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Supramolecular Construction of an Aldehyde–Cyclobutane via the Solid State: Combining Reversible Imine Formation and Metal–Organic Self-Assembly

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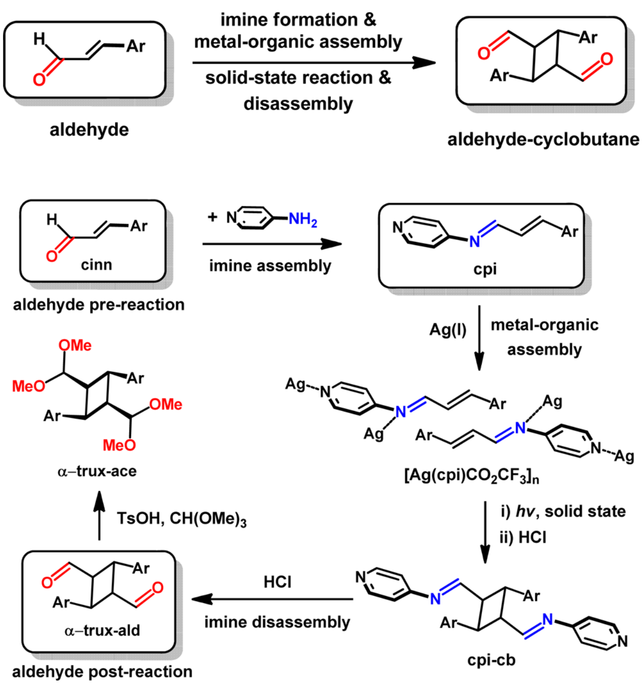
Ⓢ *Supporting Information*

ABSTRACT: A combination of metal–organic self-assembly and reversible imine formation is used to achieve an organic synthesis via the solid state. Imine bond formation is employed to install a pyridyl to the alkene *trans*-cinnamaldehyde while Ag(I) ions are used in a second step to assemble the pyridyl-functionalized alkene into a geometry in the solid state for an intermolecular [2 + 2] photodimerization. The alkene undergoes the cycloaddition reaction via a 1D coordination polymer to generate a pyridyl-functionalized cyclobutane stereoselectively and in quantitative yield. Removal of the pyridyl group affords the aldehyde-functionalized cyclobutane α-truxilaldehyde.

Scheme 1. Combined Application of Imine Formation and Metal–Organic Assembly To Afford Aldehyde *via* Solid State



Applications of noncovalent and reversible covalent bonding to achieve covalent syntheses are rapidly developing areas that are relevant to organic synthetic chemistry and materials science, being applied in solution,[1−3] on surfaces,[4] and in the solid state.[5] Recent methods to employ supramolecular assistance to covalent synthesis, for example, have involved uses of protecting group strategies[6,7] and post-modifications of metal–organic frameworks[8−12] to unite noncovalent interactions with organic synthesis. Dynamic imine bond formation, likewise, exploits reversible covalent chemistry to generate complex organic macrocycles,[13] covalent–organic frameworks,[14] and molecular cages.[15] All of these approaches can enable the generation of molecules and/or materials unattainable through traditional methods of synthesis.

In this report, we describe a method that combines both noncovalent bonding and reversible covalent bonding to achieve an organic synthesis via the solid state. We combine reversible imine formation and metal coordination in separate and sequential steps to functionalize, assemble, and preorganize the carbon–carbon double (C═C) bond of an alkene for an intermolecular [2 + 2] photodimerization. The imine formation reversibly functionalizes the alkene with a pyridyl group while metal–organic coordination generates a crystalline coordination polymer that assembles and preorganizes the C═C bonds for an intermolecular photocycloaddition. The two-step approach generates the simple yet rare cyclobutane α-truxilaldehyde (**α-trux-ald**) via **[Ag(cpi)CO$_2$CF$_3$]$_n$** (**cpi** = cinnamaldehyde *N*-(4-pyridyl)imine) (Scheme 1). The Ag(I) ions assist **cpi** to undergo a regiocontrolled [2 + 2] photodimerization that occurs quantitatively to form 1,3-bis((4-pyridyl)imine)-2,4-bis(phenyl)cyclobutane (**cpi-cb**). Removal of the pyridyl groups by reversing the imine bond affords **α-trux-ald**. To the best of our knowledge, a method that combines reversible imine formation and metal–organic chemistry to achieve an organic synthesis has not been reported.

Vigorous efforts have materialized to employ principles of supramolecular chemistry to direct the formation of covalent bonds in molecular solids.[16] A main focus has been the use of hydrogen bonds and coordination-driven self-assembly to direct intermolecular [2 + 2] photodimerizations. While these methods enable the supramolecular construction of organic molecules difficult to achieve in solution (e.g., ladderanes),[17−19] a general restriction has been that the molecular recognition sites that participate in hydrogen bonds and/or metal–organic coordination are "permanently fixed" to the cyclobutane products. Our goal here was to not only utilize the metal–organic approach to generate a cyclobutane but also produce a

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product devoid of the organic groups that participate in the coordination bonds.

These principles are realized when *trans*-cinnamaldehyde (**cinn**) is studied as the alkene (Scheme 1). **Cinn** is a liquid at room temperature (mp 18.5 °F/265.5 K). A recent X-ray crystal structure analysis by cryocrystallization (248 K) shows **cinn** to assemble by C−H···O hydrogen bonds with nearest-neighbor C═C bonds separated by 5.62 Å.[20,21] The distance is outside the limit of Schmidt (4.2 Å) for a [2 + 2] photodimerization in a solid.

To render the C═C bonds of **cinn** photoactive in the solid state and under the influence of metal−organic coordination, **cinn** (32.6 mmol) was condensed with 4-aminopyridine (21.2 mmol) in toluene (50 mL) (yield: 64.9%) (see Supporting Information). Pale yellow single crystals of **cpi** in the form of plates suitable for single-crystal X-ray analysis were obtained via slow solvent evaporation from a solution of MeCN.

The imine **cpi** crystallizes in the monoclinic space group $P2_1/n$ (Figure 1). The asymmetric unit contains one full molecule of **cpi**. The **cpi** molecules interact via C−H···N forces [C···N(imine) 3.617(2)] (Figure 1a) with the 4-pyridyl and phenyl groups participating in alternating face-to-face (4.028(2) Å) and edge-to-face (4.859(2), 4.884(2) Å) π−π interactions. The alkene adopts a twisted conformation with the pyridyl rotated out of the plane of the phenyl group (57.1°). Nearest-neighbor C═C bonds lie separated by 6.06 Å, which is beyond the distance for a [2 + 2] photocycloaddition.[21] When a finely ground crystalline powder of **cpi** was exposed to broad-band UV irradiation (450 W lamp) for 100 h, **cpi** was determined to be photostable.

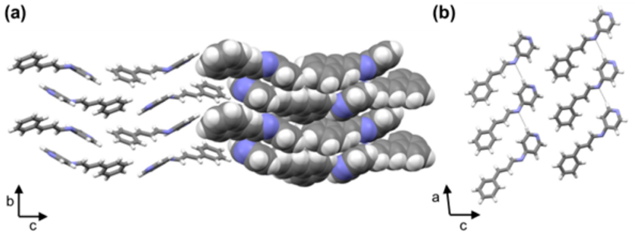

Figure 1. X-ray structure **cpi**: (a) π−π interactions and (b) C−H···N hydrogen bonds.

The C═C bonds of **cpi** are made photoactive in the solid state upon reaction with Ag(I) ions. Specifically, separate solutions of $Ag(CO_2CF_3)$ (0.5 mmol) and **cpi** (0.5 mmol) in dry ethyl acetate/MeCN (3:1, v:v) were combined to afford colorless needles of $[\mathbf{Ag(cpi)CO_2CF_3}]_n$ suitable for X-ray diffraction.

The components of $[\mathbf{Ag(cpi)CO_2CF_3}]_n$ crystallize in the monoclinic space group $P2_1/n$ (Figure 2). The asymmetric unit contains two **cpi** molecules coordinated to a Ag(I) ion. The Ag(I) coordination sphere conforms to a distorted tetrahedral geometry involving the pyridyl and imine N atoms [N−Ag−N angle: 147.5(2)°; Ag···N(pyridine): 2.244(6) Å, Ag···N(imine) 2.213(6) Å) and a chelating carboxylate ion (O−Ag−O angle: 48.42(18); Ag···O(carboxylate): 2.640(6), 2.704(6) Å) (Figure 2a). The metal coordination is manifested as a 1D zigzag coordination polymer that extends along the *b*-axis, with the $CF_3CO_2^-$ ions orthogonal to the polymer chains. The chains interdigitate along the *c*-axis to form 2D sheets (Figure 2b). The **cpi** ligands stack head-to-tail between polymers with the 4-pyridyl and phenyl rings participating in face-to-face π−π forces (4.04 and 3.96 Å) (Figure 2c) and the pyridyl being slightly twisted with respect to the phenyl group (17.4°). As a consequence of the assembly process, the stacked alkenes lie parallel with nearest C═C bonds separated by 3.96 Å (Figure 2d). In contrast to pure **cpi**, the stacking of the C═C bonds lies within the criteria of Schmidt for a photoreaction.[21]

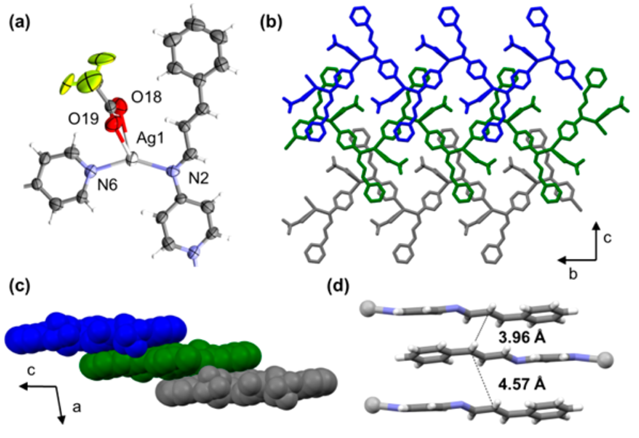

Figure 2. X-ray structure $[\mathbf{Ag(cpi)CO_2CF_3}]_n$: (a) Ag(I) coordination, (b) layering of 1D chains (blue = top; gray = bottom), (c) space-filling of stacked chains, and (d) stacked C═C bonds of **cpi** between polymer chains.

To determine the reactivity of $[\mathbf{Ag(cpi)CO_2CF_3}]_n$, a finely ground crystalline powder was spread between glass plates and exposed to broad-band UV irradiation (medium-pressure Hg lamp). A ^1H NMR spectrum revealed the complete disappearance of the olefinic signals (7.22 and 7.55 ppm) and appearance of two well-separated cyclobutane signals (4.68 and 4.25 ppm) following 45 h of irradiation (see SI). Given the head-to-tail stacking of **cpi** in the polymer $[\mathbf{Ag(cpi)CO_2CF_3}]_n$, we assigned the structure of the cyclobutane as **cpi-cb**.

In line with our strategy, the pyridyl groups that support the solid-state reactivity of $[\mathbf{Ag(cpi)CO_2CF_3}]_n$ can be readily removed from the cyclobutane photoproduct by treatment with HCl. Thus, when a sample of the photoreacted solid (0.6 mmol) was mixed with HCl(aq) (20 mL), a white precipitate formed. A yellow powder was obtained following extraction with $CHCl_3$ and evaporation of the organic phase to dryness. A ^1H NMR analysis of the yellow powder revealed a spectrum that matches ***α*-trux-ald**.[22] While the original reported synthesis of ***α*-trux-ald** is low-yielding and considers the dialdehyde as potentially useful,[22] there have been no subsequent reports on this relatively simple molecule.[23] Here, the combination of the reversible imine bond formation and metal−organic coordination has afforded a photoproduct via the solid states devoid of the ligating groups.

We generated a tetramethyl acetal of ***α*-trux-ald** by reaction of the cyclobutane aldehyde (0.3 mmol) with trimethylorthoformate (18 mmol) in the presence of TsOH (0.2 mmol) in MeOH (2.5 mL) (Figure 3). Single crystals of ***α*-trux-ace** were obtained by recrystallization from MeOH.

The acetal ***α*-trux-ald-ace** crystallizes in the monoclinic space group $P2_1/c$, with one-half of the molecule in the asymmetric unit (Figure 3). The cyclobutane is propagated as a 2D sheet in the *bc*-plane and interacts along the *c*-axis via C−H···O hydrogen bonds (C(2)···O(10) 3.658(2) Å, C(5)···O(12) 3.286(1) Å, (C(13)···O(10) 3.866(1) Å, C(13)···O(12) 3.792(2) Å) (Figure 3). Importantly, the *rctt*-configuration of the cyclobutane ring system is consistent with **cpi** having

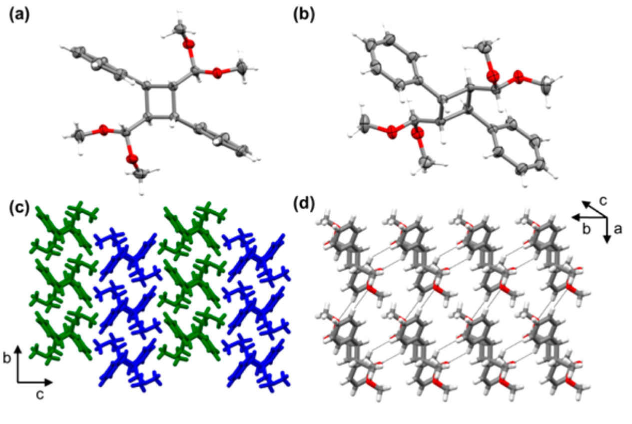

Figure 3. X-ray structure **α-trux-ace**: (a) ORTEP view, (b) highlighted *rctt*-configuration, (c) 2D sheets, and (d) C−H···O hydrogen bonds. Selected C−C distances: C(8)−C(7)(*trans*) 1.556(1) Å and C(8)−C(7′)(*cis*) 1.574(1).

undergone a head-to-tail photocycloaddition mediated by the 1D coordination polymer **[Ag(cpi)CO_2CF_3]$_n$**. Interestingly, two methoxy groups of **α-trux-ald-ace** attached to a single methane C atom lie in distinct magnetic environments, as revealed by the presence of two signals that have been assigned by a combination of variable-temperature ^{1}H NMR and 2D NOSEY experiments (see SI).

In conclusion, we have combined reversible imine formation and metal−organic coordination to perform the synthesis of an organic molecule via the solid state. We believe there are a number of salient features of the approach. First, we expect the method to be applicable for the supramolecular construction of organic molecules of increasingly structural complexity where less restriction is placed on functional groups of the alkene. Second, the method may, in principle, be applied to other reversible covalent-bond formations. Finally, the integration of the imines is valuable synthetically since the products of bond disassembly are aldehydes. Being important in organic synthesis, aldehyde−cyclobutanes have proven critical as precursors of complex natural products based on cyclobutanes (e.g., ladderanes).[18] These aspects of solid-state reactivity and crystal engineering can have important implications for organic and supramolecular syntheses, as well as materials science, which are under investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b04420.

Experimental details on syntheses, ^{1}H NMR spectroscopy, single-crystal and powder X-ray diffraction (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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