Wittig olefination “baking powder”: a hexameric halogen-bonded phosphonium salt cage for encapsulation and mechanochemical transformation of small-molecule carbonyl compounds

Joseph M. Marrett, Hatem M. Titi, and Tomislav Friščić*

Department of Chemistry, McGill University, 801 Sherbrooke St. W. Montreal, H3A 0B8 (Canada)

Abstract

We report a hexameric supramolecular cage assembled from the components of a Wittig-type phosphonium salt, held together by charge-assisted R-Br· · ·Br$^-$· · ·Br-R halogen bonds. The cage reliably encapsulates small polar molecules, including aldehydes and ketones, to provide host-guest systems in which components are pre-formulated in a near-ideal stoichiometry for a base-activated Wittig olefination in the solid-state. These pre-formulated solids enable a molecular-level “baking powder” approach for solvent-free Wittig reactions, based on a design of solid-state reactivity in which the host for molecular inclusion also acts as a complementary reagent for the chemical transformation of an array of guests. These host-guest solid-state complexes can also act as supramolecular surrogates to their Wittig olefination vinylbromide products, in a Sonogashira-type coupling that enables one-pot mechanochemical conversion of an aldehyde to an enediyne.

Introduction

Formation of multi-component crystals, such as cocrystals,[1] lattice inclusion compounds[2] and solid solutions,[3] is one of the principal crystal engineering[4] strategies for the design of reactivity in the organic solid state. Molecular inclusion in host-guest complexes in the solid state, as well as in solution, has provided access to a range of transformations, including photodimerizations,[5] isomerizations,[6] photochemical oxidations,[7] decarbonylations,[8] Diels-Alder reactions,[9] and more.[10] In the majority of cases, the host molecule or lattice acts as a chemically inert container, with reactivity confined to the included guests.[11] More recent work in the field of metal-organic frameworks (MOFs) has

introduced the concept of a “crystal as a molecule”, wherein inclusion of a small molecule guest leads to functionalization of a suitably designed host framework.[12]

Here, we present a different and, to the best of our knowledge, so far unexplored approach to the design of reactivity in organic solids, where the host component acts both as a container for inclusion and a reagent for chemical derivatization for a diversity of guests. We show the pre-formulation of two reactants into a single, well-defined host-guest inclusion crystalline material that can be used for “on demand” solvent-free Wittig olefination[13] reactions of small-molecule aldehydes and a ketone, induced by grinding with a solid base. Moreover, we show that these inclusion compounds can be used to generate 1,1-dibromoolefins *in situ* for their further derivatization, *i.e.* by a Sonogashira-type coupling[14] with terminal acetylenes. This effectively enabled the conversion of an aldehyde into an eneyne and/or an enediyne, proceeding readily and in one-pot by mechanochemistry, but not in solution.

Results and discussion

Key to this work is the herein observed ability of the salt (dibromomethyl)triphenylphosphonium bromide $(PPh_3CHBr_2)^+Br^-$ (**1**) to reliably form small molecule inclusion complexes in the solid state, based on a self-assembled hexameric cage held by charge-assisted halogen bonds (XB). Whereas phosphonium salts of the general type $(PPh_3CHX_2)^+X^-$ (X = Cl, Br, I) have been studied[15] in the context of the Wittig Olefination reaction as precursors to synthetically valuable gem-dihaloolefins,[16] their structures and solid-state properties have been largely unexplored. Compound **1** was synthesized according to a procedure reported by Wolkoff,[17] and was recrystallized from acetonitrile (MeCN) to yield large colorless crystals. Single crystal X-ray structural analysis revealed that the crystals are composed of hexameric cages, each containing six ordered MeCN molecules, held together by R-Br···Br^-···Br-R halogen bonds as part of an apparently unique motif among so far reported halogen-bonded capsules which are mostly dimeric.[18] The resulting material (**1•MeCN**) could be readily desolvated by heating (130 °C) under high vacuum for 12 hours, forming a new phase (**1**) with a distinct powder X-ray diffraction (PXRD) pattern. Dissolution of **1** in hot nitrobenzene followed by slow cooling to room temperature afforded colorless crystals, which were found to be the

solvent-free salt $(PPh_3CHBr_2)^+Br^-$ by single crystal X-ray diffraction. The PXRD pattern simulated for the structure of **1** matched to that of the bulk microcrystalline material.

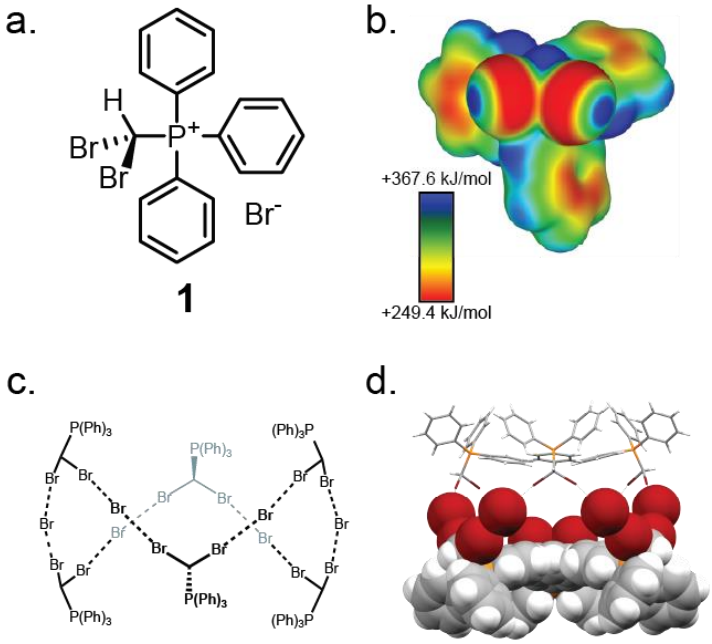


Figure 1. The XB cage based on **1**. a) Schematic representation of the salt (dibromomethyl)triphenylphosphonium bromide (**1**). b) Electrostatic surface potential (ESP) map of the (dibromomethyl)triphenylphosphonium cation of **1**, at an 0.0025 a.u. isosurface level. c) Chemical diagram of the hexameric cage based on **1**, and d) fragment of the single crystal X-ray structure of **1•MeCN** with the MeCN guest molecules omitted. One-half of the cage is displayed as capped sticks, and one-half in space-filling mode.

Compound **1** was found to consistently form the XB cage structure observed in **1•MeCN** upon crystallization from various liquids. Specifically, recrystallization of **1** from a set of 11 additional small-molecule polar liquids (Fig. 2c) provided colorless crystalline **1•guest** solids whose PXRD patterns were in all cases almost identical to that of **1•MeCN**, indicating isostructurality. Diffraction-quality single crystals were obtained for nine of these additional materials, confirming isostructurality and revealing the anticipated inclusion of solvent guest into the hexameric cage held together by R-Br· · ·Br⁻· · ·Br-R halogen bonds between 3.18 Å (for **1•MeNO$_2$**) and 3.45 Å (for **1•NMP**) in length. In most structures, the guest molecules were sufficiently ordered for single crystal X-ray diffraction to reveal six of them located within each the cage, with the electron-rich portions of each guest molecule engaging in short C-H···O (2.37 Å – 2.65 Å) or C-H···N (2.30 Å, for **1•MeCN**) interactions with the phenyl groups of **1**. In almost all cases, residual electron

density was also found at the center of each cage which could not be modelled, indicating the presence of additional and highly disordered guest.

The quantity of **guest** included in each hexameric cage was further investigated using proton nuclear magnetic resonance spectroscopy (^{1}H NMR) in $CDCl_3$ solution and by thermogravimetric analysis (TGA). Analysis by ^{1}H NMR revealed between ca. 6 and 7 **guest** molecules per cage, commensurate with the X-ray single crystal structures, and supporting the presence of additional highly disordered guests in some **1•guest** materials. Similar results were obtained using TGA, where the amount of included guest was evaluated by the height of the mass loss step observed upon heating each **1•guest** material under a flow of N_2. The number of guest molecules per cage for each **1•guest** material, as determined by NMR and TGA, is given in the Supporting Information (SI). All **1•guest** materials were also analyzed by Fourier-Transform Infrared Attenuated Total Reflectance spectroscopy (FTIR-ATR).

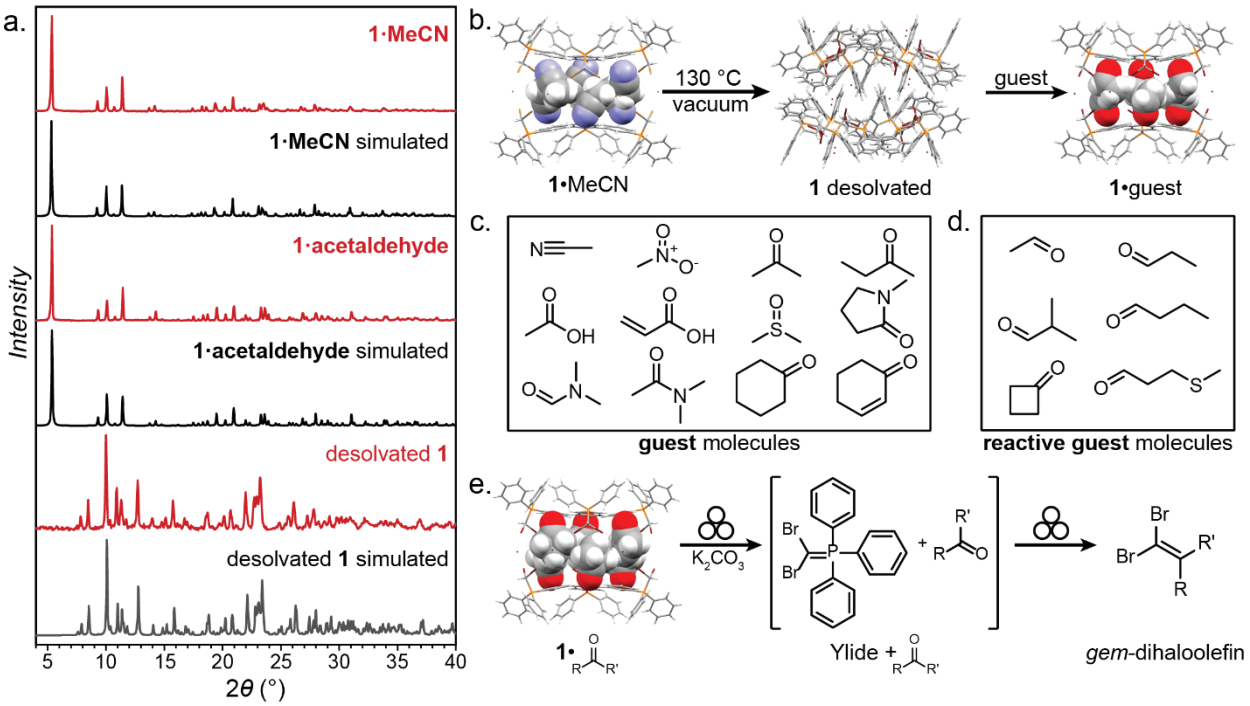


Figure 2. Selected PXRD patterns, guests, and transformations of 1. a) The PXRD patterns of **1•MeCN** and **1•acetaldehyde**, which are similar, indicating isostructurality, and the pattern for desolvated **1,** which is unique. b) Schematic of the desolvation and solvation of **1•MeCN.** c) The **guest** molecules included in the hexameric XB cage of **1**. d) The **reactive-guest** molecules

included in the hexameric XB cage of **1**. e) Reaction scheme of the Wittig olefination of **1•reactive-guest** materials induced by griding with a base (K_2CO_3).

The ready encapsulation of small polar molecules in **1** encouraged us to explore the possibility of encapsulating aldehydes and ketones, which could act as reactive complement to **1** as an ylide precursor in a Wittig Olefination reaction.

In particular, we envisaged that encapsulation of carbonyl compounds within the hexameric cage of **1** could lead to self-assembled **1•reactive-guest** materials isostructural to **1•guest** ones, but in which the included guest molecules would be susceptible to controlled chemical modification by the components of the host cage. Such an arrangement supposes that there is a sufficient barrier to the reaction between the host and guest, so that the solid-state complex can be isolated, stored and characterized without spontaneous reaction. In the herein presented case, **1** represents a stable precursor to the phosphorus ylide which can react with carbonyl compounds to form olefins and is easily and reliably accessible by exposure to a base.

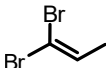
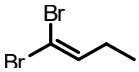
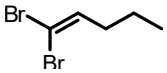
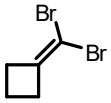
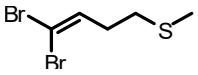
A set of aldehydes and a cyclic ketone were selected as potentially reactive guests for this purpose (Fig. 2d). The salt **1** could be recrystallized directly from cyclobutanone and 3-methylthiopropionaldehyde (methional) by slow cooling, yielding colorless crystals isostructural to **1•MeCN**, as confirmed by their PXRD patterns. Isostructurality was additionally confirmed for the cyclobutanone inclusion compound by scXRD structure determination. The other reactive guest molecules dissolved **1** only slightly, and the **1•reactive-guest** systems were obtained by soaking **1** in an excess of the pure liquid guest overnight. Soaking led to microcrystalline materials whose PXRD patterns indicated isostructurality to **1•MeCN**. Single crystals of the **1•reactive-guest** materials containing acetaldehyde and propionaldehyde were obtained by crystallization from a mixture of the reactive guest and a solvent which dissolves **1** but does not enter the cage (nitrobenzene and diethylpropionamide, respectively). For butyraldehyde and isobutyraldehyde as guests, placing a small amount of **1** in a large excess of the liquid guest overnight yielded single crystals suitable for scXRD structural analysis. Diffraction-quality single crystals could not be obtained for **1•methional** and **1•butyraldehyde**, but the PXRD patterns of these solids strongly indicate isostructurality to other XB cages.

Formation of **1•reactive-guest** was also possible mechanochemically, by milling **1** with a guest compound. In a typical experiment, 100 mg of **1** and 100 μL of the guest were milled for between 5 and 30 minutes in a 15 mL volume zirconia milling jar, using a single zirconia ball of 3.2 g weight, leading to the formation of the **1•reactive-guest** XB cages that were identified by PXRD after milling. Importantly, milling **1** on its own did not lead to the formation of a cage-type phase, instead causing amorphization evident by the disappearance of well-defined reflections in the X-ray powder diffractogram. All six **1•reactive-guest** materials were also analyzed by ^{1}H NMR, TGA, and FTIR-ATR (see SI). The ^{1}H NMR and TGA analyses indicated that the materials contained between four and seven guest molecules per each hexameric cage. Importantly, as each cage is expected to produce six equivalents of a phosphorus ylide upon milling with a base, the herein established compositions of **1•reactive-guest** materials serendipitously correspond to a near-ideal stoichiometry for a Witting Olefination reaction. Solution ^{1}H NMR spectra of all **1•reactive-guest** materials showed the presence of only **1** and the guest molecular species, confirming that the host and guest are stable when in contact and that there is no reactivity between the host and reactive guest in the XB cage.

Next, we explored the potential of the **1•reactive-guest** materials to undergo base-induced Wittig olefination by ball milling 90 mg of each material with 1.1 equivalents of K_2CO_3 for 30 minutes, using a 15 mL volume zirconia milling jar containing a single 3.2 g weight zirconia ball. Immediate ^{1}H NMR analysis of the milled materials showed complete or nearly complete absence of **1** and the presence of triphenylphosphine oxide (TPPO), consistent with a Wittig Olefination reaction.[19] Similarly, PXRD analysis of the milled materials revealed the complete disappearance of Bragg reflections corresponding to the hexameric cage materials, and the appearance of reflections corresponding to TPPO and KBr. Moreover, the signals of the reactive guests in the ^{1}H NMR spectra of milled materials were either significantly reduced or completely absent, replaced by those of the 1,1-dibromoalkenes expected from a Wittig olefination reaction using **1**. The formation of the 1,1-dibromoalkenes was confirmed by comparing solution ^{1}H and ^{13}C NMR spectra to those for isolated pure compounds, which were also characterized by high-resolution mass spectrometry (HRMS). Conversion of **1•reactive-guest** solids into 1,1-dibromoalkenes was determined by comparing the ^{1}H NMR signal integrations for the

reactive guest with those of the 1,1-dibromoalkene product in crude reaction mixtures after milling (Table 1). Conversions were generally >90% for aldehyde-based guests but were lower for cyclobutanone. For isobutyraldehyde, the reaction led to a mixture of products which has so far been challenging to completely analyze.

Table 1. ^{1}H NMR conversions for the mechanochemical Wittig reactions conducted by milling **1•reactive-guest** with 1.1 equivalents of K_2CO_3 as a base (see SI for methods of calculating conversion).

Product	Time (min)	Conversion
	30	98 %
	30	94 %
	30	99%
	60	68 %
	30	99 %

The described **1•reactive-guest** materials represent rare examples of a supramolecular host encapsulating a molecular species which it is capable of derivatizing upon chemical stimulus in the form of base addition. The robustness of the supramolecular cage motif, evident by its persistence when encapsulating a wide array of small polar molecules, presents the opportunity to include any sufficiently small and polar substrate molecule in a predictable, stable, and stoichiometrically-suitable fashion for on-demand derivatization. For volatile liquid substrates such as acetaldehyde, propionaldehyde, and cyclobutanone, this arrangement also provides the additional benefit of mitigating issues related to the storage and measurement of these liquids. Whereas small-molecule aldehydes and ketones are volatile, with boiling points between 20° C and 100° C, their

associated **1•reactive-guest** forms are stable to higher temperatures, as shown by TGA (Figure 3). Additionally, the formation of **1•reactive-guest** materials by crystallization, soaking, or milling acts as a means to select a stoichiometrically-appropriate quantity of substrate.

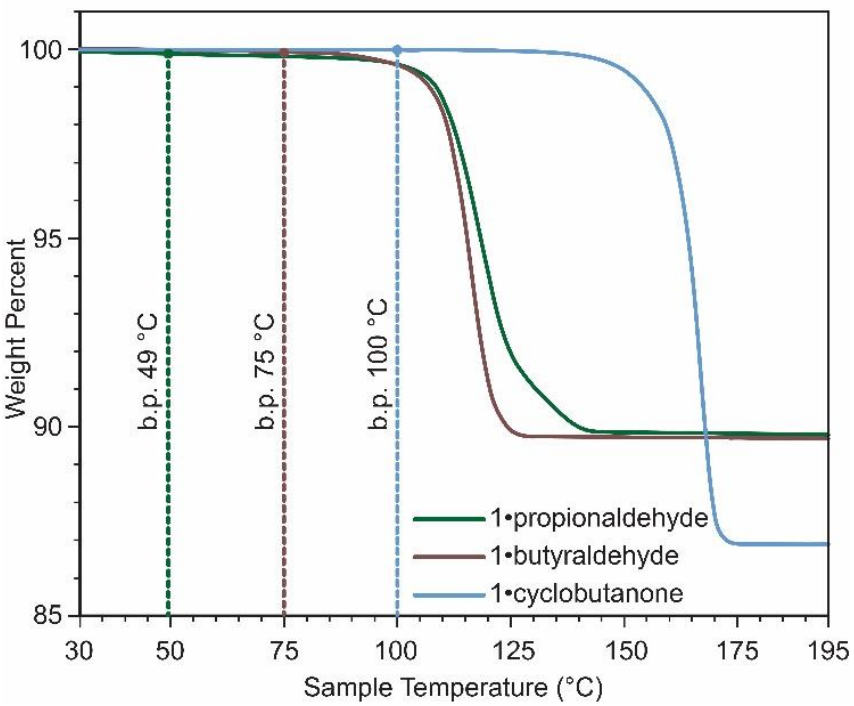


Figure 3. TGA thermograms of **1•reactive-guest** materials with the boiling point of each **reactive-guest** marked with a dotted line. Encapsulating low-boiling liquids using **1** mitigates their volatility; **1•reactive-guest** materials containing propionaldehyde, butyraldehyde, and cyclobutanone are stable to temperatures beyond the boiling points of the guests themselves.

Based on the reliability and simplicity of the olefination reactions conducted by milling **1•reactive-guest** with a base, we hypothesized that these materials could also act as supramolecular solid-state equivalents of normally volatile and difficult to store 1,1-dibromoalkenes in the context of further chemical derivatization. Such a possibility would allow for the replacement of volatile, reactive *gem*-dihaloolefins with stable precursor **1•reactive-guest** solids based on aldehydes or ketones. To validate this possibility, we focused on the palladium- and copper-catalyzed Sonogashira cross-coupling of alkynes with vinyl dibromides (Figure 4) as a model reaction.[20] Milling of solid **1•butyraldehyde** with 2 equivalents of anhydrous K_2CO_3 and 2.2 equivalents of (trimethylsilyl)acetylene in the presence of 10 mol % of $PdCl_2$(**dppf**)$_2$ and 8 mol % of CuI for 30 minutes led to one-pot conversion of butyraldehyde to a mixture of mono- (eneyne) and di-coupled

(enediyne) Sonogashira products, with a significant amount of the intermediate *gem*-dihaloolefin remaining.

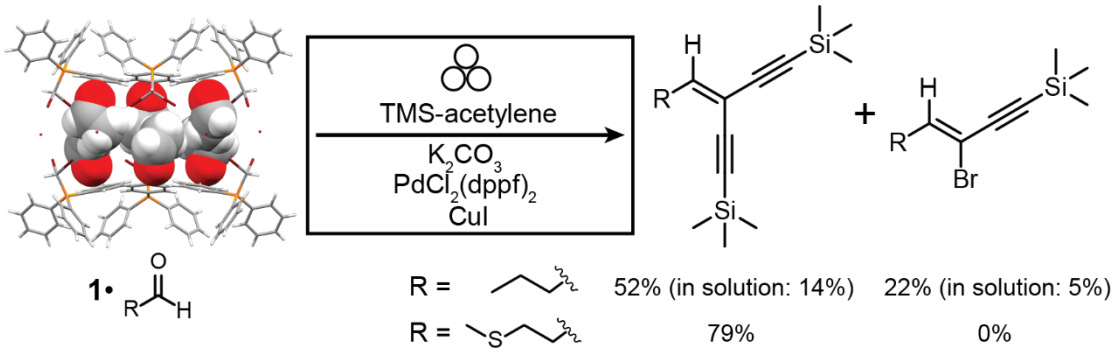


Figure 4. Reaction scheme for the one-pot Wittig olefination and Sonogashira coupling of aldehydes to form enediyne and eneyne products using **1•reactive-guest** starting materials. Conversions for mechanochemical reactions are given in comparison to those for analogous reactions attempted in solution. Overview of reaction conditions and yields for mechanochemical reactions is shown in Table 2, and those for analogous reactions in solution are given in Table S2.1 (see SI).

Optimization of the milling reaction by altering the milling time, quantity and solid form (anhydrous or sesquihydrate) of the K_2CO_3 base, and quantity of (trimethylsilyl)acetylene, allowed for the near-complete disappearance of the *gem*-dihaloolefin intermediate and conversions of 52% for the enediyne and 22% for the eneyne Sonogashira products as determined by ^{1}H NMR spectroscopy (Table 2). The enediyne product was isolated by column chromatography for the best performing reaction (reaction 6, Table 2), and gave an isolated yield of 45%, in good agreement with the 52% conversion determined by ^{1}H NMR of the crude mixture. The sesquihydrate of K_2CO_3. generally performed better than the anhydrate as a base in these milling experiments. For the cage material containing 3-methylthiopropionaldehyde (**1•methional**), the enediyne product was obtained in 79% conversion, as determined by ^{1}H NMR.

Importantly, several attempts to reproduce the one-pot Wittig Olefination and Sonogashira coupling starting from **1•butyraldehyde** in solution, using either K_2CO_3 or diisopropylamine[21] as a base, have produced zero or significantly lower conversion to eneyne or enediyne products compared to the optimized milling protocol, highlighting the efficiency and simplicity of the presented solid-state methodology (see SI). Moreover, Sonogashira coupling in solution starting from purified pre-synthesized 1,1-dihaloolefins

using K_2CO_3 as a base produced only modest conversions to eneyne and enediyne products after 24 hours. In our hands, the only route to obtain the Sonogashira reaction coupling products in high yields in solution was by first isolating the corresponding vinyl bromide reactant, followed by coupling in the presence of diisopropylamine base (see SI).[21] Overall, the use of **1•butyraldehyde** as a supramolecular surrogate of the corresponding vinyl bromide enabled direct and efficient one-pot mechanochemical conversion of butyraldehyde into corresponding eneyne and enediyne derivatives without the need, apparently necessary in the solution environment, to isolate the 1,1-dibromolefin and resort to an amine base.

Table 2. Reaction conditions and resulting conversions to eneyne and enediyne products for mechanochemical one-pot Wittig olefination and Sonogashira coupling using **1•butyraldehyde.** Conversions have been determined by ^{1}H NMR (see SI) and, unless otherwise notes, K_2CO_3 was used in sesquihydrate form. For comparison with analogous solution-based reactions, see SI Table S2.1.

entry	K_2CO_3 (equivalents)	TMS-acetylene (equivalents)	*t* (min)	1,1-dibromoalkene	eneyne conversion	enediyne conversion
1	2 (anhydrous)	2.2	30	17 %	17 %	17%
2	2	2.2	30	9 %	17 %	22%
3	2.5	2.2	30	9 %	35 %	39%
4	2.5	3.3	30	9%	43 %	22%
5	2.5	3.3	90	trace	22%	52% (45%)
6	2.5	3.3	180	trace	4%	40%

Next, we explored expanding the **1•guest** cage motif to chloro- and iodo-congeners of **1**. To this end, (dichloromethyl)triphenylphosphonium chloride (**2**) was synthesized following a modified procedure reported by Appel,[22] and was recrystallized from MeCN to yield single crystals suitable for scXRD analysis. Instead of forming a

halogen-bonded cage analogous to **1•MeCN** , **2** adopts a dense-packed non-solvated structure exhibiting C-H···Cl^- hydrogen bonding interactions. All attempts to obtain a cage based on **2** have been unsuccessful, which is rationalized by the weak σ-hole character of chlorine atoms as XB donors.

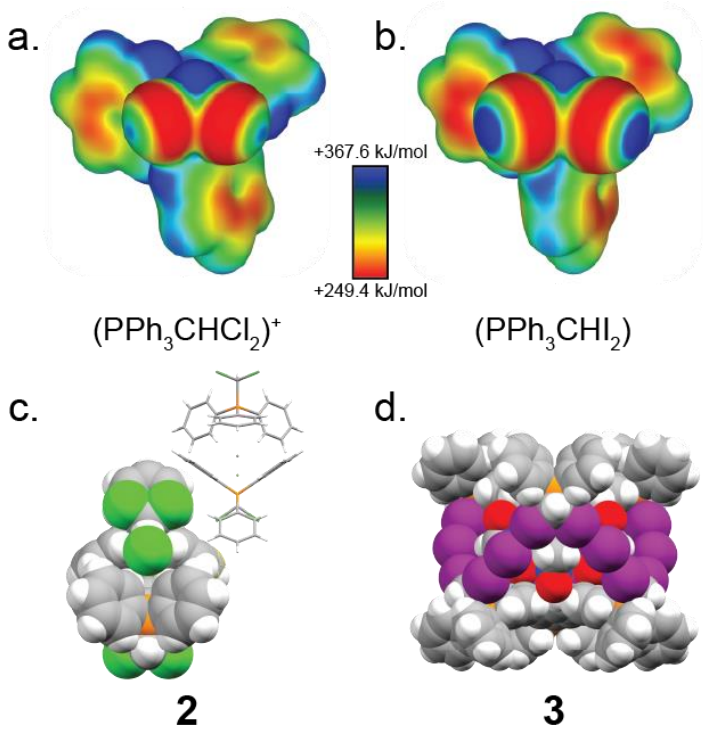


Figure 5. Overview of the structures of **2** and **3**. a) Electrostatic surface potential (ESP) map of the (dichloromethyl)triphenylphosphonium cation, **2**, plotted at an 0.0025 a.u. isosurface level. b) ESP map of the (diiodo)triphenylphosphonium cation, **3**, plotted at an 0.0025 a.u. isosurface level. c) Fragment of the single crystal X-ray structure of **2**, with one formula unit displayed in space-filling mode, and one formula unit displayed as capped sticks. d) Fragment of the single crystal X-ray structure of **4**, which adopts the XB cage structure with nitromethane as the guest.

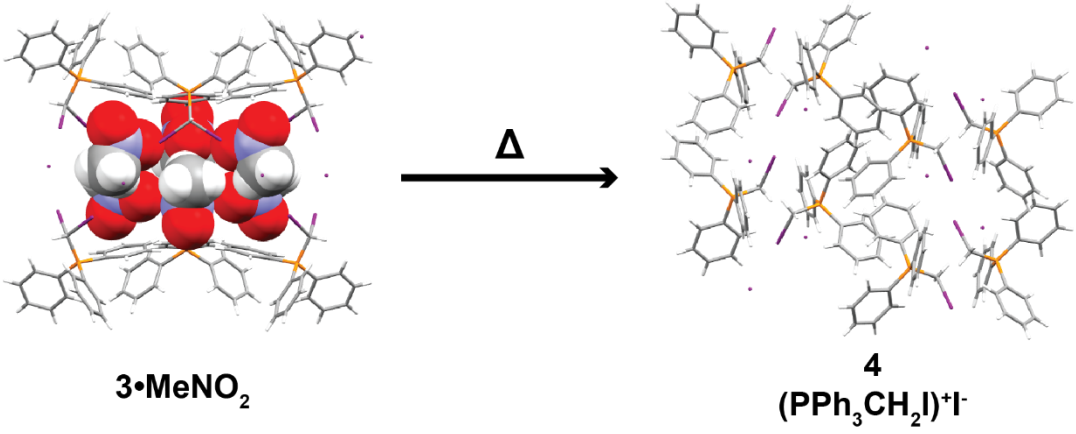


Figure 6. Reaction scheme of the decomposition of **3•MeNO$_2$** to **4** by heating. The salt **3** converts to its monoiodinated analogue, **4**, when dissolved in solvent and heated, or left to crystallize in open air for extended periods of time.

Iodine is known to engage in XB interactions with greater propensity than bromine or chlorine,[23] suggesting a way to obtain materials analogous to **1•guest**. Heating to reflux a solution of iodoform with one equivalent of triphenylphosphine in MeCN gave mostly (diiodomethyl)triphenylphosphonium iodide, **3**, as a yellow solid with a PXRD pattern suggesting a structure similar to **1•MeCN**. Dissolution of this powder in nitromethane followed by rapid crystallization under reduced pressure yielded crystals suitable for scXRD analysis, which revealed XB cages isostructural to those in **1•MeCN** (Fig. 5d). However, **3** was found to readily decompose, forming (iodomethyl)triphenylphosphonium iodide (**4**), identified by scXRD analysis of crystals grown by heating **3** in $MeNO_2$ until boiling, followed by slow cooling of the solution (Fig. 6).

Conclusion

We have presented a proof-of-principle of a supramolecular halogen-bonded host that encapsulates molecular species which are susceptible to specific and controlled chemical transformation by the host itself. This strategy allows for the creation of thermally stable complexes of guest aldehydes or ketones with a phosphonium salt host, in a stoichiometric ratio that is very close to that required for Wittig olefination reaction. Consequently, these host-guest complexes can be used as solid-state supramolecular surrogates of otherwise otherwise volatile vinyl bromides, that are readily and in high conversions generated by mechanochemical treatment of the solid-state complexes with a base. This approach also enables more complex one-pot transformations by mechanochemistry, illustrated herein by the tandem Wittig Olefination/Sonogashira coupling which proceeded readily through mechanochemistry, but was significantly less efficient when attempted in solution. These results, while currently limited in the choice of reagents, serve as a proof-of-principle to illustrate how the use of a reactive host-guest complex as a supramolecular surrogate of a vinyl bromide in the solid state not only simplifies derivatization of volatile aldehydes and a ketone, but also enables otherwise inefficient, more complex one-pot transformations. Work is ongoing to expand this

methodology to additional carbonyl-containing substrates, and to explore other reaction systems which could benefit from using host-guest assemblies as supramolecular surrogates.

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