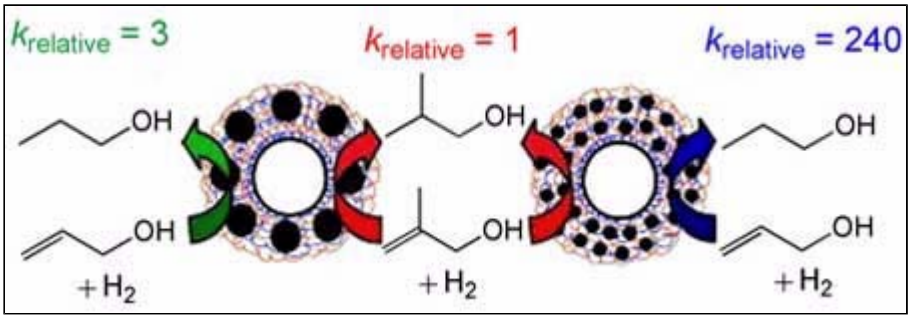
Noteworthy Chemistry

May 4, 2009

Particle size matters for catalytic selectivity in the hydrogenation of unsaturated alcohols. M. L. Breuning and co-workers at Michigan State University (East Lansing) studied the hydrogenation of a series of unsaturated alcohols using nanoparticle–polyelectrolyte catalysts with differing average nanoparticles sizes. They prepared palladium nanoparticles supported on alumina powder by layer-by-layer adsorption of poly (acrylic acid)–Pd(II) complexes and poly(ethylenimine) followed by reduction of Pd(II) with $NaBH_4$. The size of these nanoparticles was controlled by varying the ratio of poly(acrylic acid) to Pd(II) in the deposition solutions.



The researchers ruled out the diffusion effect of polyelectrolyte films on the selectivity and found that the catalytic selectivity of the nanoparticles varies dramatically with their size. Selectivity for the hydrogenation of monosubstituted versus disubstituted double bonds increases dramatically as the nanoparticle diameter decreases; this size-dependent selectivity occurs with suspended nanoparticles and nanoparticles deposited on micrometer-sized alumina. The authors hypothesize that the selectivity–particle size relationship occurs because, compared with monosubstituted double bonds, polysubstituted double bonds bind less strongly to the more hindered active sites of the smaller nanoparticles. (*J. Am. Chem. Soc.* **2009,** *131*, 3601–3602; George Xiu Song Zhao)

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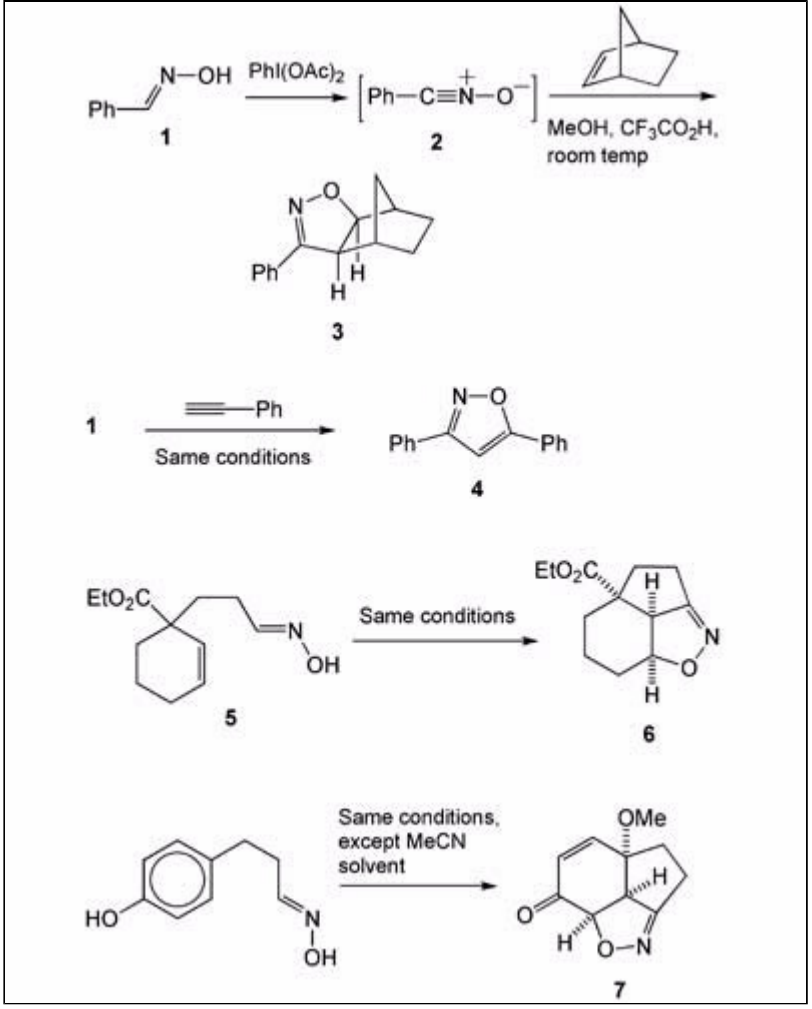

Hypervalent iodine oxidation of aldoximes leads to an array of functionalized products. M. A. Ciufolini and co-workers at the University of British Columbia (Vancouver) observed that aldoximes such as **1** are precursors to nitrile oxides (**2**), which can be trapped in situ with olefins to yield functionalized isoxazolines (**3**). They synthesized nitrile oxides by oxidizing aldoximes with $PhI(OAc)_2$.

Replacing the olefin trapping agent with a terminal acetylene provides a fully aromatic isoxazole (**4**). Intramolecular variants that feature aldoxime and olefin reactive sites in the reactant (e.g., **5**) give tricyclic products (**6**) that contain the isoxazoline ring and three stereogenic centers.

Further elaboration of this nitrile oxide construction demonstrated its reaction in tandem with the oxidative de-aromatization of a phenol to provide a densely functionalized tricyclic product illustrated by compound **7**. The authors' innovative approach to nitrile oxide intermediates may provide synthetic paths to useful bioactive compounds and natural products. (*Org. Lett.* **2009,** *11,* **1539–1542**; **W. Jerry Patterson**)

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Asymmetric chemistry or classical resolution—Why not use both? A. Nikitenko and co-workers at Wyeth Research (Pearl River, NY; Saint-Laurent, QU; and Princeton, NJ) required optically active 3-(5-fluoro-1*H*-indol-3-yl)-2-methylpropanoic acid as a chiral building block for synthesizing a novel dual-acting SSRI/5HT1a antagonist. This compound could be prepared from the equivalent acrylic ester by reduction, hydrolysis, and resolution. A screen of resolving agents showed that (–)-norephedrine gave the highest *S*/*R* isomer ratio, 72:28.

An alternative resolution method is asymmetric hydrogenation of the acrylate ester or acid. The authors found that the acid is the superior substrate; it provides the product in a 92:8 *S*/*R* ratio. Subsequent crystallization in the presence of (–)-norephedrine produces sufficiently optically pure (95% ee) propanoic acid derivative for use in subsequent reactions. (*Org. Process Res. Dev.* **2009,** *13,* **91–97**; **Will Watson**)

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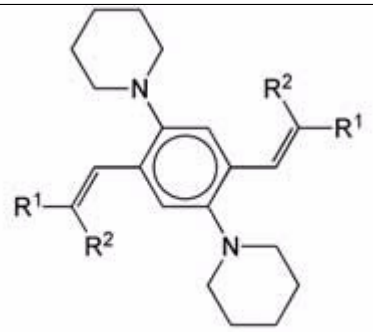
How small can an efficient fluorogen be? To design a fluorogen with redder (longer wavelength) emission, the common practice is to add more π-conjugated units (e.g., aromatic rings or olefinic double bonds) to a

chromophore. Doing so, however, makes the chromophore larger and often leads to emission quenching in the solid state because of more π–π stacking interactions between the large molecules in the chromophore aggregates. A small molecule is beneficial for avoiding unfavorable chromophoric interactions, but how small can it be without diminishing its performance as an emitter?



	R^1	R^2	λ_{max}, nm	ϕ_F
1	Me	Me	439	0.65
2	H	H	480	0.89
3	CF_3	H	526	1.00
4	CO_2Et	H	591	0.80
5	COMe	COMe	641	0.34

A team led by M. Shimizu at Kyoto University (Japan) pushed the size of the chromophore almost to the minimum: one benzene ring and two double bonds. They synthesized a set of small molecules with the general structure 1,4-bisalkenyl-2,5-dipiperidinobenzene that emits efficiently upon photoexcitation. The emission color is tunable over the entire visible spectral range by varying the R^1 and R^2 groups. In addition, the molecules emit more efficiently in the solid state than in solution; for example, the fluorescence quantum yields (Φ_F) of the crystals and film of compound **3** are extremely high: 0.98 and 1.00, respectively.

The nonplanar shapes of the molecules hamper close packing, weaken π–π stacking interactions between the chromophore units, and thus prevent the emission from being quenched by aggregation. The intramolecular rotations of the components of the molecules, however, are restricted in the solid state. This structure rigidification blocks the nonradiative decay channels caused by molecular motion and dramatically boosts the efficiencies of the solid-state emissions. (*Angew. Chem., Int. Ed.* **2009,** *48,* **3653–3656**; **Ben Zhong Tang**)

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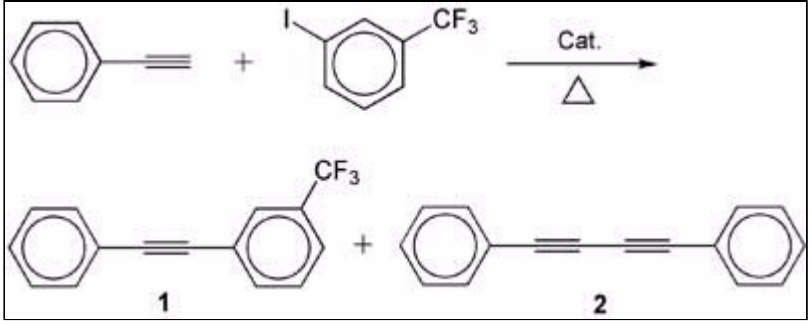
Here's a solvent- and metal-free Sonogashira coupling. The Sonogashira coupling reaction is a widely used method for C–C coupling and has applications in natural product synthesis and medicinal chemistry. The reaction usually requires organic solvents and a catalytic system, often Pd(0)–Cu(I).

R. Luque* and D. J. Macquarrie at the University of York (UK) report a solvent- and metal-free protocol for Sonogashira coupling that is catalyzed by 1,4-diazabicyclo[2.2.2]octane (DABCO). A stronger Lewis base than Me_3N or Et_3N, DABCO gives the best results in the Baylis–Hillman reaction. Because of its conformation, DABCO has two sterically unhindered nitrogen atoms that are capable of acting as nucleophilic centers.

Using the model reaction between phenylacetylene and *m*-iodobenzotrifluoride, the authors tested several amines as Sonogashira catalysts. DABCO gave the best results, with maximum conversions at 48-h reaction time and 130 °C reaction temperature. The optimum acetylene/arene/DABCO mol ratio was 1:1:2. Greater amounts of DABCO did not improve conversion; but microwave heating more than doubled conversion and increased the ratio of desired coupling product **1** to diacetylene byproduct **2**. Electron-donating substituents on arenes resulted in poor conversions; this is attributed to the stabilization of positive charges generated in the C–I bond by an inductive effect.



The authors propose two mechanistic pathways to explain this reaction, one in which DABCO acts as a nucleophile that attacks the electrophilic carbon in the triple bond, and another that involves nucleophilic replacement of the aryl halide followed by a nucleophilic carbon attack on the alkyne. Although this method is "greener" than existing Sonogashira coupling schemes, it has not yet given results superior to metal-catalyzed couplings. (*Org. Biomol. Chem.* **2009,** *7,* **1627–1632**; **José C. Barros**)

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Choose isopropyl acetate over ethyl acetate for a phase-transfer catalysis reaction. During development of a process for converting 3,5-bis(trifluoromethyl)benzyl chloride to 3,5-bis(trifluoromethyl)benzyl azide, M. E. Kopach and co-workers at Eli Lilly (Indianapolis) considered various options. The initial process was run in DMSO–H_2O in batch and continuous modes, but a second-generation approach used phase-transfer catalysis (PTC).

The authors screened several solvents for the PTC reaction. The best conversions were obtained when isopropyl acetate or ethyl acetate was used. Isopropyl acetate was chosen because the organic layer contained lower residual levels of the PTC catalyst *n*-Bu_4NBr. (*Org. Process Res. Dev.* **2009,** *13,* **152–160**; **Will Watson**)

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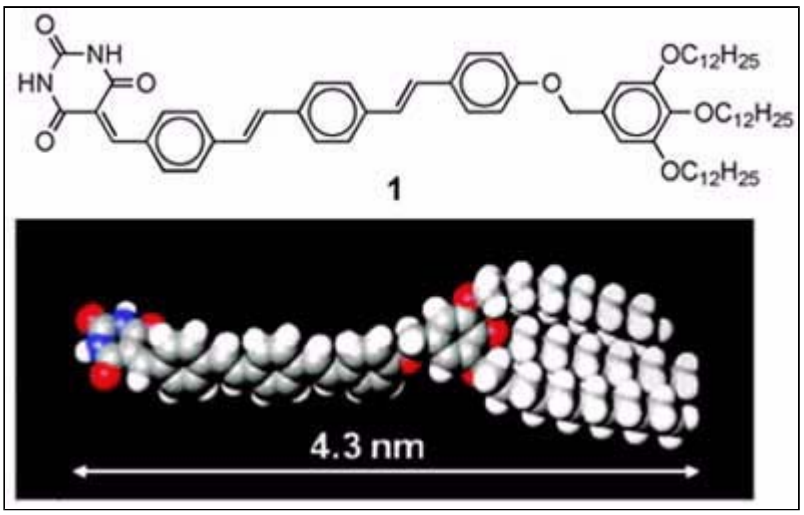
Open or closed: It's all in the concentration. S. Yagai, Y. Kikkawa, and coauthors at Chiba University (Japan), PRESTO: Japanese Science and Technology Agency (Saitama), the National Institute for Interdisciplinary Science and Technology (Trivandrum, India), and the National Institute for Advanced Industrial Science and Technology (Ibaraki, Japan) have generated novel self-assembled nanostructures by concentration-induced ordering of rigid molecules.



The rigid synthetic molecule **1** consists of an oligo(*p*-phenylenevinylene) center segment with a hydrogen-bonding barbituric acid head unit and a wedge-shaped tridodecyloxybenzyl tail group (see structure and Corey–Pauling–Koltun model). Compound **1** is soluble in warm methylcyclohexane (MCH). It forms stable solutions (>1 month in MCH) that have hypsochromic UV–vis shifts relative to its THF solutions that indicate self-assembly. Spin-coating or drop-casting a 2×10^{-5} M solution of compound **1** in MCH onto highly oriented pyrolytic graphene or mica forms nanostructures with a closed-ring morphology (i.d., ~38 nm; o.d., ~14 nm), along with a smaller amount (~10–20%) of open-ended nanostructures, including spirals, curved fibers, and

double spirals.

The authors note that the closed-ring nanostructures are most likely the result of spontaneous organization in solution. They evaluated the reversible concentration dependence of the ordering behavior of **1** via atomic force microscopy, transmission electron microscopy, and dynamic light scattering. In more dilute solutions (1×10^{-5} M), almost no open-ended assemblies exist. Increasing the concentration to 4×10^{-5} M, however, results in >70% of open-ended nano-objects. An additional increase to 1×10^{-4} M produces uniform nanorod structures (contour length ~100–300 nm, width ~25 nm, height ~5 nm) as a consequence of helical folding. IR spectroscopy and X-ray studies showed that the concentration-dependent, nanostructured morphologies are caused by linear hydrogen bonding of the barbituric acid unit into a supramolecular hexameric disk. (*J. Am. Chem. Soc.* **2009,** *131,* **5408–5410**; **LaShanda Korley**)

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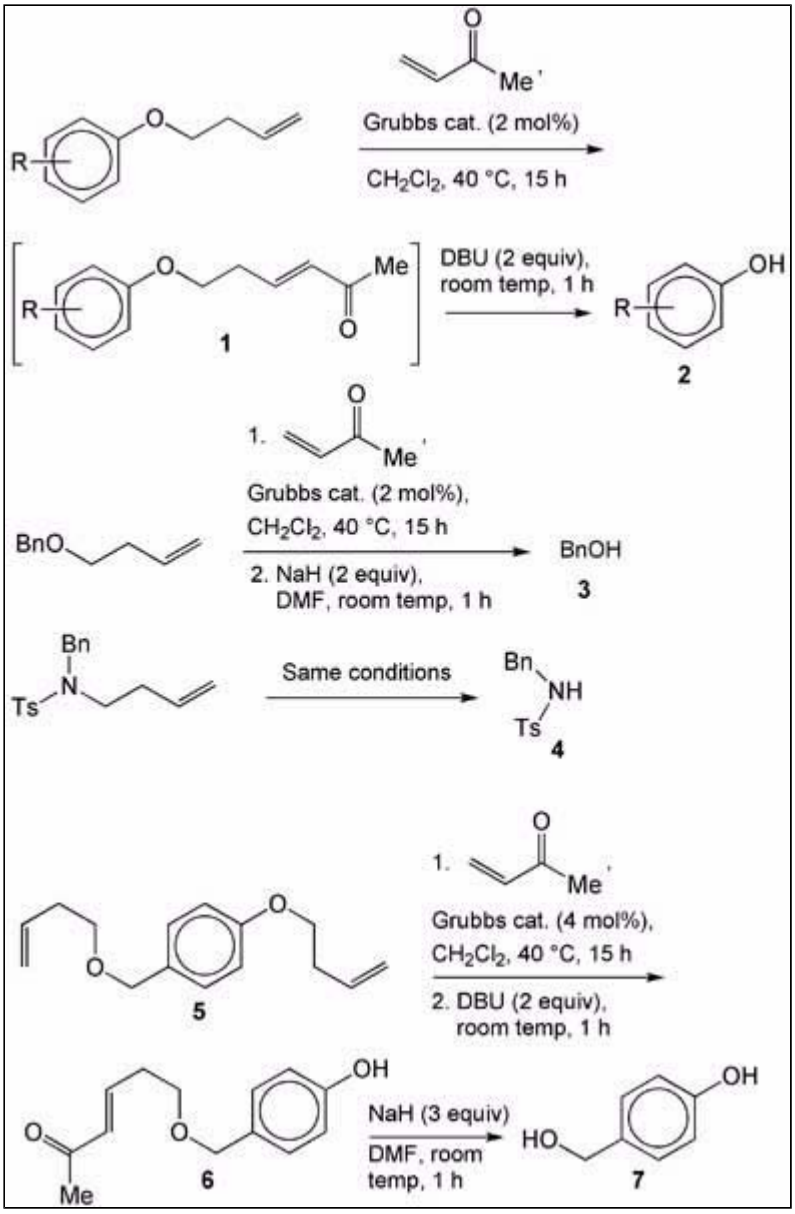
Use the homoallyl group to protect and deprotect several functionalities. The homoallyl structure is potentially useful for protecting sensitive functional groups, but its relative chemical inertness has limited its value to carry out subsequent chemoselective deprotection. B. H. Lipshutz*, S. Ghorai, and W. W. Y. Leong at the University of California, Santa Barbara, developed a useful way to overcome this limitation. They used a one-pot tandem metathesis–elimination sequence that focuses on the mild removal of the homoallyl protecting structure to regenerate the desired functional group.



The authors used methyl vinyl ketone as the coupling partner in the metathesis phase of the deprotection reaction and a commercially available Grubbs-type catalyst. The metathesis intermediate **1** is shown in brackets in the figure. The free functional group was quickly generated by the mild base 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU).

This method was efficiently used for homoallyl-masked phenols, alcohols, amine derivatives, and acids. Deprotection of a variety of homoallyl ethers of substituted phenols led to impressive yields of the free phenols (**2**), and the process tolerated an extensive array of functional groups.

Stronger bases such as NaH were required to promote elimination for nonphenolic homoallyl-protected alcohols to yield the free alcohols (**3**). This base was also necessary to generate free substituted amines (**4**; Ts is *p*-toluenesulfonyl). The amine reaction required one nitrogen substituent to be electron-withdrawing for an effective reaction.

In an extension of this method, the authors selectively unmasked homoallylic ethers (**5**) to allow recovery of the free phenol and retain the protected aliphatic alcohol (**6**). The free benzyl alcohol functionality (**7**) was then liberated by treatment with NaH–DMF, as previously described. (*J. Org. Chem.* **2009,** *74,* **2854–2857**; **W. Jerry Patterson**)

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