Crystal Engineering

DOI: 10.1002/anie.201002053

The Reaction of Organozinc Compounds with an Aldehyde within a Crystalline Molecular Flask**

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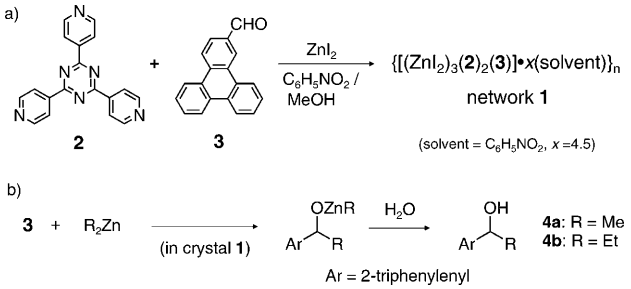
When bulky substrates and reagents exhibit pseudo solution-state mobility and reactivity within porous coordination networks,[1] the networks can be employed as "crystalline molecular flasks".[2–4] The robust crystallinity of the networks facilitates the use of X-ray crystallography, the ultimate method of structural determination, for the in-situ observation of various organic transformations.[2] Unstable products and even a transient reaction intermediate were protected within the crystalline flasks and were directly observed by X-ray crystallography.[2d] Until now, reactions have been limited to mild conditions (typically, neutral pH at room temperature), but herein we show that crystalline flasks can tolerate the inclusion of reactive organozinc reagents and that the subsequent reaction with an embedded aromatic aldehyde showed enhanced reactivity and selectivity. Recently, the addition of organozinc reagents to aldehydes in organic solvents was catalyzed in the presence of a binaphthol-containing porous network,[5] but it was unclear where the reaction occurred. In contrast, direct X-ray analysis of crystalline flasks revealed the precise reaction location[2] and underscores the potential applications of crystalline flasks toward organometallic transformations.[6]

Our porous network crystallized from ZnI_2, tris(4-pyridyl)triazine (**2**) and 2-formyltriphenylene (**3**) in nitrobenzene-methanol solvent mixture (Scheme 1). Elemental analysis elucidated the molecular formula of $\{[(ZnI_2)_3(\mathbf{2})_2(\mathbf{3})]\cdot x(\text{solvent})\}_n$ (**1**), with nitrobenzene as cocrystallized solvent ($x = 4.5$). Triphenylene guest **3** is an integral part of the network structure, which tolerates a variety of functional groups. Analogous networks containing **3** have been reported,[7,2c] but herein, the procedure was scaled up and network complex **1** prepared in large quantities (205 mg) in 21% yield (see the Supporting Information).

The porous structure **1**, determined by X-ray crystallographic analysis, exhibits two pores, A and B, which are characteristic of this type of coordination network (Figure 1a). Guest **3** is embedded in columnar stacks of ligand **2**,



Scheme 1. a) Preparation of the network **1**, and b) addition reaction of organozinc compounds to **3** within crystals of **1**.

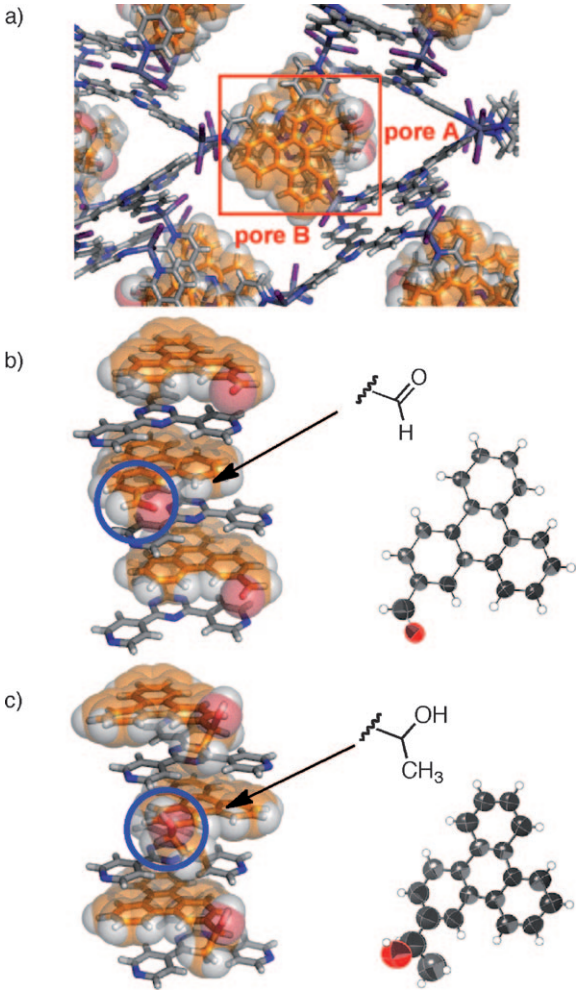


Figure 1. a) Network structure of **1** after the reaction with dimethylzinc. b, c) View of the columnar stack and triphenylene guest (ORTEP; ellipsoids set at 30% probability) in **1** b) before and c) after the reaction. In (b), only the formyl group in pore A (47% occupancy) is represented.

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[**] This research was supported by the CREST project of the Japan Science and Technology Agency (JST), for which M.F. is the principal investigator, and also in part by KAKENHI (20044006), JSPS, and Global COE Program (Chemistry Innovation through Cooperation of Science and Engineering), MEXT (Japan).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201002053.

WILEY InterScience DISCOVER SOMETHING GREAT
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which coordinate three ZnI_2 centers and generate the infinite network. The formyl group of **3** in the as-synthesized network **1** is located in pore B, and disordered nitrobenzene molecules fill both pores. As nitrobenzene can react with organozinc reagents, the included nitrobenzene was replaced with inert toluene after immersion for 2 d. Complete solvent exchange was confirmed by X-ray analysis. Pores A and B contained only toluene molecules, but now the formyl group of **3** was found in the both pores A and B with 47 and 53% occupancies, respectively (Figure 1b; see also the Supporting Information).

The addition of organozinc reagents to aldehyde **3** trapped within the crystalline flask was examined on large scale. Crystals of **1** (205 mg) were immersed in a toluene solution of dimethylzinc (2.0 M, 3.0 mL) for 24 h at room temperature. Excess dimethylzinc toluene solution was removed by decantation and the crystals decomposed with 5.0 M hydrochloric acid. The product was extracted with CH_2Cl_2 and purified by column chromatography to give methyl adduct **4a** in 85% yield. Independently, multiple small-scale reactions were quenched at various time intervals, extracted, and analyzed by NMR. Plotting the conversion ratio versus time revealed that the reaction is essentially complete in fewer than 12 h. Diethylzinc also reacted with aldehyde **3** in network **1** (77 mg) and gave the ethyl adduct **4b** in 90% isolated yield. Microscopic FT-IR spectroscopy of a single crystal of reacted **1** showed the disappearance of the strong C=O stretching vibration of the formyl group at 1697 cm^{-1} and corroborated that the reaction did indeed occur inside the crystals.

Despite the lack of an activating Lewis base, such as amines or alcohols, the addition of alkylzinc reagents to aldehydes trapped within the pores led to enhanced reactivity and selectivity. Outside the crystalline flasks, the reactivity of **3** and dimethylzinc in toluene solution was negligible (5% yield) and the addition of ZnI_2 and/or ligand **2** to the toluene reaction mixture made little difference (6–8% yield). The reaction did proceed with diethylzinc (98% conversion) but a 4:6 mixture of **4b** and the reduced alcohol ($ArCH_2OH$) was obtained. The enhanced reactivity and selectivity are presumably ascribed to high local concentrations and decreased mobility of the substrate/reagent, respectively, within the crystal. Furthermore, when diphenylzinc was employed as an organozinc reagent, aldehyde **3** was quantitatively recovered. This reagent selectivity can be ascribed to steric repulsion between bulky zinc reagent and the framework of **1**.

X-ray crystallographic analysis of the crystals immediately following the reaction revealed the robust network framework, but the final product structure was not fully solved because of strong residual electron densities in the pore; presumably from unreacted dimethylzinc, the unquenched zinc alkoxide, and partially hydrolyzed alcohol. The post-reaction crystals were immersed in toluene (not anhydrous) to wash away excess zinc reagent and byproduct and to quench the zinc alkoxide. X-ray analysis of the washed crystals was successful and the structure of **4a** fully solved (Figure 1c).

Washing the crystals with toluene removed the excessive residual electron density from the pores, and the 1-hydroxyethyl group of **4a** was clearly observed in pore A. The methyl adduct is quite large, yet enough space remained within pore A and several solvent molecules were also present. Despite the Lewis acidic character and reactivity of alkylzinc reagents, the framework of **1** was not damaged. The ZnI_2 atoms incorporated into the framework remained intact even though disproportionation between R_2Zn and ZnI_2 rapidly occurs in solution.[8]

We next attempted the one-pot transformation of **3** into acetate **5a**.[9] Crystals containing in situ formed **4a** were transferred to an acetic anhydride/toluene (1:1) solution. After immersion for 24 h at room temperature, a single C=O stretching vibration at 1734 cm^{-1} was observed by microscopic FTIR and assigned to the acylated product **5a**. The crystallinity of the robust network persisted and was confirmed by visual observation (Figure 2) and by X-ray diffraction. The crystals containing **5a** were decomposed with acid and extracted, and acetate **5a** was confirmed by ^1H NMR (>95% conversion). In a similar manner, two-step reaction with diethylzinc and acetic anhydride gave (1-acetoxy)propyl analogue **5b** in 93% yield (see the Supporting Information).

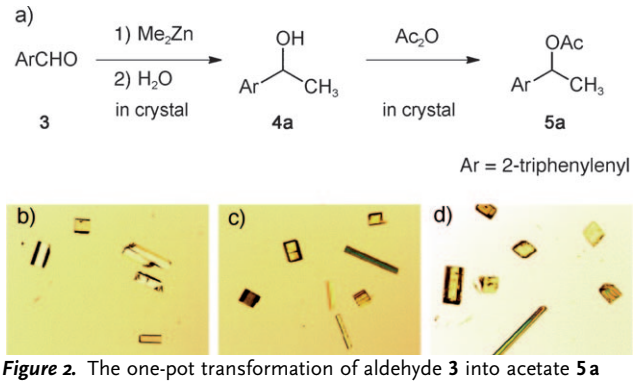

Figure 2. The one-pot transformation of aldehyde **3** into acetate **5a** within crystals of **1**. a) The reaction. b–d) Microscope images of crystals of **1** b) before the reaction, c) after treatment with dimethylzinc, and d) after subsequent reaction with acetic anhydride.

In summary, we demonstrated that even organometallic reactions proceed smoothly in a single-crystal-to-single-crystal fashion within the pores of porous coordination networks. These "crystalline molecular flasks" can tolerate highly reactive organometallic reagents while enhancing both the reactivity and selectivity. Furthermore, we envision the applications of crystalline flasks for the design of new reactions and the detailed structural and mechanistic examination of organometallic transformations through in situ crystallography.

Received: April 7, 2010
Revised: May 28, 2010
Published online: July 13, 2010

Keywords: metal–organic frameworks · organozinc compounds · porous networks · single-crystal modifications · X-ray diffraction

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