Dosage delivery of sensitive reagents enables glove-box-free synthesis

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Contemporary organic chemists employ a broad range of catalytic and stoichiometric methods to construct molecules for applications in the material sciences1, and as pharmaceuticals2–5, agrochemicals, and sensors6. The utility of a synthetic method may be greatly reduced if it relies on a glove box to enable the use of air- and moisture-sensitive reagents or catalysts. Furthermore, many synthetic chemistry laboratories have numerous containers of partially used reagents that have been spoiled by exposure to the ambient atmosphere. This is exceptionally wasteful from both an environmental and a cost perspective. Here we report an encapsulation method for stabilizing and storing air- and moisture-sensitive compounds. We demonstrate this approach in three contexts, by describing single-use capsules that contain all of the reagents (catalysts, ligands, and bases) necessary for the glove-box-free palladium-catalysed carbon–fluorine7–9, carbon–nitrogen10,11, and carbon–carbon12 bond-forming reactions. This strategy should reduce the number of error-prone, tedious and time-consuming weighing procedures required for such syntheses and should be applicable to a wide range of reagents, catalysts, and substrate combinations.

We sought to develop a system to allow for the bench-top storage of pre-measured quantities of air- and moisture-sensitive reagents and catalysts in such a way that the contained material would be liberated into a reaction mixture upon subjection to typical reaction conditions. We initially chose paraffin wax as a stabilizing agent as it has been shown to be an effective material for protecting sensitive compounds from oxygen and water in the atmosphere13–16. For instance, a paraffin wax dispersion of normally pyrophoric potassium hydride can be easily handled and is relatively stable under ambient laboratory conditions17. As such, preliminary work focused on creating dispersions of reagent and reagent mixtures using molten paraffin wax, although it was not possible to achieve a uniform distribution of the components within the paraffin matrix, making it impossible to determine the concentration of the constituents for a given sample. Moreover, reagents located on the surface are exposed to the atmosphere, and free to react with air and water. To address these shortcomings, we developed a simple method to enclose premeasured amounts of catalysts and reagents within paraffin capsules, isolating them from the atmosphere. Hollow paraffin (melting point 58–62°C) shells were manually prepared and filled with catalyst and reagent combinations, thus providing a single stabilized entity with which to conveniently carry out a variety of transformations (Supplementary Figs 1–4). To probe the effectiveness of the encapsulation technology, we first studied the oxygen- and moisture-sensitive palladium-catalysed nucleophilic fluorination of aryl triflates (ArOTfS) (Fig. 1a)7–9. Fluorinated aromatics are a common motif found in pharmaceuticals and agrochemicals, and are introduced to impart metabolic stability and enhanced lipophilicity8. The introduction of a fluorine atom can also increase protein-binding affinity18 and affect the orientation and conformation of a molecule when binding to a protein19. As a result, the synthesis of fluorinated compounds has generated great interest20. Traditional methods22,23 of incorporating a fluorine atom onto an aromatic ring typically require harsh conditions, which limits the scope of these transformations and necessitates the introduction of fluorine early in the synthesis. In contrast, palladium catalysis allows for the late-stage transformation of ArOTfS and aryl bromides (ArBr) to the corresponding aryl fluoride (Ar–F), providing good yields and exhibiting a much broader substrate scope. In addition to the well-documented challenges associated with this transformation24,25, which includes a difficult reductive elimination (RE) step, care must be taken to exclude water to prevent proto-demetallation (ArH) and formation of phenol (ArOH) and biaryl ether (Ar–O–Ar) side products. The metal fluoride salts (caesium fluoride (CsF) and silver(I) fluoride (AgF)) used in these reactions are hygroscopic, and the Pd(0) precatalyst is sensitive towards oxygen8, which requires the reaction to be set up in a glove box.

To address problems arising from stability, the hollow paraffin shells were charged with 2 mol% P1 (4 mol% of Pd) using L1 as the supporting ligand and 3 mmol of CsF (Fig. 1b, blue capsule), and stored on the bench top. With the capsules in hand, the reaction set-up is inherently simple. The desired ArOTfS (1 mmol) is added to an oven-dried reaction tube equipped with a stir bar, followed by a capsule. After evacuating the tube and backfilling with argon, solvent is added. Upon heating to the specified temperature, the capsule melts and releases its contents, initiating the transformation. When the reaction is complete, the paraffin is easily removed by precipitation, filtration, and silica gel chromatography.

With this method, a variety of aryl (1–4) and heteroaryl (5, 6) fluorides could be prepared in yields that are comparable to those obtained with the aid of a glove box (Fig. 1c). While some examples were previously reported using lower catalyst loadings (2–3 mol% Pd), 2 mol% P1 (4 mol% Pd) was loaded into each capsule to provide a universal reagent capable of transforming all desired ArOTfS—facilitating operational simplicity. To demonstrate the robustness of this technology, a capsule was suspended in a beaker of water for 24 h, dried with a paper towel, and used in a reaction to provide the Ar–F in undiminished yield (Fig. 1c, 3). However, a capsule that was kept on the bench top at room temperature for over eight months showed decreased activity and required elevated reaction temperatures to achieve full conversion of the starting material (Supplementary Table 1).

With this initial success, we applied the capsule method to the palladium-catalysed nucleophilic fluorination of aryl bromides (ArBr) (Fig. 2). As previously described9, two fluoride salts are required for this transformation (KF and AgF), as well as a palladium(0) precatalyst with either L2 or L1 as the supporting ligand. Because the L2-supported precatalyst (P2) is effective for the fluorination of both aryl and heteroaryl bromides, it was selected as the optimal catalyst for use with the wax capsules. As in the preceding example, the hollow paraffin shells were charged with both P2 and the reagents necessary to transform 1 mmol of ArBr to the desired Ar–F (Fig. 2a, red capsule).

These three-component capsules were able to provide a range of aryl (7–9) and heteroaryl (10–12) fluorides from commercially...
Figure 1 | Wax capsules for the glove-box-free Pd-catalysed nucleophilic fluorination of aryl triflates. a, The catalytic cycle of a typical palladium-catalysed cross-coupling reaction; sensitive aspects are highlighted for clarity. L is a ligand, OA is oxidative addition, TM is transmetallation, and RE is reductive elimination. M is either a counter cation or a proton. COD is 1,5-cyclooctadiene.

b, Contents of the wax capsule for the fluorination of ArOTf. The green F (fluorine) highlights the site of the transformation.
c, Glove-box-free fluorination of ArOTf. Isolated yields are reported as an average of two runs. *Isolated yields that were previously reported and obtained using a glove box to set up the reactions. †Isolated yield after soaking a capsule in water for 24 h.

available ArBr in good yields, which rival those that were obtained when the reactions were set up in a glove box (Fig. 2b). Again, to test the capsules’ robustness, a capsule was placed in a beaker of water for 24 h. Once dried, the activity of this capsule matched that of a capsule that never made direct contact with water (Supplementary Table 3).

To highlight the generality of this approach, we applied the paraffin capsule technology to other reaction types that are useful in a variety of research areas. The first method we pursued was the palladium-catalysed cross-coupling of aryl halides with amine nucleophiles, which has become an indispensable tool for applications in materials science, sensor synthesis, and pharmaceutical development. Over the years, our laboratory has developed a series of biaryl monophosphine ligands and highly efficient base-activated, ligated Pd(II) precatalysts for C–N bond formation that are commercially available.

Although the components of this reaction are not sensitive to oxygen, the base required is hygroscopic, and must be kept in a glove box or stored in a desiccator. Additionally, it was discovered that a dual ligand mixture composed of L3 and L4 yielded a system capable of coupling both primary and secondary amine nucleophiles. Thus, a paraffin capsule containing L3-based precatalyst (P3), L4, and sodium tert-butoxide (base, Fig. 1a) would be capable of coupling a breadth of primary and secondary amines by the addition of a single universal encapsulated reagent (Fig. 3a, orange capsule), eliminating the need for time-consuming reaction optimizations. Indeed, these capsules coupled a primary alkyl amine (13), an acyclic secondary amine (14), a cyclic secondary amine (15), anilines (16 and 17), and a primary hetero-aromatic amine (18) to aryl halides and heteroaryl chlorides (Fig. 3b). The capsules were stored on the bench top and showed no signs of degradation over a period of over eight months, even though the base-activated P3 was stored in close contact with sodium tert-butoxide (Fig. 3b, 18).

The palladium-catalysed Negishi cross-coupling of 2-pyridylzinc dioxanate with aryl halides and triflates was also adapted for use with...
paraffin wax capsules. The 2-pyridyl group has found applications in functional materials and is a component of biologically active compounds. Traditional 2-pyridyl nucleophiles such as boronates suffer from instability, which makes them difficult to employ in Suzuki–Miyaura cross-coupling reactions. In contrast, the dioxane-stabilized 2-pyridylzinc reagent is a solid, competent nucleophile that can be briefly manipulated in air, although long-term storage is problematic owing to its sensitivity to water.

Encapsulation of the basic 2-pyridylzinc dioxanate (MNu, Fig. 1a) with base-activated palladium precatalyst (P4) within a paraffin wax capsule provides a bench-top-stable reagent and an efficient means of introducing this important functional group to a variety of (hetero)aryl halides and triflates (Fig. 4a, purple capsule). With this technology, (hetero)aryl chlorides, (19 and 20), aryl triflate (21), and (hetero)aryl bromides (22, 23, and 24) were easily converted to the desired 2-pyridyl compounds. To demonstrate the stability of the zinc reagent, capsules containing 2-pyridylzinc dioxanate that have been stored on the bench top for one year were shown by titration to contain the original amount of active material (Supplementary Table 5).

We have reported that several valuable oxygen- and water-sensitive cross-coupling catalysts and reagents can be stabilized by encapsulation within inert, hydrophobic wax capsules. These capsules provide access to an array of desirable cross-coupled products by the convenient addition of a single, user-friendly, bench-top-stable reagent. Through collaboration with chemical providers, the manual capsule preparation process should be easy to mechanize for large-scale production, making this technology widely available for a variety of traditionally sensitive compounds. Furthermore, we envision that this concept will transform other moisture- and air-sensitive reagents (such as ZnCl₂, AlCl₃, AgF₂) by turning reactions that employ these into operationally simpler and more robust processes.

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