadzu UV-3700. Thermal gravimetric analysis (TGA) was carried out with a TA SDT Q600 thermal analyzer, with a heating rate of 10°C min⁻¹ under air. The mechanical properties of free-standing
films were measured under tensile mode in a universal mechanical testing machine (Instron 5565 A). For the mechanical testing, the films were cut with a razor blade into rectangle bars of approximate length 25 mm and width 5 mm; the distance between the clamps was 5 mm and the load speed was 10 mm/min. 

The Supporting Information contains AFM images, elemental analysis, FT-IR spectra, PXRD patterns, SEM images, and videos.

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A Highly Tunable Stereoselective Olefination of Semistabilized Triphenylphosphonium Ylides with \( N \)-Sulfonyl Imines

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Geometrically defined alkenes not only are ubiquitous structural motifs in biologically relevant molecules but also serve as a foundation for a broad range of chemical transformations. A plethora of chemical methods have been invented for the convergent synthesis of stereochemistry, which defines a pillar of modern synthetic chemistry. While no single method provides a universal solution to stereoselective alkenes, the Wittig reaction involving direct olefination of phosphonium ylides with aldehydes has enjoyed widespread prominence and recognition owing to its simplicity, efficiency, accessibility, and the selectivity, and generally high levels of geometrical control.  

Triphenylphosphonium ylides (Ph3P=CHR) have been employed most frequently in the Wittig reaction because they are readily prepared through reaction of triphenylphosphine, an inexpensive and air stable phosphine, with alkyl halides followed by treatment of the resulting phosphonium salts with bases. In general, the Wittig reaction yields preferentially \( Z \)-alkenes for nonstabilized triphenylphosphonium ylides (\( R = \text{alkyl} \)) and \( E \)-alkenes for stabilized triphenylphosphonium ylides (\( R = \text{alkoxycarbonyl, acyl, or cyano} \)). Although a number of efforts have been devoted to the modification of semistabilized triphenylphosphonium ylides by replacing the phenyl group with a substituted aryl group, a heterosubstituent group, an alkyl group, a disubstituted group, or an alkynyl group, limited success has been achieved in improving the stereoselectivity for the synthesis of conjugated alkenes, and furthermore, most of these procedures are costly, laborious, and time-consuming. In sharp contrast to the modification of semistabilized triphenylphosphonium ylides, it is surprising that little has been done with the electrophiles in the Wittig reaction to improve the stereoselectivity for alkenes. As early as 1963, Bestmann and Seng disclosed an olefination reaction of semistabilized triphenylphosphonium ylides with N-phenyl imines at 150–180 °C (or 190–200 °C) to yield (E)-stilbene and (1E,1E)-1,4-diphenyl-1,3-butadiene. However, this protocol has not been improved toward a practical stereoselective synthesis of conjugated alkenes probably owing to the high reaction temperature and inconvenient operation. Nevertheless, the fact that alkenes possess distinct electronic and sterically properties relative to aldehydes, together with our interest in stereoselective alkenes synthesis, prompted us to develop a tunable stereoselective synthesis of conjugated alkenes through an olefination reaction of semistabilized araphosphonium ylides with appropriate imines instead of the aldehydes used in the Wittig reaction.  

We planned to employ an electron-withdrawing group to activate an imine and facilitate subsequent carbon–nitrogen bond cleavage for the stereoselective olefination of a semistabilized triphenylphosphonium ylide. The use of a more reactive imine would require lower temperature relative to the reaction with an N-phenyl imine. Moreover, the electron-withdrawing group could serve as a handle to tune the stereoselectivity. As proposed by Bestmann and Seng, the olefination of a triphenylphosphonium ylide with an imine could potentially proceed through a Wittig-type reaction pathway involving formal \( 2 + 2 \) cycloaddition to generate a 1,2-azaphosphole intermediate followed by elimination of an iminophosphorane yielding an alkene (Scheme 1, \( X = N \)-EWG). The Z/E ratio of an alkene product would rely totally on the stereoselectivity for the formation of the 1,2-azaphosphole intermediate, during which an additional electron-withdrawing group could interact with the phenyl group, the \( R^1 \) group, and the \( R^2 \) group to tune the stereoselectivity when compared to a 1,2-azaphosphole intermediate generated in the Wittig reaction (Scheme 1, \( X = O \)).  

**Scheme 1. Olefination of Semistabilized Triphenylphosphonium Ylides with Aldehydes (a) or Imines (b)**

- \( R^1 \) = general hydrocarbon group; \( R^2 \) = aryl, vinyl; EWG = electron-withdrawing group. (a) The Wittig reaction; \( X = O \), with low stereoselectivity. (b) Our approach; \( X = N \)-EWG, EWG facilitates the carbon–nitrogen bond cleavage and tunes the stereoselectivity for alkene synthesis.

We have recently demonstrated that a sulfonyl group is one of the most effective electron-withdrawing groups in activating imines and in facilitating carbon–nitrogen bond cleavage under mild reaction conditions. In addition, N-sulfonyl imines are reasonably stable in the air at room temperature and are easily prepared through the condensation reaction of aldehydes with primary sulfonamides. Thus, a number of sulfonyl groups were evaluated with regard to their ability to activate an imine and affect the stereoselectivity in the model reaction of benzylideneaziridinophosphorane Ph3P=CHPh, prepared in situ from phosphonium salt 2a and lithium diisopropylamide (LDA), with N-benzylidene sulfonamide 1a in tetrahydrofuran at –78 °C to room temperature (Table 1). As demonstrated by the results summarized in Table 1, a sulfonyl group could significantly affect the yield and stereoselectivity for the synthesis of stilbene. To our great delight, the use of a \( p \)-toluenesulfonyl group to activate the imine resulted in the formation of (Z)-stilbene (Z3aa) with greater than 99:1 stereoselectivity (Table 1, entry 1). Moreover, (Z)-stilbene (Z3aa) was also obtained with the same level of stereoselectivity when an \( n \)-hexadecane-sulfonyl group was employed (Table 1, entry 11). A broad range of \( p \)-toluenesulfonyl-activated aromatic or heteroaromatic imines underwent olefination reaction with various benzylidenephosphoranes to afford structurally diversified (Z)-stilben derivatives in good to excellent yields and with greater than 99:1 stereoselectivity (Table 2, entries 1–7 and 11–18). In
**Table 1. Survey of the Sulfonyl Groups**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imines</th>
<th>R</th>
<th>Yield (%)</th>
<th>Z (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1aa</td>
<td>4-MeC,H₄</td>
<td>79</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>1ab</td>
<td>4-MeOCC,H₄</td>
<td>59</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>1ac</td>
<td>4-CNCC,H₄</td>
<td>61</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>4</td>
<td>1ad</td>
<td>2-NO₂NC,H₄</td>
<td>63</td>
<td>50:50</td>
</tr>
<tr>
<td>5</td>
<td>1ae</td>
<td>2-Cl₂C,H₄</td>
<td>64</td>
<td>50:50</td>
</tr>
<tr>
<td>6</td>
<td>1af</td>
<td>2,3,5,6-Me₄C,H₄</td>
<td>53</td>
<td>3:77</td>
</tr>
<tr>
<td>7</td>
<td>1ag</td>
<td>1-naphthyl</td>
<td>79</td>
<td>78:22</td>
</tr>
<tr>
<td>8</td>
<td>1ah</td>
<td>2-naphthyl</td>
<td>43</td>
<td>98:2</td>
</tr>
<tr>
<td>9</td>
<td>1ai</td>
<td>2-phenyl</td>
<td>69</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>10</td>
<td>1aj</td>
<td>Me</td>
<td>47</td>
<td>50:50</td>
</tr>
<tr>
<td>11</td>
<td>1al</td>
<td>n-C₆H₄</td>
<td>81</td>
<td>&lt;1:99</td>
</tr>
<tr>
<td>12</td>
<td>1am</td>
<td>Ph₂CH₂</td>
<td>58</td>
<td>28:72</td>
</tr>
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</table>

*Reaction conditions: phosphonium salt 3a (0.60 mmol), LDA (0.65 mmol), THF (1.0 mL), 74°C, 1 h; then imine 1a (0.50 mmol), lid 1 (1.0 mL), 74°C to rt. *Isolated yield. *Determined by 1H NMR analysis.

**Table 2. Tunable Stereoselective Olefination of Benzylidenealanylphosphonates with N-sulfonyl imines**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>Ar</th>
<th>R</th>
<th>Product yield (%)</th>
<th>Z (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>4-MeC,H₄</td>
<td>Z=1a</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>4-CNCH₃</td>
<td>Ph</td>
<td>4-MeC,H₄</td>
<td>Z=1a</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>4-CNCH₃</td>
<td>Ph</td>
<td>4-MeOCC,H₄</td>
<td>Z=1a</td>
<td>75</td>
</tr>
<tr>
<td>4</td>
<td>4-CNCH₃</td>
<td>Ph</td>
<td>4-MeOCC,H₄</td>
<td>Z=1a</td>
<td>75</td>
</tr>
<tr>
<td>5</td>
<td>4-CNCH₃</td>
<td>Ph</td>
<td>4-MeOCC,H₄</td>
<td>Z=1a</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>4-CNCH₃</td>
<td>Ph</td>
<td>4-MeOCC,H₄</td>
<td>Z=1a</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>4-CNCH₃</td>
<td>Ph</td>
<td>4-MeOCC,H₄</td>
<td>Z=1a</td>
<td>75</td>
</tr>
<tr>
<td>8</td>
<td>4-CNCH₃</td>
<td>Ph</td>
<td>4-MeOCC,H₄</td>
<td>Z=1a</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>4-CNCH₃</td>
<td>Ph</td>
<td>4-MeOCC,H₄</td>
<td>Z=1a</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>4-CNCH₃</td>
<td>Ph</td>
<td>4-MeOCC,H₄</td>
<td>Z=1a</td>
<td>75</td>
</tr>
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</table>

*Reaction conditions: phosphonium salt 3a (0.60 mmol), X = Br (for entries 15, 17, and 30, X = Cl), LDA (0.65 mmol), THF (1.0 mL), 78°C, 1 h; then imine 1a (0.50 mmol), lid 1 (1.0 mL), 78°C to rt. *Isolated yield. *Determined by 1H NMR analysis.

"Communications" is a section in scientific literature that provides concise reports of recent findings or updates on ongoing research. It often includes results that are not comprehensive enough for a full research article but are still important to share with the scientific community. The content mentioned in the table and text indicates a study on the stereoselective olefination of sulfonated phosphonates with various imines, exploring the stereochemistry and potential applicability in various chemical transformations. The use of phosphonium salts and LDA (lithium diisopropylamide) as catalysts is highlighted, indicating a focus on reaction conditions and yield optimization.

"Stereoselectivity" refers to the preference of reaction pathways leading to one of the possible stereochemical outcomes. In this study, the researchers are examining the conditions under which one stereoisomer is produced preferentially over another, which can be crucial for the development of more selective and efficient synthetic methods. The isolated yields and 1H NMR analysis (a technique used to determine the molecular structure of substances) suggest a successful investigation into the stereoselective properties of these reactions, which could have implications for the design of new pharmaceuticals or materials.

Mitochondrial clustering and p53-independent apoptosis in cancer cells are areas of ongoing research due to their relevance in cancer biology. This study may contribute to the understanding of such mechanisms through the development of new synthetic methodologies.
Table 3. Tunable Stereoselective Olefination of Allyldienethiophosphoranes with N-Sulfonyl Imines*

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>product yield (%)</th>
<th>Z/Z*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>4-MeC6H4</td>
<td>95aa</td>
<td>77 &lt;1.99</td>
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<tr>
<td>2</td>
<td>4-CIC6H4</td>
<td>H</td>
<td>4-MeC6H4</td>
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<td>88 &lt;1.99</td>
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<td>4-OCIC6H4</td>
<td>H</td>
<td>4-MeC6H4</td>
<td>95aa</td>
<td>76 &lt;1.99</td>
</tr>
<tr>
<td>4</td>
<td>4-OMeC6H4</td>
<td>H</td>
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* Reaction conditions: phosphonium salt (4.00 mmol), X = Br (For entries 6–20, X = Cl), LDA (0.65 mmol), THF (1.0 mL), –78 °C, 1 h, then imine (0.50 mmol), THF (1.0 mL), –78 °C to rt. Isolated yields were determined by 'H NMR analysis.

Scheme 2. Stereoselective Synthesis of DMU-212 (E6) and Its Isomer Z6

3-imines bearing appropriate N-sulfonyl groups smoothly undergo olefination reaction with various benzylidenephosphoranes or allyldienethiophosphoranes under mild reaction conditions to afford an array of both Z and E-isomers of conjugated alkenes, in good to excellent yields and with greater than 99:1 stereoselectivity. Moreover, this tunable protocol has been successfully applied to the highly stereoselective synthesis of two anticancer agents, DMU-212 and its Z-isomer.

Acknowledgment. We are grateful for the financial support from the National Natural Science Foundation of China (2072147 and 20723006, and 20672105), National Basic Research Program of China (973 Program 2010CB833300), and Chinese Academy of Sciences.

Supporting Information Available: General information, experimental procedures, characterization data, and copies of 'H and 13C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.
High-Throughput Screening of Dendrimer-Binding Drugs

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Abstract: A convenient approach for the high-throughput screening of dendrimer-binding drugs by NMR techniques including saturation transfer difference (STD) NMR and Hadamard-encoded nuclear Overhauser effect measurements is presented. The screening results for insoluble drugs show that phenylbutazone and sulfamethoxazole prefer to localize in the interior pockets of dendrimer, while mycophenolic acid mostly binds on the dendrimer surface, and noncharged insoluble drugs like trimethoprim and primidone do not interact with dendrimers. In another path for soluble drugs, n-butanoic acid and dimethylformamide are screened as dendrimer-binding compounds from a screening pool containing eight soluble compounds by STD NMR. The screening of dendrimer-binding insoluble or soluble compounds can be finished within an hour.

High-throughput screening (HTS) is an essential approach to drug discovery that has revolutionized the pharmaceutical industry in the past decade. 1 It identifies the binding of a large number of biologically active compounds to a target of interest to facilitate the fast discovery of new chemical entities. 2 Today, dendrimer-based drug delivery systems have become more and more important in the pharmaceutical sciences. 3,4 Lots of drugs were reported to benefit from the formulation of dendrimer—drug complexes mediated by ion/dihydrogen-bond binding or hydrophobic encapsulation. 5 There is a potential for significant fragmentation of the literature if the physiochemical properties of dendrimer—drug complexes are published in a “one drug at a time” fashion. The greater availability of drugs in the libraries and the growth numbers of functional dendrimers have made it difficult for a pharmaceutical to design the most effective dendrimer—drug formulations in a relatively short time. In addition, the size/surface charge—tunable properties of dendrimers make them excellent candidates in the biomimicry of proteins or protein/DNA complexes. 6 Screening of potential ligands for these “artificial proteins” is essential for the methodology of HTS in molecular recognitions between drugs and an interested biological target. Here we describe the use of NMR techniques including normal nuclear Overhauser effect (NOE) and Hadamard-encoded NOE measurements and saturation transfer difference (STD) NMR for the fast screening of dendrimer-binding drugs, which delivers meaningful hits for the optimization of dendrimer-based drug delivery systems.

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Figure 2. (a) Hadamard-encoded NOE and (b) normal NOESY of the dendrimer-insoluble drug complexes at mixing time of 300 ms. (c) $^1$H NMR and (d) STD spectra of dendrimer-insoluble compound complexes at high-field region. The chemical shift assignments of the insoluble and soluble compounds in the screening pool are assigned from the TOCSY results shown in Figure S2 and Figure S8, respectively (F, L-alanine; G, L-2-amino-2-butanobutyric acid; H, ethyl triphenyl phosphonium bromide; I, pyridine; J, nicotinamide; K, N,N-dimethylformamide; L, n-butyric acid; M, sodium salicylate).

PAMAM dendrimer is charge-dependent and that electrostatic interaction between the guest and the cationic dendrimer is the first step of encapsulation. On the other hand, macromolecules exhibit negative NOE effect with a fast buildup rate, while the low-molecular-weight ligands (≤1000 Da) have positive NOE signals with a slow buildup rate. If the low-molecular-weight ligand binds to the macromolecular receptor, it obtains motional correction time of the receptor, thus developing a negative NOE in the bound state.74 The negative intramolecular TNOE signals (red) of the drugs in Figure 1 and Figure S3 indicate phenylbutazone, sulfamethoxazole, and mycopHENolic acid are in the bound state. The positive intramolecular cross-peaks (green) for primidone and trimethoprim reveal that most of these drugs are in the free state. Previous studies have reported that the solubilization factor of mycopHENolic acid is much higher than that of sulfamethoxazole and phenylbutazone by dendrimer.80 The weak NOE signals between mycopHENolic acid and dendrimer suggest that most of the guests were bound on the surface by ionic or hydrogen-bond interactions (Figure S11). These results confirm that TNOE is useful in the fast screening of dendrimer-binding ligands, giving information on molecular encapsulation/ionic binding, spatial distance, and molecular orientation in the host–guest systems.

To further reduce the experimental time in 2D nTOE experiments, we use the Hadamard-encoded cross-relaxation spectroscopy to speed up the HTS of dendrimer-binding drug molecules. The Hadamard-encoded NOESY measures NOE interactions for selected proton frequencies of dendrimer or drugs.9 Figure 2a and Figure S4 show the NOE interactions between the protons in dendrimer and insoluble drugs from the Hadamard-encoded NOE experiment. The results are consistent with that obtained from a normal NOESY experiment in Figure 2b and Figure S5. To validate the screening results from NOESY and Hadamard-encoded NOE studies, we conducted NOE experiments for G5 dendrimer and single guest in the screening pool in Chart 1. As demonstrated in Figure S6, G5 dendrimer interacts with phenylbutazone, mycopHENolic acid, and sulfamethoxazole but does not bind trimethoprim and primidone, which are fully consistent with the results obtained from the mixing pool. The Hadamard-assisted NOE spectrum provides the same information with reduced experimental time from whole days to several minutes, which is essential in the HTS of dendrimer-binding guests.

For a screening pool containing eight water-soluble compounds (Chart 2), no obvious cross-peaks between dendrimer and the guests can be observed in the NOESY spectrum in Figure S7, suggesting that the dendrimers have a low tendency to encapsulate hydrophilic drug molecules. In this case, we use STD NMR to analyze the competitive binding of the ionic interactions between dendrimers. STD NMR, which has been proven to be a sensitive and robust tool to study complexes involving receptor/ligand recognitions and host–guest interactions, is able to screen multiple compounds with relatively high binding affinity toward dendrimer simultaneously.90 The $^1$H NMR and STD NMR spectra of a G5 dendrimer solution with eight soluble compounds are shown in Figure 2c,d, respectively. The presence of strong STD signals for n-butyric acid and N,N-dimethylformamide and medium STD signals for sodium salicylate, L-alanine, and L-2-amino-2-butanobutyric acid in Figure 2d and Figure S9 proves that these compounds in the solution bind to dendrimer. No STD signal for pyridine, ethyl triphenyl phosphonium bromide, and nicotinamide is observed, suggesting weak binding affinity of these compounds toward dendrimer. We also determined the binding behaviors of G5 dendrimer toward the soluble guests in Chart 2 without N,N-dimethylformamide and n-butyric acid by STD NMR. As shown in Figure S10, the presence of strong STD signals for L-alanine and L-2-amino-2-butanobutyric acid indicates that a competitive binding occurs between G5 dendrimer and the ligands in the screening pool and that dendrimer is capable of binding drugs with weaker binding affinities. Compounds including n-butyric acid, sodium salicylate, L-alanine, and L-2-amino-2-butanobutyric acid have negative charges in their structures which are responsible for the ionic interactions between dendrimer and the compounds. Strong binding affinity between N,N-dimethylformamide and dendrimers is due to the presence of a strong hydrogen-bond donor in the molecule which mediates hydrogen-bond interactions with dendrimer. The highest binding affinity of n-butyric acid to the dendrimer among sodium salicylate, L-alanine, n-butyric acid, and L-2-amino-2-butanobutyric acid is due to weak steric hindrance for the electrostatic attachment of n-butyric acid on dendrimer surface.

In summary, we demonstrated the use of NMR techniques for HTS of dendrimer-binding guests. The whole HTS experiment for insoluble/soluble compounds by a combination of Hadamard-encoded NOE and STD NMR can be finished within an hour. To the best of our knowledge, this is the first report of screening dendrimer-binding guest molecules. The acquired NMR data also give information on the localization of guests, i.e., in the interior cavities or on the surface of dendrimers. The hydrophobic encapsulation of guest molecules in the interior means slower release rate which is expected in a sustained drug delivery system. The attachment of soluble guests on the surface of dendrimer via hydrogen-bond and ionic interactions leads to a much faster release rate in comparison with the encapsulations, and the formulations are important in the transdermal delivery of hydrophilic compounds to penetrate through the skin barrier consisted of phospholipids and...
membrane proteins. It offers several features for the physicochemical properties of dendrimer-based host–guest systems and the design of dendrimer-based drug formulations. The findings obtained in this study can help with the generation of a large family of guest molecules which may benefit from the dendrimer inclusion/binding technique. Also, the methodology developed for the dendrimer system is essential for fast discovery of new host–guest systems and molecular-recognition processes.

Acknowledgment. We thank the Talent Program of East China Normal University (No.772022201) and the Specialized Research Fund for the Doctoral Program of Higher Education (No.20093402110041) for financial support to this program.

Supporting Information Available: Experimental procedures and further information on NMR-assisted high-throughput screening of dendrimer-binding drugs. This material is available free of charge via the Internet at http://pubs.acs.org.

References


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Insights into Initial Kinetic Nucleation of Gold Nanocrystals

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Abstract: Understanding the initial nucleation mechanism of monodisperse nanocrystals (NCs) during synthesis process is an important prerequisite to control the desired sizes and to manipulate the properties of nanoscale materials. The acquisition of information for the small nanocluster nucleation process, however, still remains challenging. Here, using a continuous-flow in situ X-ray absorption fine structure (XAFS) spectroscopy for time-resolved studies, we have clarified the initial kinetic nucleation of Au clusters under the grain size of 1 nm for the classical Au NCs synthesis via the reduction of AuCl₄⁻ in aqueous solution. The in situ XAFS results present the experimental revelation of the formation of intermediate Au₄Cl₈− dimer and the subsequent higher complexes ‘Au₄Cl₈−’ in the initial nucleation stage. We propose a kinetic three-step mechanism involving the initial nucleation, slow growth, and eventual coalescence for the Au NCs formation, which may be helpful for the synthesis of metallic nanomaterials.

Introduction

Noble metallic nanocrystals (NCs) of controlled size and shape have attracted increasing research attention during the past decades due to their interesting dimension dependent optical, electronic, and catalytic properties.¹¹−¹⁰ Colloidal chemical synthetic methods involving the reduction of a precursor by various reducing agents at an elevated temperature in the presence of a polymeric stabilizer such as polyvinyl pyrrolidone (PVP) have been widely developed for the production of uniform Au NCs.⁴,⁵ Recently, the nucleation mechanism of metallic NCs in solution have been a subject of the increasing study, but are still poorly understood due to the limitation of the conventional characterization methods.⁶⁻⁷ A number of approaches have been developed to address this technical challenge, both from experimental and theoretical points of view.⁸⁻¹² Theoretically, Frenkel et al.⁸ and Bawendi et al.⁹ have developed a simple and general model to simulate the nucleation rate and size evolution. Further computational studies need to be guided by more solid experimental evidence of nucleation event. In situ experimentation with a time-resolution represents the most likely means by which the key stages of dynamic processes in the NCs nucleation can be unraveled. Many in situ researches have been devoted to the studies on the NCs nucleation using various techniques such as SAXS/WAXS, UV−vis, and transmission electron microscopy (TEM).¹⁰,¹¹,¹³ For example, Abécasis et al.¹⁰ have reported an in situ study on the nucleation and growth of Au NCs by using SAXS/WAXS and UV−vis spectroscopy. More recently, Alivisatos and co-workers¹¹ have successfully observed the growth trajectories of P NCs starting from the size of 2.2 nm in solution by in situ TEM.

These experimental methods are mainly utilized to study the growth process of NCs in a size larger than 1−2 nm, however, they could hardly provide effective information about the initial nucleation process from the atomic level. Currently, there are two pathways describing the generation of the initial nuclei of metallic nanoclusters from the precursors.⁶⁻⁸,¹⁰ One is the classical path of nucleation where metallic ions are fully reduced into the zerovalent atoms first and then aggregate into nuclei and grow into NCs.¹⁰,¹¹ The other is the formation of cluster
complex by unreduced metal species prior to full reduction to the metallic state.\textsuperscript{14,15} We summarize these two pathways by the following equations:

Path 1: $M^{2+} + xe^{-} \rightarrow M^{0}$, $M^{0} + M^{0} \rightarrow M_{n}^{0+}$
Path 2: $M^{4+} + e^{-} \rightarrow M^{2+}$, $M^{2+} + M^{2+} \rightarrow M_{2}^{2+}$

Therefore, a technique sensitive to the temporal evolution around an atomic species is essential to fill the gap of the knowledge about the initial stage of NCs growth. Fortunately, due to the deep penetration of X-ray and atomic species identity, time-resolved \textit{in situ} X-ray absorption fine structure (XAFS) spectroscopy is a powerful method to carry out a direct investigation for the local structural change during the reactive processes in a bulk or a solution system.\textsuperscript{18-20}

Here, we report an \textit{in situ} time-resolved XAFS technique with an atomic scale sensitivity to monitor the initial formation kinetics of Au NCs under the grain size of 1 nm. The developed time-resolved XAFS setup with continuous-flow mode is shown in Figure 1. This online characterization technique can enable us to detect the structural changes in the initial nucleation process of Au clusters without an additional sample preparation step. The synthesis of Au NCs was performed through the reduction of HAuCl$_4$ by citric acid in an aqueous surfactant solution (PVP). The use of citric acid as the reducing agent together with low reaction temperature has permitted us to study the moderate nucleation kinetics over relatively long period of a few hours. The reduction process can be monitored by the color changes in the solution from the initially transparent yellow to finally dark brown (see Figure S1, Supporting Information).

**Experimental Section**

\textbf{Synthesis}.

Au nanocrystals were prepared by modifying the method of ref 5. Briefly, the aqueous solution containing 7.4 mM Auric acid (HAuCl$_4$), 28 mM citric acid, and 29 mM poly(vinyl pyrrolidone) (PVP) were mixed in a three-necked flask. The flask was connected with the \textit{in situ} cell and the peristaltic pump through the microtubes. The reaction mixture was heated at 70 $^\circ$C in air for 240 min with stirring.

\textbf{Characterizations}.

At different reaction times, a small volume of liquid samples was extracted from the batch of reaction solution during the course of a reaction and spread as a droplet onto a copper grid for TEM measurements. The UV–vis absorption spectra were recorded on UV-2501PC/2550 spectrophotometer to detect the reduction of Au ions in the solutions.

\textit{In situ} quick XAFS (QXAFS) measurements at Au $L_{3}$-edge were performed in transmission mode at NW10A station in PF-AR (Photon Factory Advanced Ring for Pulse X-ray, Japan) and U7C XAFS station in NSRL (National Synchrotron Radiation Laboratory, P.R. China). The storage ring of PF-AR was operated at 6.5 GeV with the maximum current of 450 mA. An approximate X-ray photon flux of $10^{11}$ photons s$^{-1}$ was monochromatized using a Si(311) monochromator. The storage ring of NSRL was run at 0.8 GeV with the maximum current of 200 mA. In the QXAFS measurements, the Si(311) monochromator was moved continuously, so that quick measurement (less than several seconds to minutes) became possible. The reactive solution prepared by the procedure mentioned above was continuously circulated along the tubes by peristaltic pump during the acquisition of XAFS spectra and flowed into Teflon cell sealed with Kapton windows. The \textit{in situ} Teflon cell has a path length in X-ray direction of about 5 mm. Because the static reacted vessel is not suitable for the \textit{in situ} measurement directly, we used recirculation system instead to ensure that the samples at the spot were newly formed from the reacted solution to achieve \textit{in situ} detection. The recirculation system also has additional advantages that it could avoid the precipitation of particles after a long time reaction and the possible influence of X-ray irradiation in XAFS measurements.\textsuperscript{21,22} (see more detail in Supporting Information and Figure S2). The structural parameters were determined by a curve-fitting procedure in $R$ space by using the FEFFIT program and USTC-XAFS software packages.

**Results and Discussion**

Typical TEM images of gold NCs (Figure 2a) illustrate the formation of NCs with the reaction times. It should be noted that at the initial nucleation stage before 60 min, the NCs is difficult to be distinguished in the TEM field of view. Until 120 min, the typical Au NCs of about 2.5 nm can be observed clearly. Similarly, by using \textit{in situ} TEM, Alivisatos et al. have traced the growth process of Pt NCs with the size of 3.4 nm.
Figure 2. Dynamic nucleation and growth of Au NCs studied by TEM and in situ XAFS. (a) TEM images of Au NCs obtained at different times for 30 and 120 min. Time variations in normalized Au L$_{3}$-edge in situ XANES (b) and K$_{2}$-weighted EXAFS Fourier transforms (FTs) spectra (c). The insets show the typical Au L$_{3}$-edge XAFS spectra at different reaction time. For the purpose of investigating the nucleation process fairly, several typical data are compared in XANES (d) and the corresponding FTs (e) spectra. (f) XANES calculations for various Au clusters. The structural model of the naked Au$_{9}$ cluster adopts the most stable configuration. The dimer is assumed as the Cl$^{-}$-Au$_{2}$(Cl)$^{-}$ model arises from two partially reduced AuCl$_{2}^{-}$ ions connected via Au–Au bond.

Reduced by the electron beam, no evident NCs could be found within the initial 10 s of reaction, while the NCs with the size of 2.2 nm appeared at 12 s. Up to date, however, there are few in situ studies reporting the observation of NCs with the size smaller than 2 nm, possibly because the nuclei formed in the initial stage are typically too small to be seen.

The in situ Au L$_{3}$-edge XANES and EXAFS spectra of Au colloidal solutions at sequential reaction times are shown in Figure 2b–e. As the reaction progressed, we can observe that the XANES spectra exhibit a clear decrease in intensity for the white line peak A (11922.5 eV) corresponding to a 3p$_{3/2}$ to 5d$_{4/2}$ transition of Au atoms and a slow increase for the peak B (11948.7 eV) in Figure 2b. The spectra of Fourier transforms (FTs) in Figure 2c directly demonstrate the local structure evolution around Au atoms. At the beginning, a prominent peak at 1.90 Å ascribed to the Au–Cl bonds of HAuCl$_{4}$ is visible. With increasing reaction time, a peak C at 2.44 Å (uncalibration) attributed to the Au–Au bonds appears and its intensity is gradually enhanced. To peer into the structural evolution of the initial nucleation, we put more emphasis on the XAFS spectra during the reaction time of 0–60 min as shown in Figure 2d,e. At the reaction time of 20 min, the characteristic peak B marked by arrow already emerges and the white line peak A is lowered in intensity by just about 1/10, which is different from the previous observations. An induction period is needed before the onset of metal–metal bond signal. Also, the peak C of Au–Au bond can be observed. The results indicate that the partial reduction of AuCl$_{2}^{-}$ occurs with the formation of Au–Au bonds during the initial process. Hence, the nucleation of Au clusters with the particle size smaller than


1 nm at the initial stage can be well monitored by in situ XAFS. At this stage, the distance of 260 nm from the Au foil, respectively. This means that most of Au ions in the reaction solution have been reduced to form the Au NCs at the end; in good agreement with that reported by Harada et al. and Bus et al.24,26

To investigate the initial kinetics of forming the Au NCs, we further examine the peak C of Au–Au bond produced in the nucleation process. As described before, it is generally assumed that the Au, clusters are formed first via the Path 1. Then, one may image that the Au–Au bonds observed in the starting nucleation should arise from the Au, clusters. Seen from the 30 min TEM image, the formed Au, clusters within the first 60 min are smaller than 1 nm in size, with the number of atoms less than 50. For a small Au NCs with the size of 1.6 nm, Zhang and Sham have reported the bond length contraction (1.4%) of the first shell of the Au–Au bonds with respect to the reference standard of the Au foil.25 For the small naked Au, clusters (n = 2–10), Wang et al.26 calculation results have indicated that the bond length of Au–Au bonds is in the range of 2.55–2.70 Å, significantly shorter than that (2.87 Å) of the fcc structural Au foil.27 However, in our case, the position of the peak C for the Au–Au bond as shown in Figure 2c is slightly larger than that of Au foil, which is totally different with the previous results. The succeeding quantitative fitting results of Au–Au bond length as shown later also give the evidence of the expansion of the Au–Au bond length at the initial stage compared with that for bulk Au. Both the qualitative analysis and quantitative fitting results give us an important clue that the formed Au–Au bond does not originate from the small naked Au, clusters.

To further confirm this point, we performed the XANES calculations (solid lines) for the representative Au, Au, and Au clusters (Figure 2f), using the ab initio multiple-scattering FEFF8.20 code.22 For comparison, the XANES spectra of Cl,O Au–AuCl, and the HAuCl aqueous solution are also simulated. To optimize the configuration of the dimer, we also performed the first principles calculations using Gaussian 03 program (see more details in the Supporting Information), and found that the AuCl is more energetically stable in planar geometry than in tetrahedral configuration. Also, for the calculation of stable configuration of dimer, it was found that tetrahedral complex would be transferred into the planar complex in the optimization process of Gaussian program, that is, every AuCl unit in the dimer structure is favored in planar geometry. Therefore, the planar–dimer complex is more stable than tetrahedral–dimer complex. The Au–Au and Au–Cl bond distances used in the calculation were selected from the fitting results. The structural model for the higher clusters, such as Au, and Au, were adopted from the most stable configurations which could be found in ref 26. One can see clearly that the calculated XANES spectra of Au, clusters do not exhibit any characteristic peaks like the experimental ones measured by in situ XAFS. The experimental spectra during the first 60 min, for example, the spectrum of 40 min, are more close to that of dimer configuration, and thus can be well fitted (closed squares) by a linear combination of the spectra of the initial state (HAuCl

solution) and intermediate state (‘Au,Cl’ dimers). The proportion of the dimers at this time is about 20%. This means that the Au–Au pairs arise from the complex composed of partially reduced Au ions, indicating the nucleation of Au NCs through Path 2. Once the AuCl is reduced through the loss of Cl–, the reduced Au ions would possibly form an Au,Cl, complex cluster via the Au–Au bond.

The above discussions lead us to believe that the peaks B and C are most likely related to the partial reduction of Au ions, and the expansion of Au–Au bond length can be attributed to the effect of surrounding Cl– ions. Similar phenomenon of forming noble metal dimer has been predicted by Ciach et al.17 On the basis of molecular dynamics simulations, they showed that the Pt dimer could be stabilized by Cl– preferably, and the formation of zerovalent metal clusters is not thermodynamically favored in solutions. Like our results, their simulated bond length (2.90 Å) of Pt–Pt is also larger than that (2.75 Å) of Pt foil. On the other hand, from the viewpoint of reaction condition, Path 2 is more favored under the moderate reduction condition adopted here. For example, in the PdCl reduction in the presence of a moderate reductant citrate, Henglein et al.14 have ruled out the existence of Pd atoms but postulated the monovalent Pd dimer as the first reaction intermediates. If in case of strong reducing agents, it has been indicated that the nucleation starts from the full reduction of precursor ions and then the metal clusters are formed.13 Analogously, it is reasonable to conclude that, under moderate reduction conditions, some kind of Au complex clusters could be formed in the initial nucleation stage prior to the complete reduction of the Au ions to zerovalent Au atoms.

To obtain quantitative structural parameters around Au atoms in reaction process, a least-squares curve parameter fitting was performed using the ARTEMIS module of IEPFPIT and USTCXAFS software packages.29,30 In the curve-fitting analysis, the peaks in the range of 1.2–3.4 Å were attributed to Au–Cl and Au–Au bonds without any contribution of the Au–O bond, which coincides with the fitting strategy used in the references.30,31 The curve-fitting results for the samples at typical reaction times are displayed in Figure S3. The obtained coordination number (N) and bond distance (R) are shown in Figure 3 against time. The NAu–Cl (Figure 3c) was found to be around 4 in the absence of the reducing agent and decreased to 3 at about 30 min, indicating the reduction of AuCl to AuCl (AuCl) species.13,15 At the same time, the NAu–Au is almost equal to 1. Thus, this suggests the formation of the Cl,O Au–AuCl (‘Au4Cl’ dimers) from two reduced AuCl at first. Then, these Au4Cl clusters could be further reduced and aggregated to form larger Au,Cl, complex clusters consisting of several Au atoms in the early stage. The reaction of other Au ions species with the clusters is expected to occur preferentially via electron transfer from the reducible to these dimeric and trimeric units.13 Therefore, with the reduction continued, the higher polymers are evolved on the basis of these dimers and trimers. Additionally, the Au–Au bond length evaluated by EXAFS fitting analysis at the beginning of the formation of

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The Au–Au bond is 2.92 Å, which is 1.7% larger than the corresponding value (2.87 Å) for bulk Au. For these AuCl₄⁻ clusters formed in the early stage, Au ions are almost enclosed by Cl⁻ ions. The charge transfer between Au and Cl⁻ ions would thus overcome nanosize effects and lead to the expansion of the Au–Au bond length in the Au complex clusters as revealed by the Figure 2e. Moreover, because the number of Au atoms in clusters increases with the reaction time, the specific surface area per Au atom and the Cl⁻ capping efficiency are therefore lowered. The competition between size and ligand effects tunes the R₂₃₋₄ₓ smaller than that of bulk gold for Au NCs larger than 9 nm, which can be seen from the trend in Figure 3b.

Furthermore, according to the temporal evolutions of N₃₋₄₃ and N₄₋₃₄ shown in Figure 3c,d, we can classify the whole reaction into three stages, that is, stage I, II, and III as marked by the highlight. Stage I can be considered as the initial nucleation step, exhibiting a faster process compared with stage II which stands for the growth step. In stage III, however, N₄₋₃₄ increases quickly along with the decreased N₃₋₄₃, indicating the rapid increase in size of Au NCs. This three-step mechanism can also be supported with a time evolution of UV–vis absorption spectra shown in Figure 3e. Within the first 80 min (stage I), the intensity of the absorbance at 327 nm from the gold salt in AuCl₄⁻ rapidly decreases, while the surface plasmon resonance (SPR) peak of Au colloid gradually appears, corresponding to the nucleation stage. In the middle stage from 120 to 180 min (stage II), these two peaks show little variations and finally in stage III, pronounced SPR peaks can be observed.

Summarizing the above results, we present a possible schematic pathway to illustrate the initial nucleation and growth kinetics of Au NCs in Figure 4. In the early nucleation (stage I), two dispersed AuCl₄⁻ ions were first connected via the Au–Au pair with the bond length significantly larger than that of the bulk Au, yielding the Cl₄⁻Au–Au–Cl₄⁻ dimers which could then react with an AuCl₄⁻ ion to form trimers. Analogously, the higher polymers and small Au clusters (such as Au₁₅₁ cluster) could be formed in the subsequent reduction (stage II). In these clusters, the Au atoms are mostly coordinated with other Au atoms, resulting in much larger N₄₋₃₄ than in dimers or trimers. Then, the formation of small Au NCs could be observed by TEM, which showed the appearance of 2.5 nm NCs, corresponding to the N₄₋₃₄ of about 7 at the reaction time of 120 min. The structural transition from two-dimensional (2D) to three-dimensional (3D) Au clusters has been predicted by theoretical calculations.²⁷,³⁴ Wang et al.²⁷ and Madsen et al.³⁴ have suggested that this transition occurs at the critical atomic number of about 7. When the number of Au atoms in a complex cluster exceeds the critical value of 13–15, fcc structured Au NCs are developed.³⁵ Therefore, the fast nucleation might be due to the fact that Au atoms are nearly all surface atoms and have high surface energy for AuCl₄⁻ complex clusters with n ≤ 7. However, the growth kinetics could in principle be slowed by the steric hindrance of the ligands such as PVP.³¹,³² For the larger ‘AuCl₄’ clusters with Cl⁻ ions surrounding on the surface, which are further stabilized by the capping agent of citric acid together with the PVP protection, the proportion of active sites located at the surface is decreased. Hence, the transition to 3D structure and then the formation of fcc Au NCs occurring at the beginning of stage II lead to the slow growth as witnessed

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Figure 4. A schematic representation of the formation process of Au NCs. The ruleless line represents the surfactant. At first, the \text{AuCl}_{3}^{-} ions are dispersed in the colloidal solution. Then, the dimers and trimers are formed which can be classified into the stage I. For the small Au clusters in the stage II, the representative \text{Au}_{5} cluster is shown. Finally, the large Au NCs are produced (stage III).

by the ‘plateau’ in Figure 3d. Finally, the larger Au NCs with stable size were produced. The significant accelerating of growth rate (stage III) after the accumulatively mild reaction may be attributed to the coalescence of individual particles. Considering that the nuclei serve as the foundation for the NCs growth, the \text{‘Au}_{n}\text{Cl}_{m+1}^{\text{−}}\text{’ clustering structure proposed here plays an important role in directing the later growth. Controlling the initially formed complex clusters may provide an effective mean to obtain the shape-controllable nanocrystals.}

Conclusions

Using continuous-flow \textit{in situ} XAFS spectroscopy, we have determined the initial nucleation kinetics of Au NCs reduced from the \text{AuCl}_{3}^{-} in the aqueous solution. The analysis of XAFS indicates that, in the moderate reaction condition, the partially reduced \text{AuCl}_{3}^{-} ions would be combined through the slightly elongated Au−Au bond to form the \text{Au}_{n}\text{Cl}_{m+1}^{\text{−}} complex clusters rather than to form \text{Au}_{n}^{0} clusters. These complex clusters play an important role in delaying the following growth and inducing the eventual coalescence. These findings enrich our understanding of the nucleation process of nanocluster formation, and the \textit{in situ} XAFS spectroscopic method could be broadly applicable to the study of the kinetics of chemical liquid phase syntheses of other transition-metal NCs. Furthermore, since the nucleation process has scientific importance in directing the nanocrystal formation, it is expected that the understanding of the nucleation mechanism can guide the way toward the design and synthesis of nanomaterials in a controllable manner.

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Supporting Information Available: Additional details on the procedures of nanomaterials synthesis as well as the measurements of TEM, UV−vis, and XAFS. Supporting results mentioned in the text, including Figures S1−S3. This material is available free of charge via the Internet at http://pubs.acs.org.

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Mesosctructured Assemblies of Ultrathin Superlong Tellurium Nanowires and Their Photoconductivity

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Abstract: Well-defined periodic mesostructures of hydrophilic ultrathin Te nanowires with aspect ratios of at least 106 can be produced by the Langmuir—Blodgett technique without any extra hydrophobic pretreatment or functionalization. Packing the arrayed nanowire monolayers will allow construction of nanomesh-like mesostructures or more complex multilayered structures composed of ultrathin nanowires on a planar substrate. The well-organized monolayer of Te nanowires with periodic mesostructures can be readily used as a stamp to transfer such mesostructured nanopatterns to other substrates or can be embedded within a polymer matrix. The mesostructures of ultrathin Te nanowire films show reversibly switched photoelectric properties between the lower- and higher-conductivity states when the light is off and on, and the photocurrent is influenced by the light intensity and the number of mesostructured nanowire monolayer films. This method can be extended for fabrication of other mesostructured assemblies of ultrathin nanowires or nanobelts.

1. Introduction

One-dimensional (1-D) nanostructures, such as nanotubes, nanobelts, nanowires, and especially ultrathin nanowires, have attracted explosive attention in nanoscience owing to their unique structures, interesting physical properties, and potential for novel applications. Some interesting phenomena will emerge after 1-D nanostructures are well assembled, which will open up many fundamental scientific opportunities, thereby further promoting related researches concerning collective magnetic, optical, and electronic properties, as well as their applications.

The Langmuir—Blodgett (LB) technique provides an attractive assembly strategy for its unique utilization in arranging numbers of nanostructures at the air—water interface. Up to now, soft LB technique has been used to prepare hard nanomaterials. in addition to nanoparticles and 2-D nanostructures, recently, 1-D stiff nanostructures such as Ag nanowires, BaCrO₄ nanorods, silicon nanowires, PbS nanowires, VO₂ nanowires, and Ge nanowires have been prepared. To our best knowledge, few studies have addressed the assembly of superlong, ultrathin, and flexible nanowires into periodic mesostructures. Despite a huge amount of experimental and theoretical work on self-assembly of nanomaterials, finding a suitable way for self-assembly of ultrathin, superlong, and flexible nanowires, which easily twist around each other, is still an ongoing challenge in the research field of nanotechnology. Herein, we report that the ultrathin nanowires with aspect ratios of at least 106 can be well aligned over a large area to form well-defined periodic mesostructures and their reversibly switched photoelectric properties. The hydrophilic Te nanowire—surfactant monolayers can be assembled by the Langmuir—Blodgett technique without any extra hydrophobic pre-treatment or functionalization after synthesis. Packing the arrayed nanowire monolayers makes it possible to construct nanomesh-like mesostructures or more complex multilayered...

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structures composed of ultrathin nanowires on a planar substrate. In addition, such uniform nanowire mesostructured patterns and their nanochannels can be easily transferred onto or embedded within an external substrate or polymer matrix.

2. Experimental Section

Synthesis of Te Nanowires. All chemicals are of analytical grade and used as received without further purification. The synthesis of uniform Te nanowires was described previously. In the typical synthesis, a 1.000 g poly(vinyl pyrrolidone) (PVP, Shanghai Reagent Company, M_{w} ≈ 40,000) and 0.0922 g of Na_{2}TeO_{3} were put into a 50 mL Teflon-lined stainless steel autoclave and dissolved in 33 mL of double distilled water under vigorous magnetic stirring for 5 min to form a homogeneous solution at room temperature. After that, 1.67 mL of hydrazine hydrate (85%, w/w %) and 1.33 mL of aqueous ammonia solution (25–28%, w/w %) were added into the mixed solution separately, under vigorous magnetic stirring for 10 min. The container was closed and maintained at 180 °C for 3 h. After that, the autoclave was cooled to room temperature naturally.

Synthesis of Ag_{x}Te Nanowires. In a typical synthesis, freshly prepared Te nanowires (0.1 mmol) from the previous experiment were precipitated with adding 21 mL of acetone and centrifuging at 3000 rpm for 5 min. The product obtained was washed by water and ethanol several times and dispersed in 20 mL of ethylene glycol (EG) with vigorous magnetic stirring at room temperature for 20 min. Then, 0.0060 g of AgNO_{3} (0.4 mmol) was added into the previous solution. The mixed solution was shaken at a rotation rate of 260 rpm in the dark using an Innova 40 benchtop incubator shaker at 60 °C for 13 h.

Synthesis of Pt Nanotubes. The synthesis of uniform Pt nanotubes was described previously by our group. In a typical synthesis, Te nanowires (0.05 mmol) synthesized from the above experiment were washed by water and ethanol several times and dispersed in 20 mL of ethylene glycol (EG) with vigorous magnetic stirring at room temperature for 20 min. Then, 1.19 mL of 77 mM H_{2}PtCl_{6} solution in EG was added into the previous solution. The mixed solution was shaken at a rotation rate of 260 rpm using an Innova 40 Benchtop Incubator Shaker at 60 °C for 13 h.

Assembly of Ultrathin Te Nanowires by Langmuir–Blodgett Technique. The monolayer was prepared at 25 °C using a Langmuir–Blodgett trough (Nima Technology, 312D). The trough was filled with Millipore Milli-Q water (resistivity 18.2 MΩ cm) and 3 cm brimmed just over the top by about 2 mm. Five milliliters of the mother liquor of Te nanowires was removed and precipitated by adding about 12 mL of acetone and centrifuging at 3000 rpm for 5 min. One milliliter of N,N-dimethylformamide (DMF) was added to disperse the Te nanowires to form a homogeneous solution at room temperature. After that, a mixture of 5 mL of DMF and 5 mL of chloroform were added into the homogeneous solution. Too much DMF will result in the precipitation of the as-prepared Te nanowires at the bottom of the LB trough, which impedes good dispersion of the nanowires on the air–water surface, whereas it will be difficult to obtain a homogeneous solution at the very beginning if the amount of CHCl_{3} used is too much. In this process, DMF is the main solvent of the as-prepared nanostuctures, such as Ag_{x}Te nanowires, Pt nanotubes.

Furthermore, the present strategy can be extended to assemble other ultrathin 1-D nanostuctures such as Ag_{x}Te nanowires, and Pt nanotubes. Te nanowires were dispersed from a 50 μL syringe drop by drop onto the water subphase. Tightly minutes later, the nanowires surface layer was then compressed slowly at 20 nm/min while the surface pressure was monitored with a Wilhelmy plate. The pressure and temperature were kept constant at least 10 h as soon as the fold formation that paralleled the barrier direction occurred (see Supporting Information, Figure S1E) The monolayer of the aligned nanowires was lifted at the pressure of 23 mN/m, and the deposition speed was maintained at 4 nm/min. The same process was repeated, and we can get more than one layer. The trough was cleaned before and after each experiment. The trough surface and barrier were then wiped with ethanol and CHCl_{3} by tapon for several times, ensuring that there is no dust or contaminants left.

PMMA Imprinting by Te Nanowire Stamp. First, poly(methyl methacrylate) (PMMA, Sigma-Aldrich, M_{w} ≈ 120,000) was dissolved in the DMF forming a 3% (w/w) solution. A 500 μL PMMA solution was dropped on the surface of the glass slide and then spin-coating proceeded at rates of 300 rpm for 30 s, and 2500 rpm for 45 s, respectively. After 8 min, the Te nanowire monolayer stamp was put onto the PMMA-coated glass slide and a moderate pressure was applied to it by a small binder clip. The stamp was pulled away from the PMMA-coated glass slide substrate rapidly, once heating was finished at 100 °C in an oven for 1 h and the slides cooled to room temperature naturally. The nanowire film glass slide was vertically separated from the PMMA-coated glass slide rapidly by hands.

Characterization. The Small-angle X-ray diffraction patterns (SAXRD) were measured on a Philips X’Pert Pro Super X-ray diffractometer equipped with graphite-monochromatized Cu Kα radiation. High-resolution transmission electron microscopy (HR-TEM) images were performed on a JEOL-2010 transmission electron microscope operated at an acceleration voltage of 200 kV. The energy-dispersive X-ray spectroscopy (EDS) analysis was also done with a JEOL-2010 TEM with an Oxford windowless Si (Li) detector equipped with a four-pulse processor. Field-emission scanning electron microscopy (FESEM) was carried out with a field-emission scanning electron microscope analyzer (Zeiss Supra 40 scanning electron microscope at an acceleration voltage of 5 kV). X-ray photoelectron spectra (XPS) were recorded on an ESCALAB MKII X-ray photoelectron spectrometer, using Mg Kα radiation as the exciting source. Raman scattering spectra were recorded with a Renishaw System 2000 spectrometer using the 514 nm line of Ar+ for excitation. An Innova 40 Benchtop Incubator Shaker was used for the chemical transformation reactions. The Te nanostuctures were prepared using a Langmuir–Blodgett trough (Nima Technology, 312D). FTIR spectra were measured on a Bruker Vector-22 FT-IR spectrometer from 4000 to 400 cm^{-1} at room temperature. Photoelectric properties of Te nanowire nanodevices were investigated with Micromanipulator 61500 probe station and Keithley 4200 SCS in a clean and metallic shielded box at room temperature in air. A SPA 300HV microscope (Seiko Instruments, Inc.) was used for AFM measurements.

3. Results and Discussion

In the present case, the area of the arrayed nanowires can reach up to approximately 100 squaremicrometers (see Supporting Information, Figure S2). The aligned hydrophilic Te nanowires have a diameter of 4–9 nm and aspect ratio of at least 10^4 without any extra hydrophobic pretreatment or functionalization after synthesis. First, the nanowires suspended in a mixture solvent made of N,N-dimethylformamide (DMF) and CHCl_{3} were randomly distributed and entwined each other. Second, after the evaporation of mixed solvent, some ordered islands consisted of parallel nanowires are observed randomly oriented at the air/water interface. Due to the action of the interfacial tension, the
interfacial nanowires shrank to form a close-packed structure\(^{19}\) and became highly arrayed after an increase in the surface pressure that should be adjusted for more than 10 h.

Figure 1A shows the surface pressure versus surface area (\(\pi-A\)) isotherm of the monolayer of Te nanowires. Figure 1B shows its corresponding TEM images of the Te nanowires collected during different stages. At the initial stage (I), the pressure is practically unaffected by the barrier movement. The nanowire units approach each other at small areas because of the capillary force and van der Walls attraction. At the second stage (II), an increase in the surface pressure is observed with a decrease in the trough area, indicating the formation of a condensed Te nanowire monolayer. At the last stage (III), the pressure remained constant when the areas decreased, which was a stage wherein the loosely arranged nanowires became tighter. The pressure rose steeply from 0 mN/m (II) to 23 mN/m (III) with a decreasing slope (Figure 1A). The slope of \(\pi-A\) isotherms directly reflects the change rate of surface pressure and indirectly reflects the behavior among the nanowires. Figure 1B shows the TEM images of a series of samples obtained after adjusting for 10 h at different surface pressures. 0, 8.5, 19.5, and 23 mN/m, respectively. Compressed uniaxially, the nanowires were arrayed with their long axis parallel to the barrier irreversibly. The best arrangement can be achieved after duration for 10 h at the surface pressure of 23 mN/m, and once this value is exceeded, the arrayed monolayer will be essentially broken into some fold that parallels the barrier direction. The corresponding TEM images after fold formation for 1, 3, 5, and 9 h, respectively, are shown in Figure S1 (Supporting Information).

With the time prolonging, the ordering of the monolayer increases, which is the result of the decrease in entropy. From the data above, it is necessary to obtain a high-quality Te nanowire monolayer after waiting for at least 10 h. Figure S3 in Supporting Information shows the atomic force microscopic (AFM) topography of the Te nanowire monolayer. The compressed layer can be transferred directly to a variety of substrates (glass, quartz, silicon, polymer surfaces, etc.) by LB deposition to yield large-scale parallel nanowires. Owing to the long and flexible characteristics of Te nanowires, there are crooked and parallel Te nanowire assemblies somewhere on the substrate (see Supporting Information, Figure S4). The building blocks can be confirmed to be Te nanowires on the basis of the analysis of selected areas of the electron diffraction pattern (SAED) (inset in Figure 2B), high-resolution transmission electron microscopy (HRTEM) image (Figure 2C), X-ray photoelectron spectra (XPS), and X-ray spectroscopy (EDS) (Figure 3).

Figure 2. (A, B) Transmission electron microscopy (TEM) images of the monolayer assembly of Te nanowires at different magnification. (B, inset) Corresponding SAED pattern taken of the nanowire arrays. The electron beam was focused along [010] axis; (C) High-resolution transmission electron microscopy (HRTEM) image of the aligned Te nanowires; (D) SAED pattern measured on the monolayer of aligned Te nanowires. The 2θ angle of 1.44° corresponds to a d value of 7.16 nm.

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Figure 3. XPS spectra for the well-aligned Te nanowire monolayers prepared freshly. (A) Survey of the sample. Te 4d, 4p, 4s, 3d_{5/2}, 3d_{3/2}, 3p_{1/2}, 3p_{3/2}, according to the binding energy of 41, 111, 170, 573, 583, 820, 871 eV, respectively. (B) Survey of the Te 3d region. (C) EDS spectrum of the Te nanowires monolayer, confirming that the sample is composed of pure Te (the detected copper and carbon signals arise from the carbon-coated copper grid on which the tellurium samples were deposited).

Direction, the nanowire was structurally uniform, and no dislocation was detected in the examined area. As shown in Figure 2C, the nanowires rest on the nanowire after alignment, with an average diameter of 7 nm and a pitch of 10 nm. Figure 2D shows that Te nanowires are transferred from the air/water surface to a glass slide for small-angle X-ray diffraction pattern (SAXRD) measurement. Only one strong reflection peak located at 2θ ≈ 1.4° is detected, corresponding to a d value of 7.16 nm. Referring to the TEM images, the period of the Te nanowire monolayer is 7.16 nm. TEM images give intuitive periodic information, while the electron diffraction displays the indirect periodic information of the structures. Obviously, such a periodicity is varied with the diameters of the Te nanowires. In addition, multilayers of Te nanowires also show small-angle X-ray diffraction (see Supporting Information, Figure S5). From two to fifteen layers, there is no significant variability with increasing the number of layers, indicating the quality of Te nanowire films is still kept well.

Panels A and B of Figure 3 show the XPS spectra of the freshly prepared monolayer of Te nanowires, and the peak values at 284.85 and 532.05 eV can be readily assigned to the binding energies of C1s and O1s, respectively. The Te 3d peak shift displayed two strong peaks at 572.7 and 583.1 eV, corresponding to the binding energy of Te 3d_{5/2} and Te 3d_{3/2} for elemental tellurium. Energy dispersive spectrum (EDS) was measured on the Te nanowires monolayer (Figure 3C), indicating that the samples are composed of pure Te (the detected copper and carbon signals arise from the carbon-coated copper grid on which the tellurium samples were deposited).

The formation of regular mesh-like mesostructures of the order of several nanometers, the so-called nanomeshes, has recently attracted intensive attention. Commonly, nanomeshes can be obtained with a high temperature and a special substrate surface. To overcome high costs and complex processes, we introduce the LB technique to fabricate two layers of periodic thin film of Te nanowires on a planar substrate which resembles a nanomesh. A schematic illustration of transferring of two layers of aligned nanowires into mesh-like structures with designed crossing angles was illustrated in Figure S6 (Supporting Information). The TEM images in Figure 4 show that the Te nanowires can be tailored into nanomesh-like crossed patterns with a tunable crossing angle. The compressed monolayer in the air/water surface was then transferred directly to a planar substrate to yield a Te nanowire monolayer. After transferring the monolayer, holding 300 s, a crossed structure of two layers can be obtained by turning an angle during deposition (Figure 4). While without turning the angle, it will result in the formation of parallel nanowire layers with the same axial direction (see Supporting Information, Figure S7). Different turning angles can result in the formation of two-layer nanowire nanopatterns with different crossed angles, for example, 45°, 60°, 65°, 70°, 85°, respectively, as shown in Figure 4A–E (see Supporting Information, Figure S8). The fast Fourier transform of the mesostructures shows diffuse streaks corresponding to crossed angles made by two layers of Te nanowires, revealing that the crossed angles between two nanowires layers increase with increasing the turning angle (Figure 4A–E, and see Supporting Information Figure S8).

The present method can be extended to assemble other ultradimensional nanowires or nanotubes into mesostructured assemblies as demonstrated by replacing Te nanowires with Ag–Te nanowires and Pt nanotubes (Figure 5). Panels A and B of Figure 5 show that the Ag–Te nanowires with a diameter of 10 nm can also be self-assembled into an ordered mesostructured monolayer. Packing a second monolayer of Ag–Te nanowires onto the first layer perpendicularly will result in the formation of crossed Ag–Te nanowire film mesostructures (C and D of Figure 5). The phase, composition, and morphology of Ag–Te nanowires were confirmed by SEM, XRD, XPS, HRTEM, and TEM (see Supporting Information, Figure S9). Further extended experiments demonstrated that this method can be used for alignment of Pt nanotubes also (Figure 5E–H).

Well-ordered two-dimensional functional nanostructure arrays have a broad range of potential applications. Here, we demonstrate a simple pattern-transfer method to convey nanochannels made of Te nanowires to a polymethylmethacrylate (PMMA) substrate. Figure 6A illustrates the process for creating a Te nanowire monolayer stamp in order to fabricate mesostructured nanopatterns. Glass slides were cleaned by ultrasonic wave in acetone for 10 min and rinsed with Milli-Q water. A Te monolayer on a glass slide was used as a stamp for nanomesh printing. A PMMA coated glass slide was obtained by spin-coating. After 8 min, the Te nanowire monolayer stamp was put onto the PMMA coated glass slide and suitable pressure was applied on it. The stamp was pulled away from the PMMA coated glass slides substrate rapidly when finishing heating it at 100 °C for 1 h and cooling to room temperature naturally. The XRD experiments were performed to obtain diffraction


Figure 4. TEM images of the nanonmesh-like assemblies formed by packing two layers of Te nanowire films with different crossed angles. (A–E) Crossed Te nanowire layers can be formed by uniformly transferring a second layer of aligned parallel Te nanowires perpendicular to the first layer and turning the angle between two monolayers of nanowires. The insets of (A–E) show the fast Fourier transform of the TEM images, and the simulation plot for the assembled mesostructures of the nanowires. (F) High resolution TEM images of crossed Te nanowires with high magnification.

Figure 6. (A–D) TEM images of Ag₃Te assembly. (E–G) TEM images of assembled Pt nanotubes. (A, B) TEM images of monolayers of Ag₃Te nanowires with different magnification; (C, D) crossed layers of Ag₃Te nanowires are formed by uniformly transferring a second layer of aligned parallel Ag₃Te nanowires perpendicular to the first layer with different magnification; (H–I) TEM images of a monolayer of Pt nanotubes with different magnification; (II) SADP pattern taken on the Pt nanotubes shown in (G).

Information on these nanopatterns. Figure 6B, C show the SAXRD patterns of Te nanowire monolayer before and after imprinting. It is found that there is no obvious change, which illuminates the mesostructures of the Te nanowire monolayer had been kept well. Figure 6D shows the SAXRD patterns of PMMA film after being detached, and the channel is 6.7 nm, which is slightly bigger than 6.3 nm of the Te nanowire monolayer in Figure 6B. C. The XPS spectrum in Figure 7A shows that no Te elements were detected on the PMMA film formed on the glass substrate after imprinting with the mesostructure stamp of Te nanowire monolayer. The FTIR spectra in Figure 7B show that the PMMA films formed on the glass substrate before (black line) and after (red line) imprinting display features similar to those of pure PMMA. The 20-layer Te nanowires with the same axial direction can be fabricated through parallel assembly of Te nanowire mono-
layers on a Si/SiO$_2$ (SiO$_2$ layer with a thickness of 500 nm) substrate by LB technique, and a type of nanodevice with reversible photoelectric properties can be constructed. Then, Au electrodes were thermally evaporated via laying a micrometer-sized Au wire on the nanowires as the mask to obtain a gap between two electrodes. The Te nanowires were vertical to the electrodes (see Supporting Information, Figure S10A). Photoelectric properties of the Te nanowire nanodevice were investigated with the Micromanipulator 6150 probe station and Keithley 4200 SCS in a clean and metallic shielded box at room temperature in air. The current–voltage ($I$–$V$) curves measured on a Te nanowire films in the dark and white light illumination of different light intensities are shown in Figure 6A and B. The $I$–$V$ curves exhibit linear behavior, confirming the ohmic contact feature. The electrical resistance of the nanowire films decreased when the light was turned on from the dark which was similar to other phtoconduction materials.$^{20}$ It is obvious that the current of the devices increases significantly with the light intensity increasing. It was highly insulating in the dark with a resistivity about 9.2 kΩ (Figure 8A). When the light intensity increased from dark to 0.37, 3.04, 5.76 mW/cm$^2$, the electrical resistance decreased, respectively, from 9.2 to 8.4, 5.9, 4.7 kΩ (Figure 8B). Moreover, the current of the device increased linearly with increasing illumination power (inset of Figure 8B, at bias 1 V), indicating the sensitivity of the devices to light. The resistance $R$ of the materials of uniform cross section can be calculated:$^{24}$

$$R = \frac{\rho L}{A}$$

where, $L$ is the length of the materials, $A$ is the cross-sectional area, and $\rho$ is the electrical resistivity (also called specific electrical resistance) of a material. Compared to the work by Wang et al.$^{25}$ the diameter of the nanowires we used is smaller and the length is much longer. According to the formula above, the resistance of the as-prepared device is thought to be larger. However, the resistance of this nanowire device is 3 orders of magnitude smaller. The reason for this could be a result of the


$^{24}$ For practical reasons, any connection to real materials will almost certainly mean the current density is not totally uniform. However, this formula still provides a good approximation for long thin wires.

nanowires used here being arrayed in parallel with the film device containing no polyelectrolyte or polymer as used previously. Figure 8C shows a reversible switching of a Te nanowire device between low and high conductivity states when the lamp was turned on and off. The bias on the nanowires was 1 V, and the light intensity was 5.76 mW/cm². After test cycles, the switch ratio remained 1.6, the same as it was at the beginning, which is a little higher than that reported previously. The device fabricated using ordered Te nanowires as building blocks shows a weak but detectable response to light; the further optimization of the devices is ongoing.

In order to investigate the photoswitching characteristics of the Te nanowire films in detail, a series of devices composed of different numbers of Te monolayers were fabricated, for example, monolayer, three layers, and five layers, respectively. From Figure 8D to Figure 8F, we can see that even monolayer device gives an obvious response to the white light. With increasing the number of layers from monolayer to 20 layers, the current of the device increased. From monolayer to 20 layers, the electrical resistance decreased rapidly from 1.6 MΩ to 4.7 kΩ. From Figure 8E and Figure S10B (Supporting Information), the photocurrent gradually weakened as the time was prolonged. Negative photoconductivity (PC) has been studied recently. Usually, the negative PC is attributed to two-center recombination effect or caused by hole-photomission. The Te nanowire films achieved on the substrate are rather stable in the air in contrast to the poor stability of the Te nanowires dispersed in a solution, which still exhibit sensitivity to light even after three months (see Supporting Information, Figure S10).

4. Conclusions

In summary, we demonstrate that large-area, well-defined, periodic mesostructures of hydrophilic ultrathin Te nanowires with aspect ratios of at least 10⁴ can be produced by Langmuir–Blodgett technique without any extra hydrophobic pretreatment or functionalization. The mesostructures of ultrathin Te nanowire films show reversibly switched phototronic properties, and the photocurrent is influenced by the light intensity and the number of mesostructured nanowire monolayers. The successful alignment of ultrathin Te nanowire mesostructures by this approach will make possible producing other hierarchical nanopatterns by combination with other techniques such as photolithography etching or depositing techniques, which can find applications such as in light detectors and switching devices for optoelectronic devices. In addition, such well-organized Te nanowire monolayers with periodic mesostructures can be readily used as stamps to transfer such nanopatterns to other substrates or can be embedded within polymer matrices. Further substitution of different nanowires and changes in structural hierarchy in different assemblies will provide us flexible and promising strategies for the fabrication of other integrated, hierarchical, and periodic nanostructures with special functionalities and multifunctionalities.

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International Science & Technology Cooperation Program of China (2010DFA41170), the National Natural Science Foundation of China (No. 50712006), and the Principle Investigator Award by the National Synchrotron Radiation Laboratory at the University of Science and Technology of China. We are grateful for the help with photoconductive measurement from Professor Wenping Hu and Dr. Koning Li from the Institute of Chemistry, Chinese Academy of Sciences. We are grateful for the help with AFM measurement from Professor Xiaoping Wang in Hefei National Laboratory for Physical Sciences at Microscale, University of Science and Technology of China.

Supporting Information Available: TEM, HRTEM, SEM, AFM images, \( \pi-\alpha \) isotherms of the Te nanowire monolayer, photograph of a substrate being pulled vertically through a Langmuir monolayer of Te nanowires, small-angle X-ray diffraction patterns, illustration of the steps for the assembly of Te nanowire film mesostructures, and reversible switching photoconducting property of a Te nanowire films with five layers measured after three months. This material is available free of charge via the Internet at http://pubs.acs.org.

JA910871S
Recently, Pd-catalyzed chelation-directed C–H activation/cross-coupling reactions have emerged as a promising set of synthetic reactions.\(^1\) Nitrogen-containing directing groups such as amidates,\(^2\) N-heterocycles,\(^3\) imines,\(^4\) pyridine N-oxides,\(^5\) and amines\(^6\) are commonly used in these reactions, but the need for such groups restricts the general applicability and atom economy. Expanding the scope to include other types of substrates remains a critical challenge.\(^7\) Here we describe a practical Pd(II)-catalyzed ortho C–H arylation reaction of phenol esters under mild conditions. This reaction provides an example of acetyloxy-directed Pd insertion into C–H bonds and a useful strategy for preparing 2-arylphenol derivatives. In comparison with the classical nitrogen-containing group-directed cycloaddition,\(^8\) Pd(II) insertion into C–H bonds promoted by oxygen-only groups coordinating to the Pd remains rare. Recent studies\(^9\) have shown that hydroxyl and carboxyl groups can be used as directing groups in Pd catalysis.\(^9\) Nonetheless, a catalytic ortho arylation of phenol esters is still elusive.\(^9\)

Our study began by attempting to synthesize a palladacycle of phenol ester. Related palladacycles of aromatic amidates were made many years ago,\(^10,11\) but there has not been any example of cycloaddition mediated by an acetyloxy group. As expected, our initial experiments with various phenol esters and Pd(II) salts failed to produce any stable complex. After extensive tests, we discovered that a crystalline compound (2a) could be obtained when 1a reacted with 1 eq. of PhCHOAc in dichloroethane (DCE). X-ray analysis revealed that 2a is the first example of acetyloxy-directed Pd insertion into C–H bonds (eq 1).\(^1\) This indicates that the presence of HOTI to tune the electrophilicity of Pd(II) may constitute a simple but useful strategy to improve Pd-catalyzed C–H activation reactions. In addition, we successfully isolated the related 2-(phenylacetyl)benzyl palladacycle 2b, as characterized by \(^1\)H, \(^13\)C, and \(^31\)P NMR spectroscopy (see the Supporting Information SI).

It was next found that 2a and 2b can react stoichiometrically with PhOTI\(^{12,13}\) to produce the ortho-arylated phenol esters 3a and 3b. However, when 2a was used as a catalyst in the reaction between 2a and PhOTI\(^{14}\), we could obtain a turnover number (TON) of only 1.3 (eq 2). Only after 1 eq of HOAc was added to the reaction mixture did the TON increase to 5.4. This observation indicates that HOAc is important either for the C–H deprotonation step or for stabilizing some active Pd intermediates.

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Replacing Pd(OAc)₂ with Pd(OPiv), (OPiv = BuCO₂) further improved the yield (Table 1, footnote b). Under the Pd(OPiv)/ H₂Ts/PivO conditions, ortho arylation occurred smoothly with phenol esters carrying various substituents (Table 2). Importantly, the isocho, bromo, and chloro substituents (4e–h) were tolerated, making possible additional modification reactions at the halogenated positions. For substrates containing strong electron-withdrawing groups (4f, 4h), the corresponding dimethylcarbamates were used because their esters are relatively unstable. Even so, the ortho-arylated products were already hydrolyzed into phenols during the reaction. Notably, the selectivity of mono- versus diarylation could be controlled by tuning the reaction temperature and reagent ratio (4a vs 4e). Moreover, the scope of the reaction with respect to the arylation reagent is presented in Table 3. Both electron-rich and electron-deficient phenyl groups could be incorporated into the phenol esters. However, ortho substituents on the arylation reagents reduced the coupling yields significantly.

Table 3. Reaction Scope with Respect to the Arylation Reagent

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8a-4-Cl</td>
<td>Me</td>
</tr>
<tr>
<td>8a-4-Me</td>
<td>Me</td>
</tr>
<tr>
<td>8a-4-CO₂Et</td>
<td>Me</td>
</tr>
<tr>
<td>8a-3-Cl</td>
<td>Me</td>
</tr>
<tr>
<td>8a-3-F</td>
<td>Me</td>
</tr>
<tr>
<td>8a-2-F</td>
<td>Me</td>
</tr>
<tr>
<td>8a-2-Me</td>
<td>Me</td>
</tr>
</tbody>
</table>

Further examination of the utility of the reaction for the synthesis of useful organic intermediates was conducted. Equation 3 describes a more efficient synthesis of hydroxyphenyl inhibitors of EGFR-stimulated cellular proliferation, and eq 4 describes a new and practical method for 3,3′-bisarylation of BINOL. HPLC analysis indicated that the purity of BINOL is fully maintained during the transformations. The resulting 3,3′-bisarylated BINOLs provide key intermediates in the development of ligands for transition-metal-catalyzed asymmetric synthesis. In comparison with previous approaches for the synthesis of these phenol derivatives, the key advantage of the new method is that the transformation is not sensitive to moisture or air and does not require flammable reagents such as BuLi.

Scheme 1. Proposed Mechanism

The mechanism of the arylation reaction most likely involves an acryloyl-directed Pd insertion into the C–H bond and subsequent oxidation of the Pd(II) complex to a Pd(IV) intermediate by Ar,OH.
Theoretical Analysis of Factors Controlling Pd-Catalyzed Decarboxylative Coupling of Carboxylic Acids with Olefins

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Abstract: Transition-metal-catalyzed decarboxylative coupling presents a new and important direction in synthetic chemistry. Mechanistic studies on decarboxylative coupling not only improve the understanding of the newly discovered transformations, but also may have valuable implications for the development of more effective catalyst systems. In this work, a comprehensive theoretical study was conducted on the mechanism of Myers’ Pd-catalyzed decarboxylative Heck reaction. The catalytic cycle was found to comprise four steps: decarboxylation, olefin insertion, β-hydride elimination, and catalyst regeneration. Decarboxylation was the rate-limiting step, and it proceeded through a dissociative pathway in which Pd(II) mediated the extrusion of CO2 from an aromatic carboxylic acid to form a Pd(II)–aryl intermediate. Further analysis was conducted on the factors that might control the efficiency of Myers’ decarboxylative Heck reaction. These factors included Pd salts, ligands, acid substrates, and metals. (1) Regarding Pd salts, PdCl2 and PdBr2 were worse catalysts than Pd(TFA)2 because the exchange of Cl or Br by a carboxylate from Pd was thermodynamically unfavorable. (2) Regarding ligands, DMSO provided the best compromise between carboxylic exchange and decarboxylation. Phosphines and N-heterocarbenes disfavored decarboxylation because of their electron richness, whereas pyridine ligands disfavored carboxyl exchange. (3) Regarding acid substrate, a good correlation was observed between the energy barrier of R—COOH decarboxylation and the R–H acidity. Substituted benzoic acids showed deviation from the correlation because of the involvement of (substituent)→(COOH) interaction. (4) Regarding metals, Ni and Pt were worse catalysts than Pd because of the less favorable carboxyl exchange and/or DMSO removal steps in Ni and Pt catalysis.

1. Introduction

Transition-metal-catalyzed decarboxylative cross-coupling using carboxylic acids as aryl sources has received considerable attention recently.1 Compared to conventional catalytic couplings2 where expensive unstable organometallic reagents are often required, decarboxylative coupling utilizes readily available and stable carboxylic acids as substrates, thus precluding the need for preparation of sensitive organometallic reagents. An additional advantage is that decarboxylative coupling generates CO2 without producing toxic metal halides.

Pioneering work by Nilsson showed that stoichiometric Cu promoted decarboxylative coupling of aromatic acids with ArZ.3 Cohen et al. found that with phenantrhileine ligand Cu(I) could mediate decarboxylation of aromatic acids, producing aryl–Cu(I) that could be protonated to yield aryl.4 Recently, Guosenn et al. discovered elegant protocols for the decarboxylative coupling of benzoic acids with ArBr via a Cu/Pd bimetallic catalysis.5 Cu was used for decarboxylation to produce aryl–Cu. It transmetalates with aryl–Pd(II) generated from oxidative addition of ArBr to Pd(0), ending up with a bis-arylated Pd(II) species. Finally, reductive elimination gives the biaryl product. Guosenn’s reaction has been nicely extended to ArCO2H and ArOTf6 as the electrophiles. Moreover, α-oxo carboxylates could be transformed under the bimetalic catalysis to give aryl ketones through decarboxylative coupling.6

In addition to Cu, Pd by itself can also promote decarboxylative coupling. In 2002, Myers et al. discovered an interesting Heck-type reaction between aromatic acids and olefins catalyzed by Pd(TFA)2 (TFA = CF3CO2H) (eq 1).7 Kinetic analysis indicated that decarboxylation was the rate-limiting step of the

References:

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2. Tsinghua University.
catalytic cycle. The proposed aryl-Pd(II) intermediate from decarbonylation was captured and characterized by NMR and X-ray methods. This aryl-Pd(II) intermediate could undergo a facile, stoichiometric reaction with an olefin to yield the coupling product. On the basis of the results, a mechanism (Scheme 1) was proposed in which initial rate-limiting decarbonylation was followed by classical mechanistic steps of Heck reactions, i.e., olefin insertion, β-hydride elimination, and catalyst regeneration.

(1)

After Myers’ pioneering work, Forgione et al. reported Pd-catalyzed decarbonylation of heteroaromatic carboxylic acids with ArBr. Lee et al. reported Pd-catalyzed decarbonylation of alkylcarboxylic acids with ArBr. Becht et al. reported Pd-catalyzed decarbonylation of benzene acids with Ar3IOTf. Wu and Crabtree11 groups reported Pd-catalyzed decarbonylation coupling of cinnamaldehyde and benzene acids with ArCl. In related studies, Tunge et al. developed novel methods for the substitution of allylic terminus via Pd-catalyzed intramolecular decarbonylation reaction of allyl carboxylic esters. Our own work in this area was the discovery of novel Pd(II)-catalyzed synthesis of aromatic esters through decarbonylation coupling of oxalate monoesters with aryl halides.

Despite the remarkable advances and great contemporary interest in catalytic decarbonylation couplings, many mechanistic details of the decarbonylation process remain ambiguous. As to Cu-based systems, Goosen et al. recently performed DFT calculations to analyze Cu([phenanthroline]-mediated decarbonylation of benzoic acids. On the other hand, almost no theoretical study has been conducted to understand the mechanistic details of Pd-catalyzed decarbonylation coupling. Only Myers’ study provided some spectroscopic and crystallographic evidence for some intermediates in the proposed process. Even so, the structural and energetic details about how these intermediates transform to each other remain largely unknown.

Here we report a thorough theoretical study on Pd-catalyzed decarbonylation couplings. Because Myers’ decarbonylation Heck-type coupling stands for the best experimentally characterized system to date, we choose to focus on this particular reaction so that the calculation results can be compared to the experiment. Through the study we have obtained detailed structural and energetic information about each step of the decarbonylation coupling. More importantly, through systematic analysis of the catalysts, substrates, and ligands, the study sheds important insights into the various factors controlling the activation barrier of the decarbonylation process. These results may have valuable implications for the development of new, more effective catalyst systems for decarbonylation couplings.

2. Methods

All calculations were performed with Gaussian 03. The 6-311G(d) basis set (i.e., LanL2dz for Ni, Pd, or Pt and 6-31G(d) for the other elements). Frequency analysis was conducted at the same level of theory to verify the stationary points to be real minima or saddle points and to get the thermodynamic energy corrections. For each saddle point, the intrinsic reaction coordinate (IRC) analysis was carried out to confirm that it connected the correct reactant and product on the potential energy surface. Natural population analysis (NPA) was performed also at the same level of theory. Single-point energy calculations were performed on the stationary points by using a larger basis set, i.e., SDD for Ni, Pd, or Pt and 6-311+G(d,p) for the other elements. Solvent effect (solvant = DMF) was calculated by using self-consistent reaction field method with PCM solvent model and UAHP radii. Single-point energies corrected by Gibbs free energy corrections and solvation energies were used to describe the reaction energies throughout the study.

3. Catalytic Cycle of the Myers Reaction

The catalytic cycle of the model reaction between benzoic acid and styrene (eq 2) is proposed on the basis of Myers’ study and the established mechanism for Pd-catalyzed Heck reaction (Scheme 2). There are four steps in the cycle: decarboxylation (CP0 → CP3), olefin insertion (CP4 → CP5), β-hydride elimination (CP6 → CP5), and catalyst regeneration (CP8 → CP0).

\[
\text{PhCO}_2\text{H} + \text{Ph} \xrightarrow{\text{Pd(TFA)2}} \text{PhCF}_2\text{CO}_2\text{Ph} + \text{CO}_2
\]

(2)

3.1. Decarboxylation. Decarboxylation starts with trans-(DMSO)\textsubscript{2}Pd(TFA)\textsubscript{2} (CP0). This complex has three possible isomers depending on how the DMSO molecules are bound to Pd. Our calculations (in DMP) indicate that the cis-S-bound isomer (CP0-cis) is the least stable (+8.4 kcal/mol), whereas CP0-trans (mono-O-bound) and CP0-oct (O-bound) are nearly isoenergetic. Thus, dynamic exchange between S- and O-bound forms must be considered at every stage of the decarboxylation coupling process. Furthermore, trans-(DMSO)\textsubscript{2}Pd(TFA)\textsubscript{2} is found to be much more stable than its cis isomer by 3.4 kcal/mol. Note that the crystal structure of (DMSO)\textsubscript{2}Pd(TFA)\textsubscript{2} also corresponds to the trans isomer but it exists as the CP0-oct isomer. The slight difference between the crystal and computational structures may be attributed to the crystal packing force.

CP0 undergoes carboxyl exchange with benzoic acid, producing intermediate CP1. The free energy change of this step is calculated to be +3.7 kcal/mol. Note that for CP1 the bis-O-bound isomer (i.e., CP1-oct) is again the most stable (Figure 1). From CP1-oct (note that in the following discussion we will only mention the most stable isomer), either the associative or dissociative pathway can take place for the expulsion of CO2. Both possibilities are examined as follows (Scheme 3).

Associative Pathway. In this pathway the two DMSO ligands remain attached to Pd during decarboxylation. Transition state TS\textsubscript{trans-oct} is successfully located in which the two DMSO are both O-bound (Figure 1). The energy barrier for this step is +41.2 kcal/mol as calculated from CP0-oct. In TS\textsubscript{trans-oct}, the C\textsubscript{aryl} atom of the phenyl ring, an O atom of the leaving CO2, the O atom of one DMSO, and an O atom of TFA form the coordination plane (Figure 1). Our calculation indicates that it is energetically more favorable for DMSO instead of TFA to occupy the trans position of C\textsubscript{aryl}. The immediate product after CO2 removal is a four-coordinated Pd complex (PD\textsubscript{trans-oct}) with two DMSO's cis to each other. PD\textsubscript{trans-oct} is expected to transform to its more stable trans-isomer PD\textsubscript{trans-cis}.


(30) Zietkiewicz, W.; Privalov, T. Organometallics 2006, 25, 6519.
Figure 1. Key intermediates and transition states in associative and dissociative decarboxylation pathway.

Scheme 3. Associative and Dissociative Pathway for Decarboxylation*

* Values in parentheses are relative Gibbs free energies in DMSO (kcal/mol).

indicate that \( \text{PD}_{\text{trans}} \) is more stable than \( \text{PD}_{\text{trans}} \) by 1.8 kcal/mol in DMSO.

Dissociative Pathway. In this pathway only one DMSO remains attached to Pd during decarboxylation. To do so, CP1-oo releases one DMSO, whose left position is immediately occupied by the phenyl ring of PhCO2H through a \( \eta^1 \) binding mode. This process produces an active intermediate CP2-oo and its isomer CP2-o (Scheme 3). Both CP2-o and CP2-o can extrude CO2 through transition state TS1-o or TS1-o. The structural difference between TS1-o and TS1-o is whether the C\( \eta^1 \) atom is trans or cis to DMSO (Figure 1). Our calculation shows that TS1-o is less stable than TS1-o by 1.8 kcal/mol in DMSO. Therefore, dissociative decarboxylation should proceed through TS1-o. It is interesting to note that, in TS1-o, four atoms (i.e., Pd, C\( \eta^1 \), C2, and O2) stay in the same plane that is perpendicular to the phenyl ring. This pathway has a relatively lower activation barrier of +29.0 kcal/mol. The immediate product of the dissociative decarboxylation is CP3-o, which can exchange CO2 with DMSO or PhCH=CH2 to produce \( \text{PD}_{\text{trans}} \) or CP4-o respectively.

3.2. Olefin Insertion. Olefin insertion begins with CP4-o (Figure 2). CP4-o inserts the coordinated olefin into the ary1-Pd bond to produce CPS-o through a four-membered cyclic transition state TS2-o. The energy barrier for this step is +15.6 kcal/mol. In CP4-o the olefin is perpendicular to the Pd coordination plane, whereas in TS2-o the olefin lies in the Pd coordination plane. After olefin insertion, CPS-o isomerizes to CPS-o and becomes more stable by 1.3 kcal/mol. In CPS-o, the C\( \nu^1 \) atom remains coordinated to the Pd center. This observation is in agreement with Myeck's crystal structure for a norbornene adduct of ary1-Pd(III)-TEA, which also turns out to be a 3-bound complex with DMSO occupying the trans position of C\( \nu^1 \). The Pd-C\( \nu^1 \) and Pd-C\( \nu^1 \) distances in Myeck's crystal are 2.24 and 2.03 Å, as compared to 2.40 and 2.09 Å in CPS-o.

3.3. \( \beta \)-Hydride Elimination. To undergo \( \beta \)-hydride elimination, CPS-o rotates its phenyl group around the C\( \nu^1 \)-C2 bond.
Our calculation shows that reductive elimination of CF₂COOH from CP₅−o has an activation barrier of +8.7 kcal/mol and is exothermic by −12.0 kcal/mol. Then, oxidation of Pd(0)(DMSO)₂ by Ag₂CO₃ in the presence of trifluoroacetic acid gives (DMSO)₃Pd(II)(TFA). This oxidation is slightly endothermic by +1.5 kcal/mol. Overall, catalyst regeneration from CP₅−o to trans-CP₀−o is exothermic by −10.4 kcal/mol and, therefore, thermodynamically favorable.

3.5. Overall Catalytic Cycle and Rate-Limiting Step. Figure 4 shows the free energy profile for the catalytic cycle of Myers’ decarboxylative Heck reaction. The path marked in blue describes the associative pathway, while the path in red describes the dissociative pathway. According to the profile, decarboxylation proceeds through the dissociative pathway with an activation barrier of +29.0 kcal/mol. Compared to decarboxylation, olefin insertion, β-hydride elimination, and catalyst regeneration are all facile steps. Thus, decarboxylation is the rate-determining step for Pd-catalyzed decarboxylative coupling of arene carboxylic acids with alkenes.

4. Factors Controlling the Efficiency of Decarboxylative Coupling

In the catalytic cycle we identify that decarboxylation is the rate-determining step. In this part, the various factors controlling the decarboxylation step are discussed, which include the ancillary ligand, the neutral ligand, substrate, and metal. As shown in Figure 4, the overall activation barrier for decarboxylation can be affected by the energy costs of three steps: (1) the energy required for carboxyl exchange (CP₀ → CP₁), (2) the energy required for dissociation of one DMSO from Pd (CP₁ → CP₂), and (3) the activation energy required for the extrusion of CO₂ (CP₂ → TS₁). To better understand why the decarboxylation efficiency changes...
Factors Controlling Decarboxylative Coupling

4.1. Orbital Analysis of the Decarboxylation Transition State.
Before studying each factor, we analyze the orbital interactions for the extrusion of CO₂ from the Pd complex. Thus, we divide TS₁ into two fragments (Figure 5), i.e., Pd(DMSO)(TFA)(Ph) and the deformed CO₂ moiety.

Calculation shows that the LUMO of the Pd(DMSO)(TFA)(Ph) fragment is mainly composed of the Pd 4dₓ²₋ᵧ² orbital and some contribution from the σ(Pd–Cᵥ₋w) antibond. The Pd 4dₓ²₋ᵧ² orbital is highly asymmetric presumably due to the stronger trans influence of the anionic TFA group than the neutral DMSO. The HOMO of the deformed CO₂ is a π bond. It overlaps with the LUMO of Pd(DMSO)(TFA)(Ph) in the manner shown in Figure 5.

From the orbital interactions we can draw the following conclusions. First, an electron-deficient Pd center leads to a low-lying LUMO orbital that can interact more strongly with the π bond of deformed CO₂. Thus, electron-deficient ligands, rather than electron-rich ones, are expected to facilitate decarboxylation. Second, anionic ligands with a stronger trans influence can stabilize the decarboxylation transition state because a stronger desymmetrization of the Pd 4dₓ²₋ᵧ² orbital can bring about a more favorable HOMO/LUMO interaction. Third, from the precomplex CP₂ to TS₁, the NPA charge on the Cᵥ₋w atom changes from −0.168 to −0.319 while the NPA charge on the carbonyl carbon increases from +0.814 to +0.934. Thus, any factor that stabilizes the accumulating negative charges on Cᵥ₋w or the positive charge on the carbonyl carbon can contribute to the stabilization of TS₁.
facilitating the decarboxylation. These conclusions can be used to explain the observed results.

4.2. Effect of Anionic Ligands on Decarboxylation. Myers and co-workers found that triphenylacetyl chloride played a key role in the decarboxylation palladation reaction, because other Pd salts such as PdC1 and PdBr2 were ineffective or gave inferior results. Moreover, added bromide completely inhibited decarboxylation. To understand these observations, PdCl2 and PdBr2 are examined to evaluate the effect of anionic ligands on decarboxylation (Table 1).

According to the orbital analysis, the anionic ligand with a stronger trans influence can stabilize the transition state of decarboxylation (namely, TS1). Indeed, the $\Delta G^o (CP2 \rightarrow TS1)$ values for Cl and Br are lower than that for TFA by ca. 2–3 kcal/mol, because Cl and Br exert a stronger trans influence than TFA. However, it is found that, in the carboxyl exchange step, the $\Delta G^o (CP0 \rightarrow CP1)$ value is only $+3.7$ kcal/mol for TFA, as compared to $+20.4$ and $+23.2$ kcal/mol for Cl and Br. Consequently, the overall activation barrier of decarboxylation is very high (over $+40$ kcal/mol) for PdCl2 and PdBr2. This explains why PdCl2 and PdBr2 provided inferior results in decarboxylation.

4.3. Effect of Neutral Ligand on Decarboxylation. Several common types of neutral ligands including phosphate, phosphite, pyridine, and $\Pi$-heterocyclic are examined for their effects on the decarboxylation step (Table 2). It is found, not without surprise, that DMSO gives the lowest activation barrier as compared to all the above popular ligands. This calculation result is in agreement with the experimental observation that DMSO is thus far the only appropriate ligand system for the decarboxylative Heck reaction. A phosphine or phosphite ligand (e.g., PMe3, or P(OEt)3) is found to be detrimental to decarboxylation as reflected by the high activation barriers. The reason is 2-fold: (1) Phosphine or phosphite ligands are relatively electron-rich and, therefore, generate a less electron-deficient Pd(II) center. This would increase the energy cost for the extrusion of CO in the transition from CP2 to TS1 (27.5 kcal/mol for PMe3 and 26.1 kcal/mol for P(OEt)3, vs 17.5 kcal/mol for DMSO). (2) Phosphine and phosphite ligands coordinate to Pd more strongly, so that the ligand dissociation step (i.e., CP1 $\rightarrow$ CP2) also becomes highly unfavorable (13.9 kcal/mol for PMe3 and 10.4 kcal/mol for P(OEt)3, vs 7.8 kcal/mol for DMSO).

Compared to phosphine and phosphite, pyridine is less electron-rich, and it does not coordinate to Pd very strongly. In agreement with this argument, we find that the energy costs of the ligand dissociation (CP1 $\rightarrow$ CP2) and CO2 extrusion (CP2 $\rightarrow$ TS1) steps are relatively low for pyridine (8.9 and 13.0 kcal/mol, vs 7.8 and 17.5 kcal/mol for DMSO). However, it is found that the energy cost of the carboxyl exchange step (CP0 $\rightarrow$ CP1) is fairly high.

Table 2. Effect of Neutral Ligand on Decarboxylation of PhCOOH (kcal/mol)*

<table>
<thead>
<tr>
<th>L</th>
<th>$\Delta G^o (CP0 \rightarrow CP1)$</th>
<th>$\Delta G^o (CP1 \rightarrow CP2)$</th>
<th>$\Delta G^o (CP2 \rightarrow TS1)$</th>
<th>$\Delta G^o$ (activation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TFA</td>
<td>3.7</td>
<td>7.8</td>
<td>17.5</td>
<td>+29.0</td>
</tr>
<tr>
<td>Cl</td>
<td>20.4</td>
<td>4.3</td>
<td>15.7</td>
<td>+40.4</td>
</tr>
<tr>
<td>Br</td>
<td>23.2</td>
<td>4.2</td>
<td>15.4</td>
<td>+42.8</td>
</tr>
</tbody>
</table>

* $\Delta G^o$ (activation) = $\Delta G^o (CP0 \rightarrow CP1)$ + $\Delta G^o (CP1 \rightarrow CP2)$ + $\Delta G^o (CP2 \rightarrow TS1)$.
activation barriers (over +33 kcal/mol) and the propensity of alkyl-Pd to undergo side reactions.

The above results appear to indicate that the activation barrier of Pd-mediated decarboxylation of RCOOH should correlate with the acidity of the R−H bond. Specifically, a more acidic R−H bond should be associated with a more readily decomposable R−COOH. This speculation is largely correct as shown by the plot of the decarboxylation barriers against the gas phase acidities of the C−H bond activation may share some common features.

Despite the above correlation, it is surprising to notice that benzoic acids with electron-withdrawing substituents dramatically deviate from the correlation line (Figure 6). In fact, an electron-donating group (e.g., OMe) reduces the activation barrier of decarboxylation whereas an electron-withdrawing substituent (e.g., NO₂) does the opposite. This theoretical prediction is in agreement with the experiment, where electron-rich benzene acids were also found to be better substrates in the decarboxylation couplings. 

![Figure 6. Correlation between the activation barrier of Pd-mediated decarboxylation of RCOOH and the acidity of the R−H bond.](image)

Detailed analysis indicates that the problem stems from the DMSO removal step (i.e., CP1 → CP2). For instance, for 4-NO₂-C₆H₄-COOH the removal of a DMSO from CP1 to generate CP2 costs +14.7 kcal/mol, whereas the same process only costs +6.7 kcal/mol for 4-OMe-C₆H₄-COOH. The large difference between the two acids can be explained by the formation of the C−H bond in CP2. Specifically, a 4-NO₂ group (as a σ acceptor) should

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destabilize the C\textsubscript{sp}2--Pd(II) bond that is perpendicular to the phenyl ring (see Figure 1). But this $\pi$(NO$_2$)--$\sigma$(C--Pd) type of interaction does not play any role in determining the R--H acidity (because the R--H bond is not perpendicular to the phenyl ring). As a result, substituted benzoic acids do not rigorously follow the correlation in Figure 6.

Furthermore, it is interesting to observe that the activation barrier of the 4-OMe-substituted benzoic acid (+25.6 kcal/mol) is about 3 kcal/mol higher than that for 2-OMe-substituted benzoic acid (+22.4 kcal/mol). Similarly, the activation barrier of the 4-NO$_2$-substituted benzoic acid (+30.7 kcal/mol) is about 5 kcal/mol higher than that for 2-NO$_2$-substituted benzoic acid (+25.2 kcal/mol). These observations indicate that the ortho substituents influence the reactivity of benzoic acids more via their influence on the $\pi$ electron density than the $\pi$ electron density. Similar effects were reported by Goosen and Thiel in their study on Cu-catalyzed decarboxylation. This effect also explains why 2-fluorocarboxylic acid has a very low activation barrier for decarboxylation as compared to benzoic acid.

4.5. Metal Center Effect on Decarboxylation. All the d$^{10}$ group elements (Ni, Pd, and Pt) are examined for the decarboxylation process. According to the results in Table 4, the overall activation barrier for the extraction of CO$_2$ from benzoic acid follows the following order: Pd $<$ Pt $<$ Ni. As to Ni catalyst, it is found that the energy cost for the CO$_2$ extraction step (CP2 $\rightarrow$ TS1, +19.9 kcal/mol) is only 2.4 kcal/mol higher than the Pd case. However, carbonyl exchange (CP0 $\rightarrow$ CP1) and removal of one DMSO (CP1 $\rightarrow$ CP2) cost a considerable amount of free energy for Ni. As to Pt, the energy cost for the decarboxylation step (CP2 $\rightarrow$ TS1, +16.5 kcal/mol) is even 1.0 kcal/mol lower than the Pd case. Unfortunately, the energy cost for the carbonyl exchange step (CP0 $\rightarrow$ CP1) is fairly high for the Pt catalyst. One may propose that the unfavorable effects of carbonyl exchange and DMSO removal steps in Ni- and Pt-catalyzed decarboxylation could be overcome by changing the ligands. It remains interesting to see whether Ni- and Pt-catalyzed decarboxylative cross-coupling could be accomplished experimentally.

5. Conclusions

Transition-metal-catalyzed decarboxylative cross-coupling with readily available carboxylic acids to replace unstable organometallic reagents. This method presents a new and important direction in synthetic organic chemistry. In the present work, we report the first comprehensive theoretical study on the mechanism of Pd-catalyzed decarboxylative Heck reaction discovered by Myers and co-workers. It is found that the overall catalytic cycle is composed of four steps: decarboxylation, olefin insertion, $\beta$-hydride elimination, and catalyst regeneration. Decarboxylation is concluded to be the rate-limiting step, in which Pd(II) mediates the extrusion of CO$_2$ from an aromatic carboxylic acid to form a Pd(II)--aryl intermediate. The dissociative pathway is favored in decarboxylation, so that dissociation of one DMSO ligand must take place prior to the extrusion of CO$_2$.

Further analysis on the various factors that may control the efficiency of Pd-catalyzed decarboxylative Heck reactions yields the following conclusions. First, PdCl$_2$ and PdBr$_2$ are much worse catalysts than Pd(TFA)$_2$, because the exchange of Cl or Br in a Pd complex with the carboxylate substrate is a highly unfavorable step in the thermodynamics. Second, DMSO presents the best compromise between the carbonyl exchange and decarboxylation steps. Phosphine and N-heterocarboxyl ligands disfavor the decarboxylation step because of their electron richness. Pyridine-type ligands, on the other hand, disfavor the carbonyl exchange step. Third, there is a good correlation between the activation barrier of R--COOH decarboxylation and the acidity of the R--H bond. A more acidic R--H bond causes a more readily decomposable R--COOH. However, substituted benzoic acids show deviation from the correlation because of the involvement of $\pi$(substitution)--$\sigma$(C=O)--Pd interaction. Finally, Ni and Pt are worse catalysts than Pd for decarboxylation because of the less favorable carboxyl exchange and/or DMSO removal steps in Ni and Pt catalysis. These results should also have valuable implications for other transition-metal-catalyzed decarboxylative reactions.

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Supporting Information Available: Detailed optimized geometries, free energies, thermal corrections. Discussion on the binding mode of DMSO. Full citation of ref 19. This material is available free of charge via the Internet at http://pubs.acs.org. J100743G7

Table 4. Metal Center Effect on the Decarboxylation Step (kcal/mol)$^*$

<table>
<thead>
<tr>
<th>Metal</th>
<th>$\Delta$G(CP0 $\rightarrow$ CP1)</th>
<th>$\Delta$G(CP1 $\rightarrow$ CP2)</th>
<th>$\Delta$G(CP2 $\rightarrow$ TS1)</th>
<th>$\Delta$G(Decarboxylation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ni</td>
<td>10.0</td>
<td>13.6</td>
<td>19.9</td>
<td>+43.5</td>
</tr>
<tr>
<td>Pd</td>
<td>3.7</td>
<td>7.8</td>
<td>17.5</td>
<td>+29.0</td>
</tr>
<tr>
<td>Pt</td>
<td>9.7</td>
<td>8.4</td>
<td>16.5</td>
<td>+34.6</td>
</tr>
</tbody>
</table>

$^*$ $\Delta$G(Decarboxylation) = $\Delta$G(CP0 $\rightarrow$ CP1) + $\Delta$G(CP1 $\rightarrow$ CP2) + $\Delta$G(CP2 $\rightarrow$ TS1).