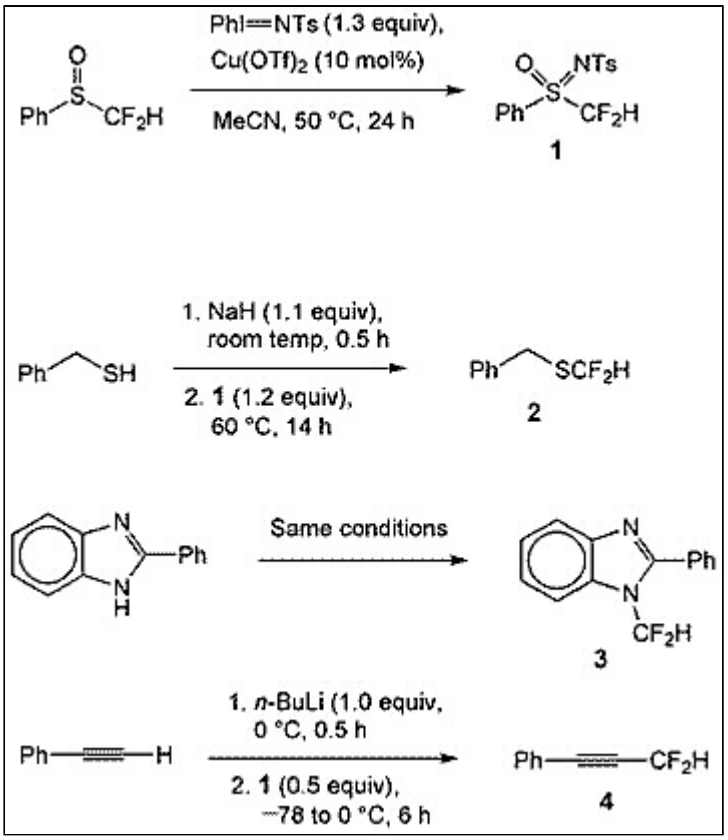
Noteworthy Chemistry

June 1, 2009

Here's a new nucleophile difluoromethylation reagent. Incorporating fluorinated groups such as $–CF_2H$ into organic structures can enhance many of their bioactive properties. W. Zhang, F. Wang, and J. Hu* at the



Chinese Academy of Sciences (Shanghai) developed a way to incorporate fluorine by using an efficient reagent, *N*-*p*-toluenesulfonyl-*S*-difluoromethyl-*S*-phenylsulfoximine (**1**). Reagent **1** was prepared from the corresponding sulfoxide via a copper-catalyzed nitrene transfer reaction and was recovered as a colorless crystalline solid. Ts is *p*-toluenesulfonyl; Tf is trifluoromethanesulfonyl.

The figure illustrates the versatility of **1** for transferring the $–CF_2H$ group to S-, N-, and C-nucleophiles under mild conditions to prepare compounds **2**, **3**, and **4**, respectively. In each case, the substrates are converted to the corresponding anions by deprotonating with NaH or *n*-BuLi before treatment with **1**.

The authors used deuterium-labeling experiments to determine the mechanism of this process. Their results ruled out an S_N2 or free-radical mechanism as a major pathway and suggested that the difluoromethylation proceeds through a difluorocarbene intermediate. They visualize **1** as a novel "CF_2H^+" equivalent in difluoromethylation processes. (*Org. Lett.* **2009,** *11*, 2109–2112; W. Jerry Patterson)

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Base removal is essential to a resolution process. M. E. Kopach and co-workers at Eli Lilly (Indianapolis) and coauthors at three Belgian companies developed a commercial synthesis of 4-benzylmorpholin-2-(*S*)-yl tetrahydropyran-4-yl ketone methanesulfonate, a key starting material for a new investigational drug candidate. During the synthesis, they converted *N*-benzylmorpholine-2-carboxylic acid to the corresponding morpholine amide via a mixed anhydride formed with isobutyl chloroformate; diisopropylethylamine (DIEA) was used as the base.

The racemic morpholine amide was resolved with 0.5 equiv of (–)-di-*p*-toluoyltartaric acid in *i*-PrOH to give the desired enantiomer in 40% yield and 100% ee. The amide coupling and resolution steps could be telescoped if the DIEA is removed by distillation. One batch that contained 10.7 mg/mL of residual DIEA resulted in a poor 24% isolated yield. (*Org. Process Res. Dev.* **2009,** *13,* **209–224**; **Will Watson**)

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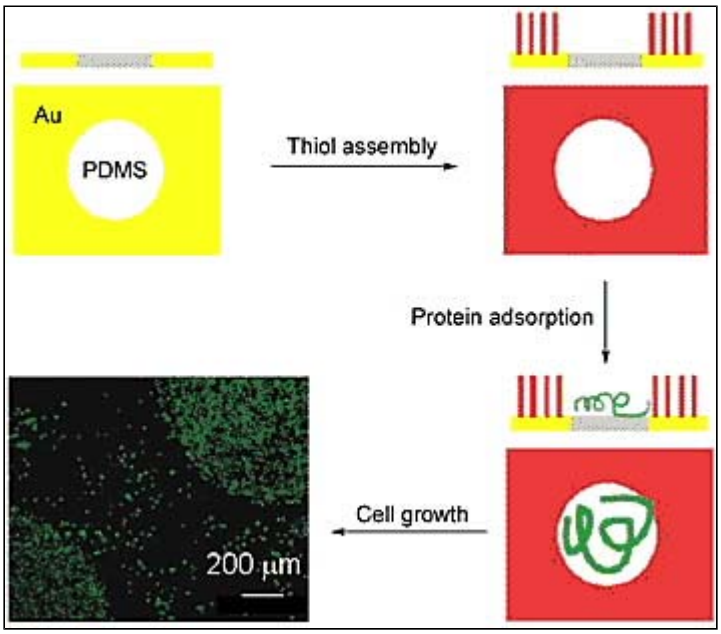
Generate cytophilic and cytophobic patterns easily and economically. Cell patterning is a useful tool that provides a platform for investigating cell interactions and making biosensor arrays. Poly(dimethylsiloxane)



(PDMS) is widely used in biomedical devices because of its excellent biocompatibility, transparency, flexibility, and machinability. A team led by H.-Y. Chen at Nanjing University (China) developed a simple, low-cost process for creating patterned PDMS substrates for cell-patterning applications.

By using chemical plating and electrochemical etching methods, the researchers prepared Au–PDMS chips with gold "island" or PDMS dot patterns. The self-assembly of ω-(1-mercaptoundec-11-yl)hexa(ethylene glycol) molecules on the gold regions and absorption of fibronectin proteins on PDMS generate cytophilic and cytophobic regions, respectively. Selective adhesion and growth of living cells in the cytophilic region accomplish the goal of cell patterning. (*Langmuir* **2009,** *25,* Article ASAP DOI: **10.1021/la900944c**; **Ben Zhong Tang**)

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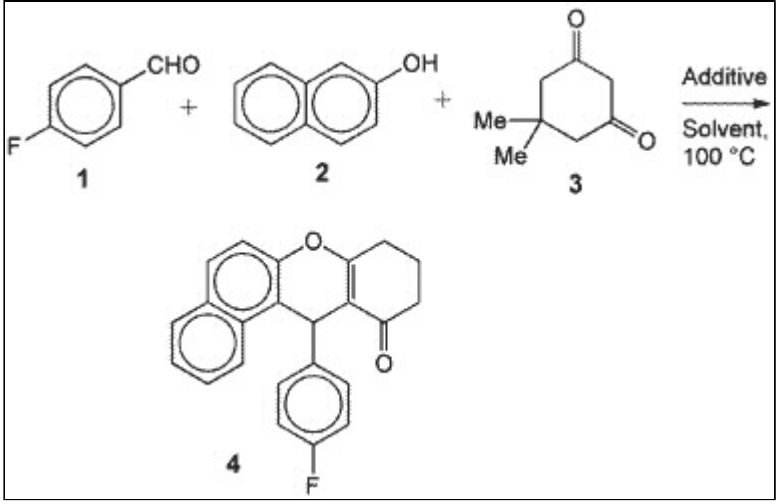
Make benzoxanthenes by a simple "green" method. Benzoxanthenes are biologically active compounds that have pharmacological activity and applications in dye chemistry and pH-sensitive fluorescent materials. C.-F. Yao and co-workers at National Taiwan Normal University (Taipei) developed a new route to this heterocyclic core that uses "green" chemistry techniques such as water-mediated organic synthesis, multicomponent reactions, and recyclable catalysts.

The target molecules were obtained by the reaction of an aldehyde, a naphthol, a 1,3-diketone, and an ionic additive in an appropriate solvent. Bu_4NF, a source of "naked" fluoride ion, was the best additive. The reaction



is faster in water than in organic solvents because of hydrophobic interactions between the reagents that induce favorable aggregation of the polar components.

The authors extended the method to several aromatic and aliphatic aldehydes. Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) can be used in place of the 1,3-diketone with good yields.

The experimental conditions are simple, mild, and fully scalable; the reagents are readily available; and the reaction workup consists of filtering the reaction mixture to collect the solid product. The aqueous phase with the additive can be recycled as many as four times without loss of activity. (*Synlett* **2009, 949–954**; **José C. Barros**)

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Use layer-by-layer–coated gold nanoparticles for siRNA delivery. A. Goepferich and colleagues at the University of Regensburg (Germany) developed a small interfering RNA (siRNA) delivery vehicle that consists of a monodisperse, discrete, 15.5-nm diam gold nanoparticle (AuNP) core and a layer-by-layer (LbL) shell of siRNA and poly(ethyleneimine) (PEI). They optimized the LbL process at the appropriate ionic strength to maintain monodisperse, unaggregated (<7% doublets) AuNPs with conformal coverage.

The authors evaluated two LbL AuNP–siRNA systems, each of which contained 780 siRNA units per AuNP and had overall negative surface charges: PEI/siRNA/PEI–AuNP and siRNA/PEI–AuNP. Upon incubation in a cell culture medium containing fetal bovine serum, the particle sizes of these siRNA delivery vehicles increased by a factor of 2.1–2.5 as a result of protein adsorption and the ζ-potential. The authors determined that protein adsorption was a key component to the stabilization of the AuNP systems and that cell uptake into endocytotic vesicles was achieved for both delivery vehicles.

The degree of cell uptake depended on the outer layer (PEI or siRNA); siRNA/PEI–AuNP uptake (2.0×10^5/cell) was greater than that of PEI/siRNA/PEI–AuNP (5.6×10^4/cell), indicating that surface properties may regulate cell uptake. Minimal aggregation of AuNPs was observed after 6 h incubation regardless of the outer layer. Cell viability was minimally influenced after AuNP uptake even with high concentrations of AuNPs and a PEI outer layer, but siRNA/PEI–AuNP did not exhibit measurable cell efficacy. The authors propose future studies on the effect of particle size and surface properties in siRNA delivery. (*Nano Lett.* **2009,** *9*, **2059–2064**; **LaShanda Korley**)

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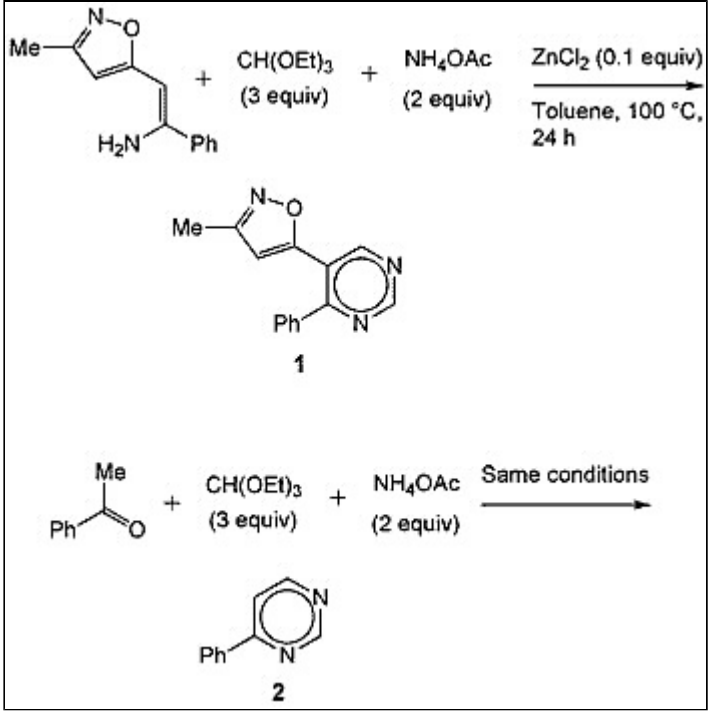
Construct 4,5-disubstituted pyrimidines in a single step. The 4,5-disubstituted pyrimidine nucleus is an



essential part of many bioactive compounds and is found in pharmaceuticals such as the antifungal agent voriconazole and avitriptan, a selective receptor agonist that is useful for treating migraine headaches. The value of this structure led T. Konakahara and co-workers at the Tokyo University of Science (Chiba, Japan) to develop an innovative, three-component coupling reaction in which a functionalized enamine, $CH(OEt)_3$, and NH_4OAc combine to form 4,5-disubstituted pyrimidines (e.g., **1**) in a single step.

This reaction is catalyzed by $ZnCl_2$ and can be visualized as a [3 +1 + 1 + 1] annulation process. The authors consider this an unprecedented method for assembling heterocycles. The scope of their study covers a range of disubstituted enamines, and the reaction conditions tolerate numerous functional groups. The enamine reactant can be replaced with a simple acyclic or cyclic ketone to form a less substituted pyrimidine derivative (e.g., **2**) by the same single-step approach. (*Org. Lett.* **2009,** *11,* **2161–2164**; **W. Jerry Patterson**)

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