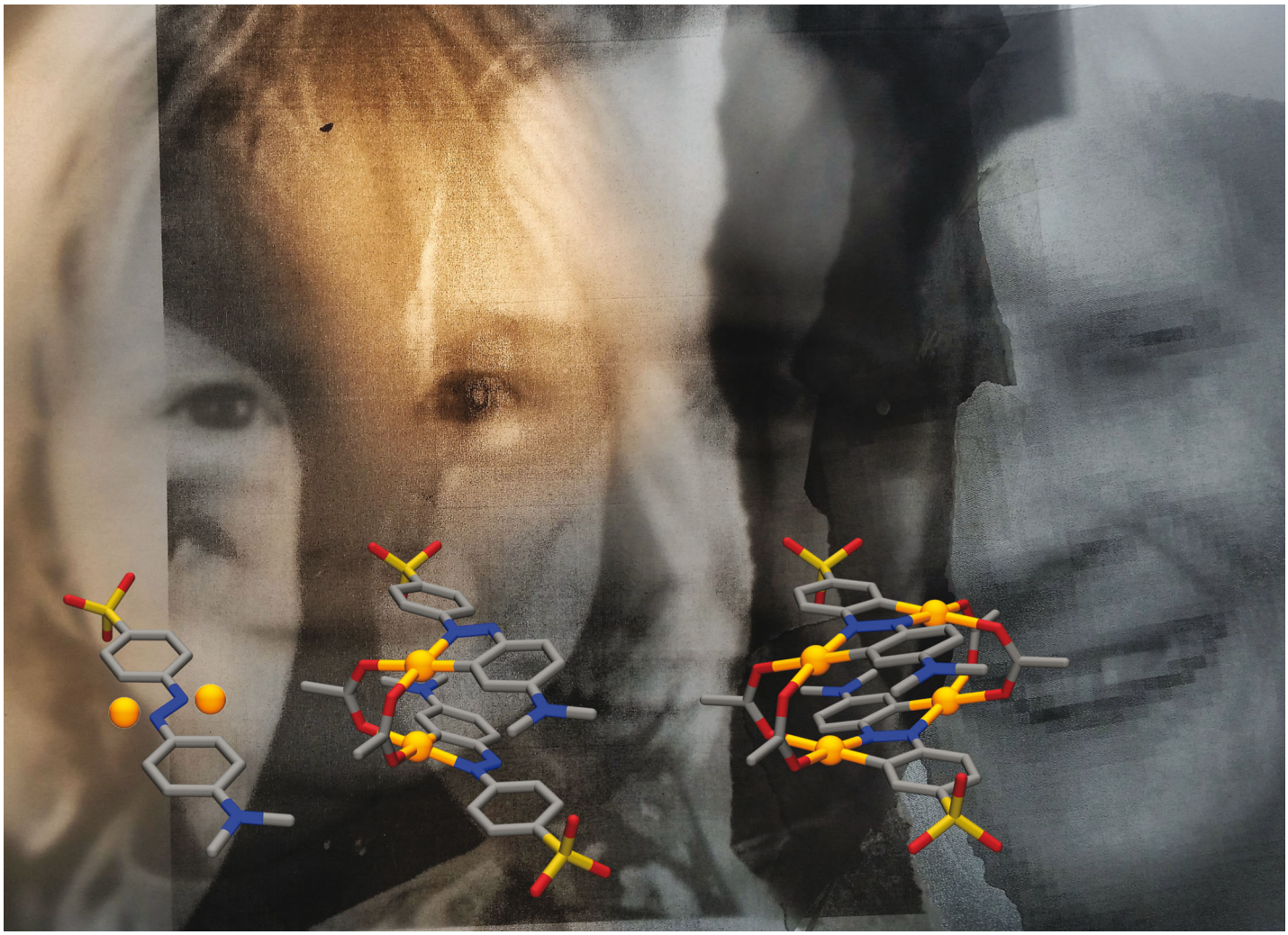

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Vapour-induced solid-state C–H bond activation for the clean synthesis of an organopalladium biothiol sensor

A unique case of C–H bond activation by accelerated aging process leads to quantitative cyclopalladation of azobenzenes. Dicyclopalladated methyl orange is a clean and water-soluble biothiol sensor. Slower aging reactions may thus overrun conventional procedures in terms of yield and product purity, essential for biological applications.

Cover art created by Danko Friščić.

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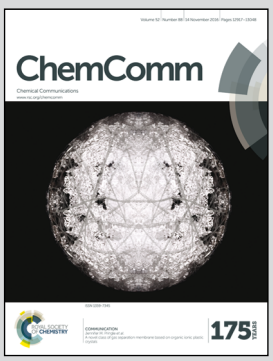

See Marina Juribašić Kulcsár, Manda Ćurić *et al.*, *Chem. Commun.*, 2016, **52**, 12960.

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Vapour-induced solid-state C–H bond activation for the clean synthesis of an organopalladium biothiol sensor†

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Room-temperature accelerated aging in the solid state has been applied for atom- and energy-efficient activation of either one or two C–H bonds of azobenzene and methyl orange by palladium(II) acetate. Organopalladium complexes are prepared in quantitative reactions without potentially harmful side products. Dicyclopalladated methyl orange is water-soluble and is a selective chromogenic biothiol sensor at physiologically-relevant micromolar concentrations in buffered aqueous media.

Palladium-mediated C–H bond activation for preparing cyclopalladated compounds[1] is a long-standing research topic with applications in organic synthesis and catalysis,[1,2] in materials science[1] and, recently, in the design of photosensitizers and biomolecular labels.[1,3,4] Conventional synthetic procedures for the preparation of organopalladium compounds are usually based on reactions in toxic organic solvents and often require elevated temperatures.[1b] Recently, however, mechanochemical reactions in the solid-state have emerged as a viable alternative to conventional solvent-based chemistry[5,6] and have thus far been applied for the synthesis of a large variety of compounds,[7–12] including transition-metal catalysed C–H bond functionalization.[13] Mechanochemical reactions, however, may not be suitable for the synthesis of soft or solvated materials, especially when prolonged milling is required.[14] Next to mechanochemical methods, it was only recently shown that solid-state reactions can be carried out by controlled exposure of solid mixtures to vapour. Such an approach is called vapour digestion, accelerated aging or simply aging.[6] Despite its reported efficiency, it has been used in the preparation of only a limited number of compounds.[6,15–17] By avoiding agitation of the reaction mixture, aging reactions are often slower than the corresponding milling reactions while still providing clean products in quantitative yield as well as unique reaction selectivity.[15a,17a] Moreover, aging reactions offer easier handling and processing of the reaction mixture and require a far lower energy input. In addition, due to their purity, compounds and materials prepared by aging may be more suitable for biological applications.

Our group has focused on azobenzene organopalladium compounds that exhibit strong light absorption and emission in the visible region which can be tuned by ancillary ligands on the azobenzene moiety.[3a,18] This property, coupled with the ability of amino acids and other biomolecules to bind to Pd(II) centres,[19] qualifies them as candidates for biomolecular labelling. In particular, discrimination among various amino acids and small biothiol molecules (*e.g.* cysteine, homocysteine, glutathione, cystine) under physiological conditions is challenging due to their similar molecular structures and reactivity.[20] Herein, we demonstrate vapour-induced room-temperature C–H bond activation in the solid state as a new, clean and energy-efficient methodology for the preparation of cyclopalladated azobenzene compounds (Fig. 1). The dicyclopalladated product, obtained directly from palladium(II) acetate and

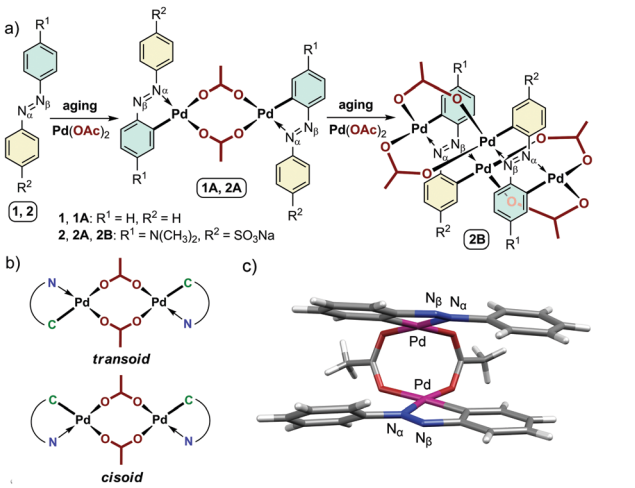

Fig. 1 (a) C–H bond activation in azobenzenes by accelerated aging; (b) cisoid and transoid isomers in obtained products; and (c) molecular structure of the transoid monocyclopalladated compound **1A**.

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methyl orange, proved to be a highly sensitive chromogenic biothiol sensor even in the vast excess of amino acid competitors.

Prior to aging reactions, solid reactants in the molar ratio 1 : 1 or 1 : 2 of either azobenzene (**1**) or methyl orange (**2**) and $Pd(OAc)_2$ were mixed by gentle grinding in an agate mortar. Thus prepared mixtures were placed in closed vials saturated with vapours of selected liquids: *N*,*N*-dimethylformamide (DMF), acetic acid (AcOH), water or equimolar mixtures H_2O/DMF and H_2O/AcOH. Aging of solid mixtures has also been performed in air (20–23 °C, relative humidity 50–70%). Reaction progress and completion was monitored by ^{1}H NMR spectroscopy (Fig. S1–S11, ESI†), which also confirmed that no reaction occurred during the initial mixing of reactants. Reactions were repeated at least five times and were fully reproducible. The azobenzene ligands were used to evaluate conversion. Products were characterized in the solid state by attenuated total reflectance infrared spectroscopy (ATR-IR) (Fig. S12 and S13, ESI†) and powder X-ray diffraction (PXRD) (Fig. S14 and S15, ESI†).

First, we have studied the solid-state reactivity of the parent azobenzene towards palladium(II) acetate. Regardless of the starting reactants' molar ratio, aging in DMF vapour yielded exclusively the monocyclopalladated product **1A** with complete conversion of **1** in two days (Fig. S2, ESI†). Aging reaction in AcOH vapour was extremely slow and incomplete even after 35 days whereas aging in H_2O vapour or in air did not yield any product. The corresponding mechanochemical dry milling reaction in PMMA vials using steel balls resulted in a mixture of **1A** and both the ligand and $Pd(OAc)_2$ after more than 60 hours milling at 30 Hz operation rate. In liquid-assisted grinding[5] (LAG) reactions, even with very small amounts of DMF, the reaction mixture would get stuck on the vial wall or on the milling balls forming a hard lump, which most likely prevented proper mixing and complete formation of product **1A**. Reaction in DMF solution resulted in **1A** with 55% isolated yield after four weeks stirring at room temperature.

^{1}H NMR spectra of complex **1A** obtained by aging and solvent-based reactions are characterized by a double set of signals (Fig. S2–S5 and Table S1, ESI†) due to the presence of cisoid and transoid geometric isomers (Fig. 1b and Fig. S1, ESI†).[1b,11] The more intense set of signals in the ^{1}H NMR spectra of **1A** have been assigned to the more stable transoid isomer according to DFT calculations. The ratio of the two isomers in solution did not change during variable temperature ^{1}H NMR experiments from −25 to 50 °C (Fig. S5, ESI†). The transoid configuration in solid **1A** was confirmed after isolation and single-crystal X-ray diffraction structure determination of two polymorphs of **1A** (Fig. 1c and Fig. S16–S19, ESI†). Conformations of molecules of **1A** in both polymorphs are almost identical to two monocyclopalladated azobenzene moieties bonded by two bridging acetate ligands in an anti open-book arrangement.[11,21] PXRD analysis of bulk samples obtained from aging reactions in DMF showed exclusive formation of one polymorph (Fig. S14, ESI†).

Our second target, methyl orange, which bears a strong electron-donating substituent on the phenyl ring, is far more reactive than the parent azobenzene and, more importantly, provides water-soluble cyclopalladated products. NMR monitoring of aging reactions of methyl orange and $Pd(OAc)_2$ revealed the formation of one regioisomer of the monocyclopalladated **2A** as an intermediate on the path to the dicyclopalladated **2B**, confirming the regioselectivity of the aging reaction (Fig. S6 and S7, ESI†). The first C–H bond activation occurs on the *p*-(*N*,*N*-dimethylamino)phenyl ring (Fig. 1a). Quantitative formation of **2B** in DMF vapour required 2 days (Fig. S8, ESI†). Aging in AcOH vapour afforded the product in 7 days whereas aging in H_2O vapour was the slowest taking at least 35 days. However, when the reaction mixture of **2** and $Pd(OAc)_2$ was exposed to vapour mixtures H_2O/DMF or H_2O/AcOH, quantitative formation of **2B** required only 1.5 or 1 day, respectively. Aging of the reaction mixture of **2** and $Pd(OAc)_2$ in air for several months did not yield any product, confirming that all employed vapours promote cyclopalladation in the solid state (Fig. S7, ESI†). Product **2B** could also be obtained quantitatively in 3.5 hours using LAG mechanochemical synthesis with DMF as the liquid additive. The synthesis of **2B** in DMF solution required a large excess of $Pd(OAc)_2$ (4 : 1) and resulted in 48% isolated yield after 3 weeks of stirring at room temperature. A double set of signals has also been observed in the ^{1}H NMR spectrum of **2B** obtained by aging, mechanochemical or solvent-based reactions corresponding to a mixture of cisoid and transoid isomers (Fig. S8–S10, ESI†). According to the literature[11] more intense signals have been assigned to the cisoid isomer (Fig. 1a and Table S1, ESI†). The ratio of the cisoid to transoid isomers of **2B** in solution did not change in the temperature range from −25 to 50 °C (Fig. S9, ESI†). The ratio depended on the synthetic method and was the highest for the aging product from DMF where the cisoid isomer isolated was almost pure (Fig. S10, ESI†). All attempts to prepare pure monocyclopalladated **2A** were unsuccessful regardless of the employed synthetic method. It was always isolated with **2B** and ligand impurities (Fig. S6 and S11, ESI†), suggesting a high affinity of methyl orange towards dicyclopalladation. Faster reactions with methyl orange and formation of the dicyclopalladated product **2B** can be attributed to the strong electron-donating effect of the *N*,*N*-dimethylamino group.[1a,18a,c,22]

Breaking of the trimeric structure of palladium(II) acetate, $Pd_3(OAc)_6$, is essential for its reactivity.[1,23] Cyclopalladation reactions with palladium(II) acetate primarily follow the ambiphilic concerted metallation–deprotonation mechanism *via* an agostic intermediate where the coordinated ligand (acetate, carbonate, *etc.*) acts as an intramolecular base to accept the proton simultaneously with Pd–C bond formation.[1,21,24] The acetate is a stronger base in AcOH and binds better to the Pd(II) centre, which accelerates the cyclopalladation reaction.[1a] Furthermore, the active role of basic DMF as an external base in the proton abstraction was supported by mechanistic studies of cyclopalladation of *N*-donor ligands, *N*-benzyl triamines[25] and azobenzenes,[18c] in DMF solution and of nucleophilic substitution on the carbonyl group in the solid state.[8a] Thus, two key steps in the reaction mechanism could be influenced by the choice of vapour: first, breaking of the trimer $Pd_3(OAc)_6$ which could be facilitated by H_2O vapour;[1,21,23] and second, the cyclopalladation step which could be promoted by basic DMF or AcOH.

Since organic bases facilitate proton abstraction in the solid state,[8a,15a,b,26] we performed aging reaction of **2** with $Pd(OAc)_2$ in H_2O/*N*,*N*,*N*-triethylamine (TEA) vapour. ^{1}H NMR spectra revealed that TEA reacted with $Pd(OAc)_2$ and consumed the Pd source which hampered the cyclopalladation reaction. This is a consequence of

coordination of TEA to Pd(II) *via* nitrogen whereas DMF, AcOH and H_2O coordinate to Pd(II) *via* oxygen.[18c,21,23a,c,27] Overall, these results suggest that the progress of C–H bond activation by aging may be influenced by proper selection of the azobenzene ligand as well as by the acid–base of the vapour used for the reaction.

Product **2B** obtained by aging using H_2O/AcOH seems to be most convenient for biological applications. It is readily soluble in water and stable in buffered media, which makes it suitable for studies under physiologically-relevant conditions using aqueous phosphate buffer (pH 7.4).

Biomolecules, especially amino acids, are known to bind to Pd(II) centres, enabling these compounds to be used as biosensors.[19] In this context, the affinity of **2B** with its four readily exchangeable acetate ligands towards representative natural amino acids (AAs) was explored. Special attention was dedicated to biothiols (AAs–SH) which, together with their derivatives, play a crucial physiological role in biological processes, ranging from protein folding to cellular metabolism and oxidative stress response, and have been investigated as potential indicators of disease risk and health status.[28] UV-vis spectroscopy was used to study reactions of **2B** with glycine (Gly), L-alanine (Ala), L-tryptophan (Trp), L-glutaminic acid (Glu), and L-lysine (Lys). In addition, three groups of natural sulphur-containing molecules were examined: biothiols, *i.e.* L-cysteine (Cys), L-homocysteine (hCys) and L-glutathione (GSH, γ-L-glutamyl-L-cysteinylglycine); their derivatives, *i.e.* *S*-methyl-L-cysteine (MeCys) and L-methionine (Met, *S*-methyl-L-homocysteine); and their oxidized dimers, *i.e.* L-cystine (CSSC, oxidized Cys) and L-glutathiol (GSSG, oxidized GSH).

Compared to previously explored cyclopalladated compounds,[4b] **2B** reacts readily with AAs at room temperature, allowing rapid visual distinction of compounds with free thiol groups from other common AAs and compounds with substituted or oxidized thiol groups. Complex **2B** clearly differentiates thiol derivatives Cys/MeCys/CSSC, hCys/Met and GSH/GSSG. At least four AA equivalents are required for the chromogenic change. The "naked-eye" biothiol detection limit is extended down to a low micromolar concentration range (*e.g.* about 10 μM for Cys) (Fig. 2) which is comparable with physiological concentrations of Cys, hCys and GSH in human plasma, *i.e.* about 200, 7 and 4 μM, respectively.[28b]

The light purple colour of an aqueous solution of **2B** changed in *ca.* 10 minutes after addition of AA (4 eq.) at 20 °C, indicating the high affinity of **2B** towards AAs (Fig. 2). Thiol-containing AAs changed the solution colour to red whereas other AAs changed it to blue, clearly differentiating biothiols from other AAs (Fig. 2b). These colour changes were observed for both 3 and 6 μM solution of **2B** (Fig. 2c and d, Fig. S21, S22, ESI†). Reactions with Cys and hCys took only a few minutes, which were faster than with other AAs. GSH, CSSC and GSSG reacted slowly (up to 10, 40 and 70 hours, respectively) with **2B**. In addition, CSSC disulphide bridge reduction in solution could be monitored by a gradual colour change from violet to red.

The chromogenic response of **2B** to amino acids and biothiols was followed by UV-vis spectroscopy (Fig. 2a) starting with the spectrum of **2B**, which is characterized by a band at 540 nm and a broad band in the range of 600–800 nm. After addition of Cys (4 eq.), the solution of **2B** exhibited a strong absorption band at

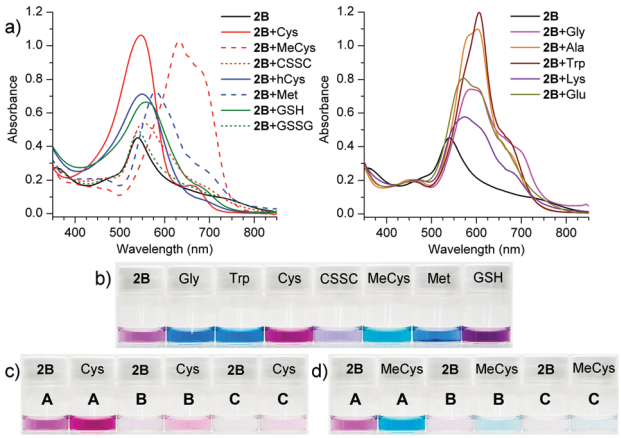

Fig. 2 Chromogenic behaviour of **2B** with AAs: (a) UV-vis spectra of **2B** (24 μM) after adding 4 equivalents of AA showing selected S-containing AAs separately (left) from other AAs (right). (b) Solutions of **2B** after adding selected AA (4 eq.). Solutions with different concentrations of **2B** and (c) Cys (4 eq.) or (d) MeCys (4 eq.). 24, 6 and 3 μM concentrations of **2B** in (c) and (d) are marked A, B, and C, respectively. Data were collected at 20 °C in 20 mM sodium phosphate buffer (pH 7.4).

547 nm and a lower intensity band at 665 nm, whereas adding GSH or hCys (4 eq.) induced an intensity increase and broadening of the band at 540 nm. Addition of other AAs to **2B** solution shifted the band at 540 nm to longer wavelengths.

The high selectivity of **2B** for SH-containing compounds was further confirmed by competition experiments using a mixture of AAs (30 eq. of each Gly, Ala, Trp, Met, Glu and Lys) (Fig. 3a). The blue solution of **2B** and the mixture of AAs changed to red immediately upon addition of AA–SH (4–30 eq.), clearly indicating significantly stronger affinity of **2B** to thiols with respect to other functionalities. The red solution of **2B** containing AA–SH (4 eq.) remained unchanged upon addition of an excess of other AAs (30 eq.). AA–SH pairs were used for testing the differences in the affinity of **2B** toward biothiols (Fig. 3b) and it was revealed that the exchange of coordinated thiols was slow at room temperature and could be accelerated by incubating at elevated temperatures (Fig. S25, ESI†).

Reactions of **2A** with AAs could not be studied in detail as a pure **2A** sample could not be obtained. Qualitative evaluation of the reaction of the mixture of **2A** and **2** with the selected AAs

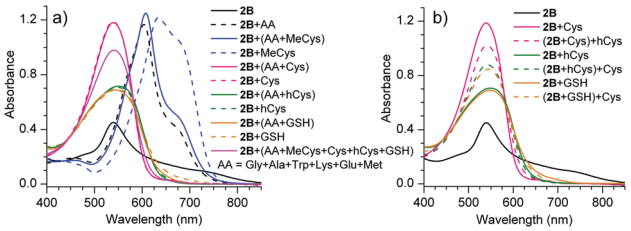

Fig. 3 (a) UV-vis spectra of **2B** (24 μM) recorded 5 hours after adding selected AA (30 eq.) or AA mixtures (30 eq. of each AA). (b) Competition experiments for AAs–SH (30 eq.). One selected AA–SH (Cys, hCys or GSH; 30 eq.) was added to the solution of **2B** (24 μM) and the UV-vis spectrum was recorded after 5 hours at 20 °C (full lines). Another different AA–SH (30 eq.) was added to the above prepared solutions and the UV-vis spectra were recorded after 5 hours at 20 °C (dashed lines).

(Ala, MeCys, Cys and hCys, Fig. S26, ESI†) showed small changes in UV-vis spectra, resulting in almost the same solution colour.

As a possible explanation for the observed differences, we propose different binding modes of AAs and AAs–SH. Since palladium(II) prefers the coordination *via* five-membered chelate rings and has a strong affinity for sulphur and nitrogen and a weaker affinity for oxygen donor atoms,[1b] we propose a N,S–chelate mode for AAs–SH and their derivatives, whereas a N,O–chelate mode for other AAs, which is in accordance with previously described palladium complexes with amino acids.[19]

In summary, we have presented the first and unique case of solid-state C–H bond activation performed by mild and clean aging of solid reactants in vapours of suitable liquids. Even the vapour of "green liquids", such as acetic acid or water, activated an inert C–H bond, yielding clean cyclopalladated products. For the unsymmetrical methyl orange, C–H bond activation proceeded regioselectively, over a monocyclopalladated intermediate, while the extent and time needed for the reaction to finish are highly dependent on the employed vapour mixture. Using H_2O/AcOH vapour, the reaction was fastest and over in under 24 hours. Dicyclopalladated methyl orange is water-soluble and shows a high affinity towards amino acids, where its selective chromogenic behaviour allows for visual detection of physiologically-relevant levels of biothiols. These properties make this compound a promising candidate for biological applications. A more detailed study in this direction is in progress.

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