nanotubes also enable highly anisotropic material properties. The authors have grown forests of 11-nm-diameter carbon nanotubes and then pulled the entangled tubes into ribbons composed of oriented bundles. Their densities are extremely low—a little higher than that of air, and similar to that of the lightest materials known. The ribbons are very stiff for their weight in the stretch direction. Perpendicular to the stretch direction, they may be as much as one million times less stiff, and are far more compliant than rubber (*2*). This apparently unprecedented degree of anisotropy is akin to having diamond-like behavior in one direction and rubber-like behavior in the others. If the ribbons are stretched along the orientation axis, the other axes collapse dramatically—20 times as much as most materials do—leading to an overall shrinkage that is again unique in its magnitude and direction.

The nanotube ribbon's combination of the high stretch-direction modulus and low density is well suited for creating thin, stiff beams and plates for aerospace and other applications, in which minimizing mass is critical. The ribbons would require less than 10% of the mass needed by composites, wood, metals, or other materials, but are bulkier because of their extremely low densities (*3*).

The application of a voltage charges and expands the ribbons in milliseconds, as the repelling charges maximize the surface area by pushing apart loosely interconnected bundles (see the figure). Although carbon nanotube actuators have previously been activated by charging in an electrolyte, the resulting relative changes in length were much smaller. The large strains of the new actuation mechanism suggest that high electromechanical coupling and efficiency should be achievable. This is because large changes in the distance between charges lead to a substantial change in electrical potential energy that can be converted to work.

The actuators can deflect light, but are otherwise so compliant in their large strain axis that applications requiring large displacement and any appreciable force are excluded. This limitation might be overcome by greatly increasing the transverse stiffness of the ribbons by densification of the nanotube ribbons and increasing the degree of interconnection between adjacent fibres. When forces are increased, the ribbon artificial muscles will become candidates for use in medical devices, robots, and perhaps even implants.

How can a material that is so stiff in one direction be so compliant in the others? Entanglement of adjacent bundles might be expected to lead to a rubber-like elasticity, in which thermal agitations resist the uncoiling of weakly intertwined tubes. However, the nanotubes are much too stiff to bend due to thermal energy, and their response shows virtually no temperature dependence—the elasticity is "enthalpic" rather than entropic in origin. So what keeps the films together? Small bundles wind around and perhaps interconnect with the larger oriented fibers [supporting figure S10 in (*1*)]. These tiny but stiff wires may act as springs that bend to provide a restoring force when the ribbons are deformed (see the figure). If so, then altering the density and stiffness of interconnects should allow tuning of the mechanical properties of the ribbons.

The discovery of the stiff yet compliant, light yet strong, electrostatically deformable ribbons should inspire the development of new nanostructured materials whose stiff, long, and carefully arranged elements enable exquisite tailoring of material properties. For example, it may be possible to create custom materials with unique properties by assembling nanometer-thick beams into carefully designed three-dimensional structures. The beams in this case are stiff macromolecules or nanowires that can resist attractive surface forces from neighbors. Creating the desired property combinations is a challenge, but reports of engineered three-dimensional structures composed of stiffened DNA (*4*), zinc oxide ribbons, and other stiff materials suggest that it will ultimately be possible.

References and Notes

1. A. E. Aliev et al., *Science* **323**, 1575 (2009).
2. Aliev *et al.* do not report modulus in the compliant axes; I have estimated the modulus from the resonant frequency during actuation.
3. In such applications, prestrain may be needed because of the low initial modulus. Creep may also pose a problem.
4. N.C. Seeman, *Nature* **421**, 427 (2003).

10.1126/science.1171169

CHEMISTRY

Copper Puts Arenes in a Hard Position

Robert E. Maleczka Jr.

Copper catalysts enable substitution reactions on a benzene ring to occur at positions that normally are unfavorable.

As a professor of chemistry, I have written many letters of recommendation for nonchemistry majors. This task gives me the opportunity to ask what the students remember most from their year of organic chemistry. Electrophilic aromatic substitution—the replacement of hydrogen atoms on aromatic rings, or arenes, with substituents—often tops the list. With surprising regularity, students can recall the rules (or at least remember that rules exist) predicting whether substituted benzenes will react at their ortho, meta, or para positions (see the figure, panel A). A report by Phipps and Gaunt on page 1593 of this issue (*1*) might give my students pause. The authors show how ortho/para-directing amido groups can facilitate a difficult reaction, carbon-carbon (C–C) bond formation, at the less favored meta position, courtesy of a novel copper(I)/copper(III) catalytic sequence.

The problem addressed by Phipps and Gaunt is a long-standing one. Shortly after Faraday isolated benzene, chemists began to explore its reactivity. These studies soon revealed that benzene reacts in a way that replaces a hydrogen atom with a functional group such as NO_2 or Cl (*2*). Moreover, even before Kékulé suggested benzene's structure, a number of disubstitution reactions were known to yield three different isomers. Assigning the absolute structures of such isomers fell to Körner, who in 1869 introduced the terms ortho, meta, and para.

In 1877, Friedel and Crafts discovered reactions that formed C–C bonds at aromatic rings (*3*). By the turn of the 20th century, reliable predictions could be made of how substituent effects govern the reactivity and selectivity of reactions that would later be described as electrophilic aromatic substitutions (*4*).

A substituent on a benzene ring influences both where a second substituent will preferentially react and whether these reactions will be accelerated or inhibited. Benzene molecules bearing groups that release electron density into the ring, which include alkylbenzenes, as well as anilides and phenols, activate electrophilic aromatic substitution reactions and

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Department of Chemistry, Michigan State University, East Lansing, MI 48824, USA. E-mail: maleczka@chemistry.msu.edu

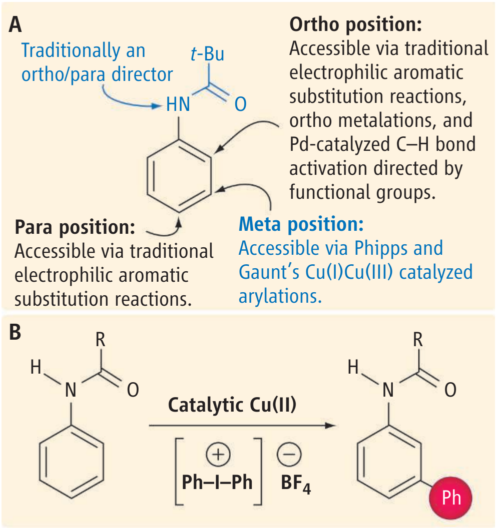
favor substitution at the ortho or para positions, or both (see the figure). Halides also direct substituents to these positions, but because they pull electron density from the ring relative to H, the reactions are relatively slower. Lastly, benzenes bearing electron-withdrawing groups (such as NO_2) are deactivating and direct substituents to meta positions.

These "rules" made preparation of many arene substitution reactions predictable and also practical on an industrial scale. The benzene nucleus can be found in ~30% of all industrial chemicals and over half of the top 50 drugs (*5*). Unfortunately, arenes in which the substitution patterns do not fit these rules (and which are said to be contra-electronic) can be extremely difficult to prepare. For example, obtaining only ortho products in the presence of a para- or meta-directing group was long considered a challenge. Multistep syntheses, which tend to be time consuming, more expensive, and lower yielding, were often needed to achieve the desired substituted benzene.

In the 1980s, directed metalation chemistry, developed by Snieckus, emerged as a powerful tool for selective ortho substitution to certain functionalized groups, including some that are normally meta directors, such as carbamides (*6*). In this approach, an existing group guides a base to the nearby ortho proton. Acid-base chemistry leaves a metal such as lithium at the ortho position, which then exchanges with a nonmetal substituent. More recently, functional group–directed carbon-hydrogen (C–H) bond activation, especially with palladium catalysts in the Pd(II)/Pd(IV) oxidation states, has allowed the introduction of various atoms, such as carbon, oxygen, and halogens, at ortho positions (*1*, *7*).

The complementary problem of achieving selective substitution meta to ortho/para donors has been more aggravating to chemists. For example, one relatively simple and synthetically useful (*8*) molecule, 3-bromo-5-chlorophenol, has three ortho/para directors, two of which are deactivating, and all occupy meta positions with respect to the others. Thus, phenol and either halobenzene are poor starting materials—each would direct the next substituent to the wrong position. Until recently (*9*), the best effort at synthesizing this contra-electronic molecule was a 10-step procedure reported in the 1920s that used the explosive TNT (trinitrotoluene) as the starting material.

Partial solutions to this meta problem have relied on steric preferences, catalyst choice, acidity differences, and, most often, multistep syntheses (*1*, *10*). Some of these approaches are quite clever, including Wilhem and Lautens' palladium-catalyzed alkylation hydride reduction sequence (*10*). Sterically guided iridium-catalyzed C–H borylations also afford meta-substituted products regardless of the electronic preferences (*11*). However, none of these methods could start with benzene bearing a single ortho/para donor and directly afford a single meta-substituted benzene.



Location, location, location. (**A**) Many reactions readily add a second substituent to a benzene molecule at the positions across from the first substituent (para) or next to it (ortho), but addition at the remaining meta positions is usually slow and low in yield. The copper-catalyzed route described by Phipps and Gaunt forms carbon-carbon bonds to arene substituents at positions meta to an amide group; *t*-Bu is a tertiary butyl group. (**B**) The overall reaction; Ph is a phenyl group.

Phipps and Gaunt changed that landscape by tapping into the electrophilicity of Cu(III) (see the figure, panel B). In their scheme, a Cu(III) species is generated from Cu(I) and a bisarylated hypervalent iodine (that has lost two electrons to form two bonds and developed a positive charge). That reagent apparently does not undergo traditional electrophilic aromatic substitution without the aid of the amide. The electrons on the basic amide oxygen attack the ortho position of the benzene. The ring electrons are effectively then pushed out to form the C–Cu bond, which breaks the ring's aromaticity in the process. Further reaction with base rearomatizes the ring, and then the aryl group, originally bonded to iodine, forms a C–C bond at the meta position occupied by the Cu(III) group. The Cu(I) is regenerated, and the whole process begins anew.

Cross-coupling reactions are among the most common C–C bond–forming reactions used for the preparation of drug candidates (*12*). Cross-coupling reactions that avoid the preparation of haloaromatics are among the aspirational reactions recently identified by the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (*13*). The organocopper components of Phipps and Gaunt's reaction need not be isolated, nor do the anilides require a halogen to effect C–Cu bond formation, so this part of the method can be considered green.

Phipps and Gaunt's methodology also represents new advances in both C–H activation and Cu(III) chemistry. Although their approach builds on their previous studies on copper-mediated indole arylations, the work does open a new chapter in electrophilic aromatic substitution chemistry. The chapter is still being written; the authors' putative mechanism is speculative, and there are drawbacks to hypervalent iodides (such as availability, by-product formation, and cost). Relatively small changes to the reaction conditions can change the products (*14*). Moreover, the yield of an anilide disubstituted with a deactivating meta director was a disappointing 11%.

Nonetheless, this study inspires the imagination. What besides aryl groups can be transferred? Can the approach be used in combination with other Cu(III) methods (*15*)? Finally, the role of Cu(III) in biological systems suggests that there may be biochemical or biosynthetic implications to these findings.

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