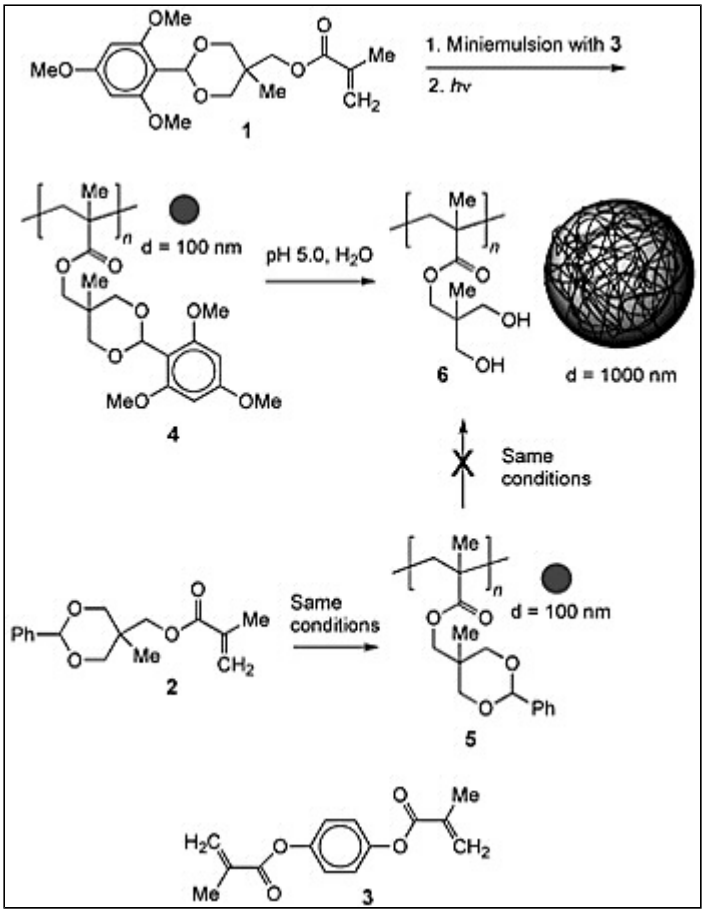
# Noteworthy Chemistry

**March 16, 2009**



**These nanoparticles can expand for drug delivery.** Y. L. Colson, M. W. Grinstaff, and coauthors at Boston University and Brigham and Women's Hospital (Boston) designed cross-linked nanoparticles that deliver therapeutics by means of pH-regulated volume expansion. They used a miniemulsion process and subsequent photo-cross-linking to generate smooth 100-nm diam nanoparticles (**4** and **5**) from methacrylate monomers **1** and **2** and cross-linker dimethacrylate **3**.




The key differences between **4** and **5** are the conditions under which hydrolysis of the benzaldehyde groups occurs. Upon exposure to aqueous buffer solutions at pH 5.0, expansile nanoparticles (eNPs) **4** become hydrophilic as a result of the cleavage of the 2,4,6-trimethoxybenzaldehyde protecting group and expand ~350 times by volume (**6**). Nonexpansile nanoparticles (neNPs) **5** are stable and remain hydrophobic because the benzaldehyde protecting unit hydrolyzes only under highly acidic conditions.

To evaluate drug release, the authors loaded the eNPs and neNPs with 1 wt% (85% encapsulation efficiency) of the lung cancer therapeutic drug paclitaxel before they were miniemulsified. A pH-dependent release profile for the eNPs showed that in the expanded state (pH 5.0), drug release is almost complete within 24 h, whereas at pH 7.4 paclitaxel release is minimal in the same time period. Release from the neNPs is rapid—~60% within

5 h—regardless of pH.

The researchers confirmed that paclitaxel encapsulated in the eNPs remains active. Based on a subcutaneous Lewis lung carcinoma tumor model with proper controls, they determined that eNPs that contain paclitaxel (2 and 20 μg) effectively inhibit tumor growth via localized delivery, especially when compared with a 20-μg conventional dose of paclitaxel, without adversely affecting the body. This low-dose, localized drug-delivery strategy may transform current cancer treatments. (*J. Am. Chem. Soc.* **2009,** *131,* **2469–2471**; **LaShanda Korley**)

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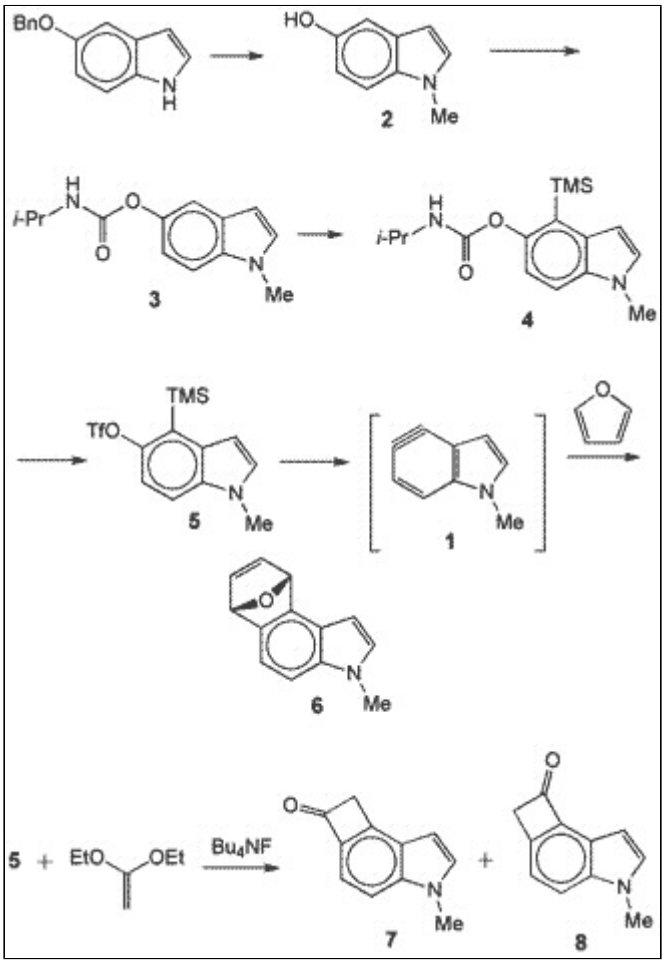
**Indolynes promote unusual indole reactivity.** The bicyclic indole framework forms a key structural component of many bioactive compounds, but its reactivity is typically limited to that of nucleophiles that participate in electrophilic aromatic substitution reactions. S. M. Bronner, K. B. Bahnck, and N. K. Garg* at the University of California, Los Angeles, reasoned that a strategy for reversing inherent indole reactivity from nucleophilic to electrophilic would open the way for synthesizing indole-based compounds that are difficult to prepare conventionally. Their method is based on generating aryne derivatives—indolynes—that function as electrophilic indole surrogates. The indolyne structure is nucleophilic at the C3 position and electrophilic at the C4 and C5 sites.




Their target structure was 4,5-indolyne (**1**), which is generated from precursor **5**. The preparative sequence starts with commercially available 5-benzyloxyindole.

The starting material is readily converted to hydroxyindole **2**, which is treated with isocyanate to produce carbamate **3**. Treatment with a lithium reagent and quenching with $Me_3SiCl$ provides silyl carbamate **4**. Next, a deprotection–trifluoromethanesulfonation sequence gives the desired silyl triflate **5**, the precursor to **1**. Treating **5** with furan provides the predicted Diels–Alder adduct **6**, verifying the formation of intermediate **1** and the desired reactivity of its triple bond at C4–C5.

The authors used a variety of trapping agents that react with **5** as a common indolyne precursor to yield an impressive array of functionalized indole structures. One example is the use of 1,1-diethoxyethylene, which undergoes a [2 + 2] cycloaddition with **5** to yield indolylcyclobutanones **7** and **8**. They extended this method by using a similar synthesis to form a precursor of 5,6-indolyne and demonstrated similar adducts based on the

reactivity of the C5 and C6 ring positions. Their studies point to a general preference for attack at C5 in these electrophilic indole surrogates. (*Org. Lett.* **2009,** *11,* **1007–1010**; **W. Jerry Patterson**)

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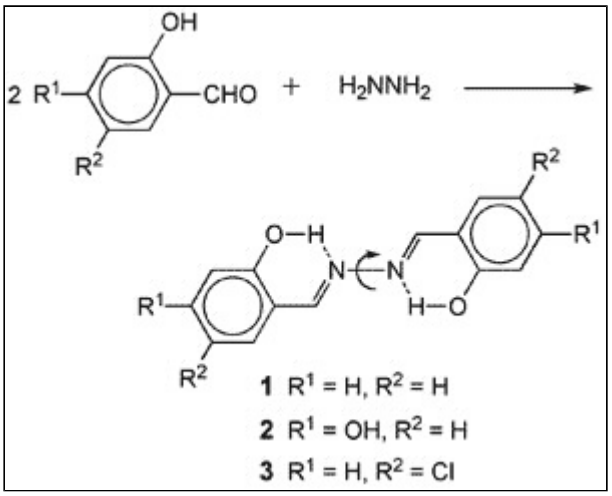
**Salicylaldehydes are sensitive hydrazine detectors.** Luminogenic molecules with chromophoric blades linked by freely rotatable C–C single bonds are often more emissive in the aggregate state than in solution. Synthesizing these luminogens, however, can be very demanding. W. Tang, Y. Xiang*, and A. Tong* at Tsinghua University (China) developed a group of salicylaldehyde azines (**1**–**3**) with chromophoric rotors linked




by N–N single bonds. The new luminogens show aggregation-induced emission enhancement (AIEE) and can be readily prepared in one step.

Taking advantage of the high reactivity of salicylaldehydes with hydrazine, the researchers developed a "reactive AIEE" chemodosimeter system. For example, simply mixing *m*-chlorosalicylaldehyde with hydrazine at room temperature gives emissive aggregates of azine **3** in an aqueous medium. This fluorescent probe is very sensitive, making it possible to detect hydrazine at the sub-ppm level. It is also highly selective and performs well in the presence of such interferants as $NH_2OH$, $NH_2CH_2CH_2NH_2$, $NH_3$, $MeNH_2$, common metal ions, and anions of various inorganic acids. (*J. Org. Chem.* **2009,** *74,* **2163–2166**; **Ben Zhong Tang**)

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**Minimize solvent waste during solvent switches.** Solvent switching is a common unit operation in pilot plant operations. There are two options for carrying out solvent exchanges: stepwise and constant volume. In the traditional stepwise method, the initial solvent is reduced by distillation to a low volume and the second, chasing, solvent is added. Distillation is repeated until the content of the initial solvent is reduced to the desired level.

In the constant-volume solvent exchange method, the first step is the same—reduction to low volume—but then a constant volume is maintained by the continuous simultaneous addition of the second solvent while the initial solvent is further distilled. In the example described by Y.-E. Li and co-workers at Abbott Laboratories (North Chicago, IL), a solvent switch from a $H_2O$–*i*-PrOAc–*i*-PrOH mixture to *i*-PrOH alone using the constant volume method resulted in a 30% reduction in waste solvent generation compared with the traditional stepwise method. (*Org. Process Res. Dev.* **2009,** *13,* **73–77**; **Will Watson**)

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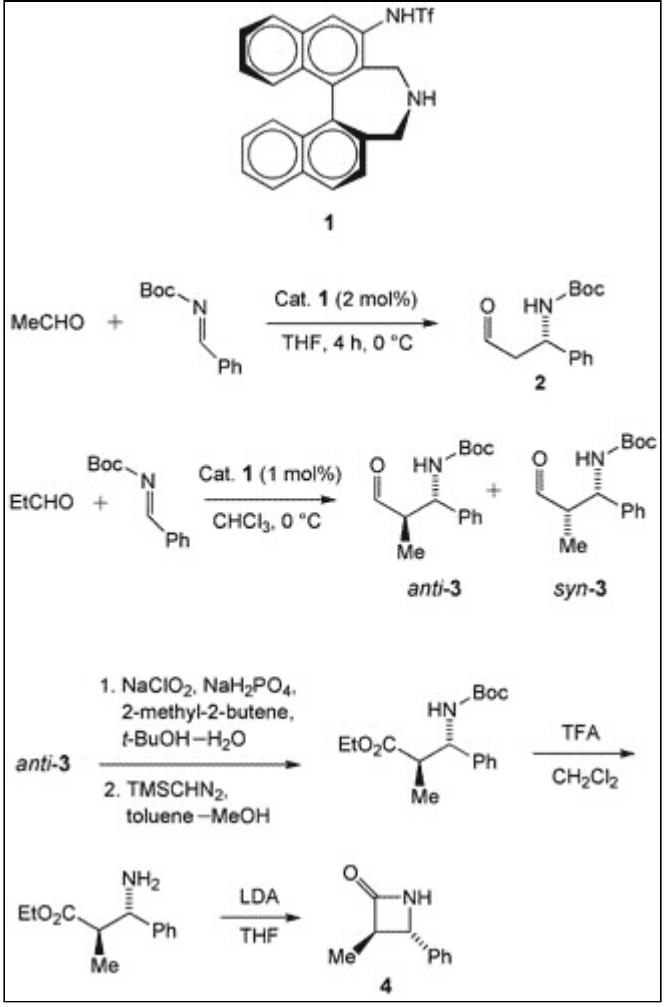
**Run direct asymmetric Mannich reactions on protected imines.** Until now, the proline-catalyzed reaction between acetaldehyde and *N*-*tert*-butoxycarbonyl–protected imines provided the Mannich product, although undesired side reactions were difficult to suppress because the secondary amine catalyst is highly nucleophilic. T. Kano, Y. Yamaguchi, and K. Maruoka* at Kyoto University (Japan) addressed this problem by designing an axially chiral bifunctional amino sulfonamide catalyst (**1**). They found that **1** successfully mediates the




previously difficult direct asymmetric Mannich reaction between acetaldehyde and *N*-Boc-protected imines, providing the products (**2**) in almost optically pure form (99% ee).

They also note that anti-selective Mannich products from aldehydes and *N*-Boc-protected aromatic imines remain generally unattainable. Surprisingly, the use of **1** in this reaction provides the corresponding anti Mannich adducts represented by *anti*-(**3**) with good anti selectivity (anti/syn as high as >20:1) and similarly high enantioselectivity (99%). Tf is trifluoromethanesulfonyl.

The scope of this procedure was broadened to substrates such as *N*-Boc-protected heteroaromatic imines and similarly protected aliphatic imines.

The authors extended the synthetic utility of this protocol by converting *anti*-**3** to the useful β-lactam structure **4** in four highly efficient steps. (TMS is trimethylsilyl; TFA is trifluoroacetic acid; LDA is lithium diisopropylamide.) They compared the optical rotation of **4** with the literature value to determine that the absolute configuration of *anti*-**3** is 1*S*,2*R*.

The reactions in this study represent rare examples of an efficient direct Mannich reaction of *N*-Boc-protected imines via an enamine intermediate. (*Angew. Chem., Int. Ed.* **2009,** *48,* **1838–1840**; **W. Jerry Patterson**)

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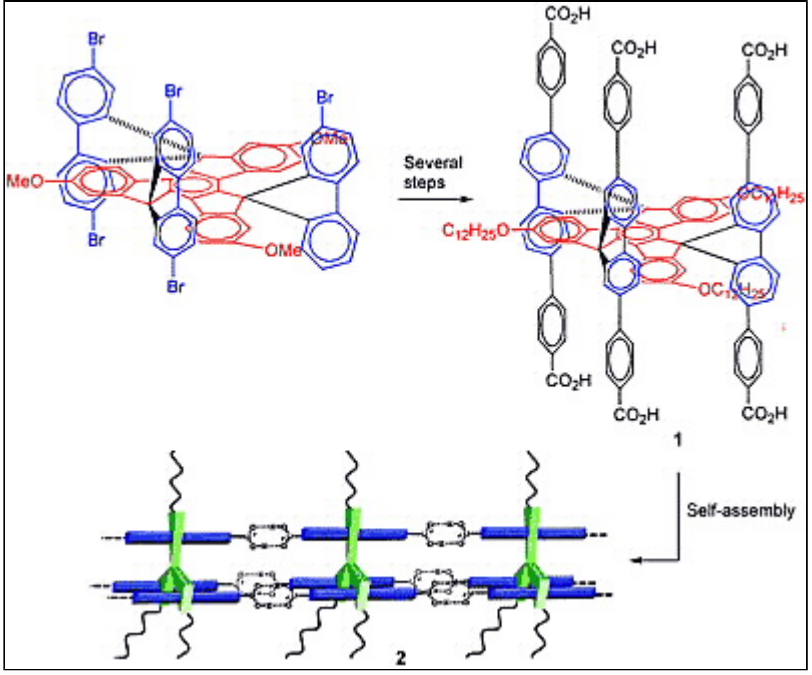
**Use multiple hydrogen bonds to form supramolecular nanowires.** J. Wang, J. Pei, and coauthors at Peking University (Beijing) and South China University of Technology (Guangzhou) examine the role of multiple hydrogen bonding interactions on the supramolecular assembly of fluorescent polymeric nanowires. Multiple hydrogen bonding sites in structure **1** (a 3-D hexaacid) direct the self-assembly of rigid and uniform supramolecular nanowires **2** (100–200 nm diam, >100 μm long) upon exposure of a THF solution of **1** to hexane vapor. The addition of water to the hexaacid **1** THF solution disrupts hydrogen bonding and limits the supramolecular assembly.




The authors also explored the directionality of the hydrogen bonding interactions by observing assembly behavior from dilute solution ($2.4 \times 10^{-6}$ M) on mica surfaces. Uniform 1-D "molecular" nanofibers (1.3–1.6 nm height, about the same as their planar diameter) formed upon deposition and evaporation of **1** in THF–$(CHCl_2)_2$. The authors propose that the 1-D nanowires consist of molecular wires connected via hydrogen bonding, assisted by weak van der Waals forces between alkyl chains arranged parallel to the substrate and the shape-persistent building block structure **1**.

Examination of the photophysical properties of monomer **1** showed an absolute photoluminescence efficiency of 22% in the solid state. The authors attribute this high efficiency to the rigidity of **1** and directional nature of hydrogen bonding, which promotes a dispersed morphology and reduces self-quenching phenomena. (*J. Am. Chem. Soc.* **2009,** *131,* **2076–2077**; **LaShanda Korley**)

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