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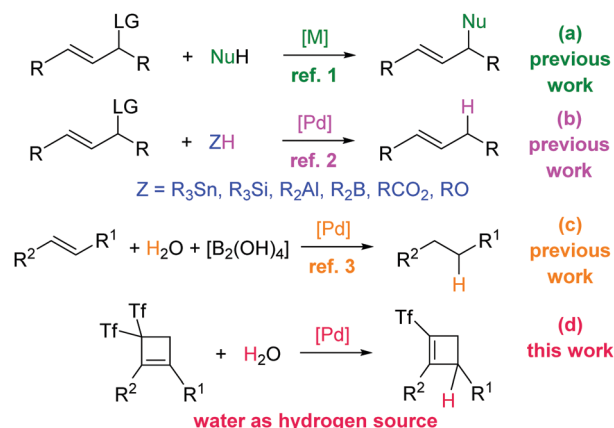
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Triflyl-assisted reductive Pd-catalyzed Tsuji–Trost type reaction†

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New (triflyl)cyclobutenes have been prepared by palladium-catalyzed hydrodetriflylation reaction using water and deuterium oxide as convenient hydrogen and deuterium sources. In addition, an investigation of the possible mechanism for this Tsuji–Trost type reaction of bis(triflyl)cyclobutenes has been facilitated by labelling studies and density functional theory (DFT) calculations.

The Tsuji–Trost reaction, which consists of a metal-catalyzed reaction of allylic substrates bearing a good leaving group (LG) with nucleophiles, is one of the most convenient methods for carbon–carbon and carbon–heteroatom bond formation (Scheme 1a).¹ Carbon, nitrogen, oxygen, sulfur, phosphorous, and selenium nucleophiles successfully lead to the corresponding functionalized allylic products. Regarding allylic hydrogenolysis that could provide naked olefins, the most commonly used hydrogen transfer agents are typical reducing reagents such as aluminohydrides, borohydrides, hydrosilanes, tin hydrides, formic acid and ammonium formate (Scheme 1b).² The utilization of these very reactive reagents leads to difficulties regarding selectivity and functional group compatibility. However, water is the cheapest and most environmentally friendly hydrogen source. Taking into account that recent reports pointed out the use of water as the hydrogen source in Pd-catalyzed hydrogenation reactions (Scheme 1c),³ we decided to study the feasibility of a novel palladium-catalyzed allylic substitution reaction using water as the hydrogen source as a direct route to (triflyl)cyclobutenes⁴ (Scheme 1d).



Scheme 1 Mode of reaction between activated alkenes and nucleophiles: previous studies and the present work.

The starting materials, cyclobutenes **1**, were easily prepared from the corresponding alkynes through a formal [2+2] cyclization reaction using Yanai's reagent.⁵ Initial experiments were performed using cyclobutene **1a** as a model substrate (Table 1). Pd(OAc)₂, Pd(TFA)₂, PdCl₂, Pd(CH₃CN)₂Cl₂, Pd(PPh₃)₂Cl₂, Pd(amphos)Cl₂, Pd(dba)₂, Pd(dppf)₂, and Pd(PPh₃)₄ were tested as the palladium salts. The above screening demonstrated that 5 mol% Pd(PPh₃)₄ was the best choice (Table 1, entries 1–9). A lower catalyst loading had a detrimental effect on the yield. Different bases (K₂CO₃, Cs₂CO₃, K₃PO₄, and Et₃N) and solvents (THF, acetonitrile, DMF, and 1,4-dioxane) were tested, with the combination of K₂CO₃/1,4-dioxane providing the highest yield (93%; Table 1, entry 9). The integrity of the catalyst decreases under exposure to air, leading to diminished yields of (triflyl)cyclobutene **2a**. The absence of (triflyl)cyclobutene **2a** was noticed when either the Pd complex or water was not present.

With the best conditions for obtaining adduct **2a** in hand, the substrate scope was next studied. Thus, bis(triflyl)cyclobutenes **1a–i** were smoothly converted into (triflyl)cyclobutenes **2a–i** under the optimal reaction conditions (Scheme 2). The transformation tolerated aryl groups bearing substituents of different electronic

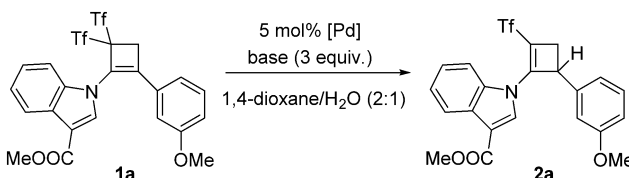
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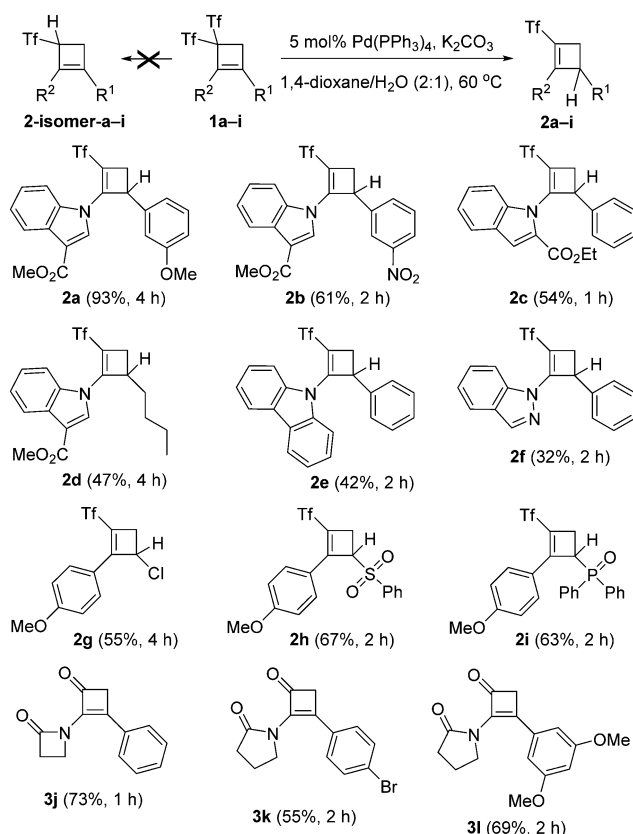
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† Electronic supplementary information (ESI) available: Computational details, experimental procedures, characterization data of new compounds, and copies of NMR spectra for all new compounds. See DOI: 10.1039/d0cc02146f

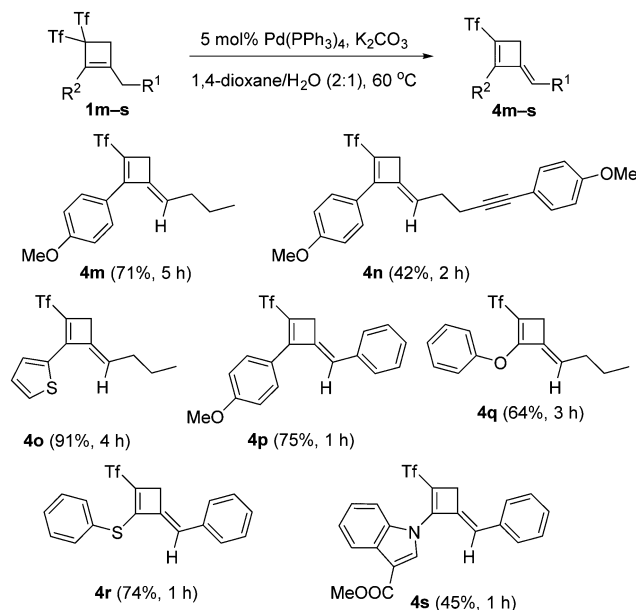


Table 1 Screening of palladium-catalyzed reaction conditions for a water-promoted hydrotetriflylation reaction


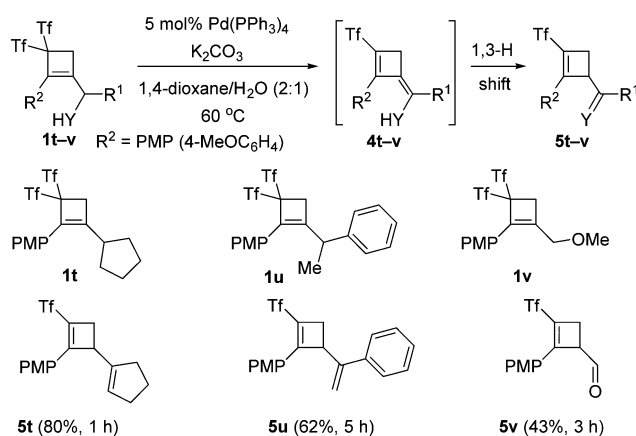
Entry	Catalyst	Reaction conditions	Yield ^a (%)
1	Pd(OAc) ₂	K ₂ CO ₃ , 60 °C, 12 h	45
2	Pd(TFA) ₂	K ₂ CO ₃ , 60 °C, 12 h	48
3	PdCl ₂	K ₂ CO ₃ , 60 °C, 12 h	23
4	Pd(CH ₃ CN) ₂ Cl ₂	K ₂ CO ₃ , 60 °C, 4 h	73
5	Pd(PPh ₃) ₂ Cl ₂	K ₂ CO ₃ , 60 °C, 5 h	85
6	Pd(amphos)Cl ₂	K ₂ CO ₃ , 60 °C, 12 h	40
7	Pd(dba) ₂	K ₂ CO ₃ , 60 °C, 3 h	83
8	Pd(dppf) ₂	K ₂ CO ₃ , 60 °C, 12 h	—
9	Pd(PPh ₃) ₄	K ₂ CO ₃ , 60 °C, 4 h	93
10	Pd(PPh ₃) ₄	K ₂ CO ₃ , RT, 24 h	5
11	Pd(PPh ₃) ₄	Et ₃ N, 60 °C, 12 h	—
12	Pd(PPh ₃) ₄	K ₃ PO ₄ , 60 °C, 6 h	75
13	Pd(PPh ₃) ₄	CS ₂ CO ₃ , 60 °C, 4 h	81

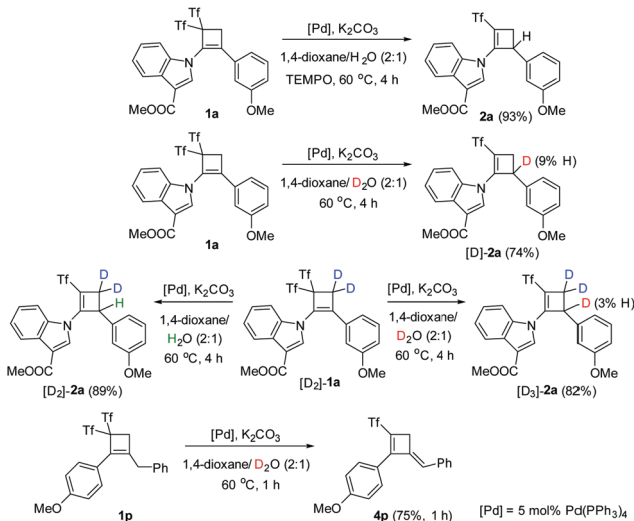
^a Yield of pure, isolated product with correct analytical and spectral data.**Scheme 2** Palladium-catalyzed preparation of (triflyl)cyclobutenes **2** using water as the hydrogen source.

properties such as methoxy (**2a**) and nitro (**2b**), as well as heteroaryl moieties such as indole (**2a–d**), carbazole (**2e**) and indazole (**2f**). Besides, heteroatomic substituents such as chlorine (**2g**), sulfone (**2h**), and phosphine oxide (**2i**) were well accommodated. As shown

**Scheme 3** Palladium-catalyzed preparation of (triflyl)cyclobutenes **4**.

in Scheme 2, the allylic substitution reaction is totally regioselective because isomeric products **2-isomer-a-i** were not detected. However, bis(triflyl)cyclobutenes **1j–l** bearing a lactam substituent reacted to give unexpected cyclobutenones **3j–l** (see ESI† for a plausible reaction path for the formation of products **3**) rather than (triflyl)cyclobutenes **2j–l** (Scheme 2). It is worth noting that the palladium-catalyzed hydrotetriflylation reaction of bis(triflyl)cyclobutenes **1m–s** bearing an alkyl substituent resulted in the formation of (triflyl)cyclobutenes **4m–s** having an extra alkene functionality (Scheme 3). Olefins **4m–s** were obtained with total stereoselectivity as single *E*-isomers. At first glance, the formation of the exocyclic alkene moiety in 1,3-dienes **4m–s** can be viewed as a formal molecular hydrogen release⁶ in non-detected (triflyl)cyclobutenes **2m–s**. Of particular interest was the reactions of bis(triflyl)cyclobutenes **1t–v**, which were converted into 1,4-dienes **5t,u** and cyclobutenal **5v** by the evolution of 1,3-dienes **4t–v** via a 1,3-H shift (Scheme 4). This attractive synthesis sequence

**Scheme 4** Palladium-catalyzed preparation of (triflyl)cyclobutenes **5**.

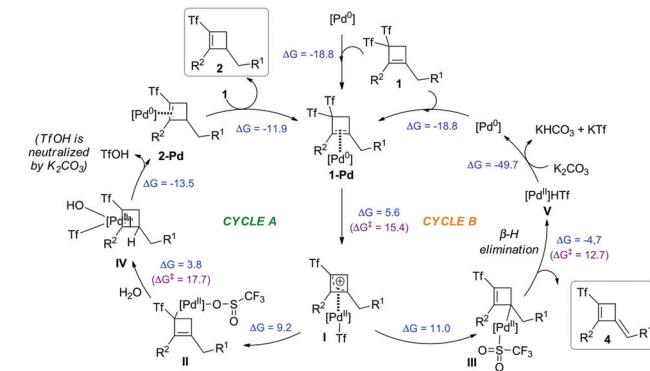


Scheme 5 Control and deuterium labelling experiments.

constitutes a striking example of the versatility of the above palladium-catalyzed reaction in organic synthesis.

To gain a better understanding of the hydrode-triflylation process, control and deuterium-labelling experiments were carried out. Under otherwise identical conditions, adduct **2a** was obtained in a similar yield independent of the presence or absence of TEMPO as an additive (Scheme 5), which probably ruled out a radical mechanism.⁷ When bis(triflyl)cyclobutene **1a** was treated under the optimal conditions using D₂O instead of H₂O, (triflyl)cyclobutene [D]-**2a** was obtained with 91% deuterium incorporation (Scheme 5).⁸ Thus, the deuterium atom can be easily incorporated into the cyclobutene ring by the current hydrode-triflylation reaction, which uses inexpensive water as the stoichiometric hydrogen source. Bis(triflyl)cyclobutene [D₂]-**1a** with total deuterium incorporation at the methylenic carbon of the small ring was prepared from the novel deuterated Yanai's reagent [D₂]-**Y** (see ESI† for details). It was observed that the reactions of bis(triflyl)cyclobutene [D₂]-**1a** with H₂O and D₂O formed deuterium-labeled (triflyl)cyclobutenes [D₂]-**2a** and [D₃]-**2a**, respectively (Scheme 5). As expected, no deuterated cyclobutene **4p** was detected starting from **1p** (Scheme 5).

We performed a detailed computational study at the DFT level on the possible catalytic reaction pathways that may account for the formation of cyclobutene-triflones **2** and **4** from bis-(triflyl)cyclobutenes **1** in the presence of water (Scheme 6).⁹ The bis(triflyl)cyclobutene with the alkene substituted with Ph and Et groups was used as the model substrate, and (PPh₃)Pd was used as the catalytically active species.¹⁰ All the computed energies are compatible with a process that takes place at 60 °C. The first step of the catalytic cycle is the coordination of palladium to the alkene moiety of bis(triflyl)cyclobutenes **1**. This reaction is a favorable exergonic process ($\Delta G = -18.8$ kcal mol⁻¹) and gives the intermediate **1-Pd**. The oxidative addition to form π -allyl Pd(II) **I** is endergonic ($\Delta G = 5.6$ kcal mol⁻¹) and occurs with a moderate activation energy of 15.4 kcal mol⁻¹. Therefore, the two step process leading to the allyl-Pd intermediates proceeds downhill. An alternative stepwise reaction in which π -allyl Pd(II) **I** is formed



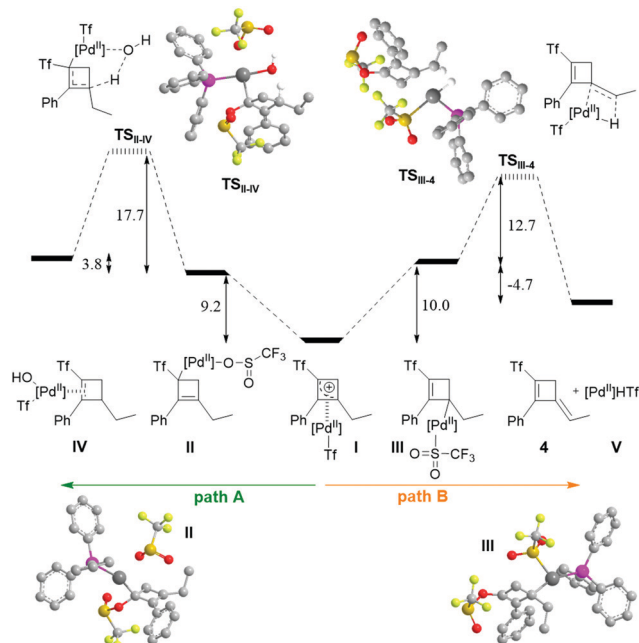
Scheme 6 Plausible pathways for the formation of (triflyl)cyclobutenes **2** (Cycle A) and **4** (Cycle B). The values of reaction free energies and activation energies (kcal mol⁻¹) were calculated at the B3LYP/6-31G(d) (C,H,O,S,F,P,K) and LANL2DZ (Pd) level in the gas phase with R¹ = Me, R² = Ph, and [Pd] = (PPh₃)Pd.

through oxidative addition paired with the liberation of Tf⁻ that then coordinates with Pd is highly unfavorable (see ESI† for details). The formation of two different σ -allyl Pd(II) complexes, **II** and **III**, is feasible from **I**, with the energy difference of 1.8 kcal mol⁻¹. Interestingly, **II** is more stable in the form that presents the triflyl group coordinated through one of the oxygen atoms, whereas the form of **III** that has the lower energy is the one in which the triflyl group is coordinated through the sulfur atom (see ESI† for details). The difference in energy between the coordination bond isomers is ~5 kcal mol⁻¹, pointing to an equilibrium in solution between these species. The fact that both σ -allyl Pd(II) complexes are higher in energy than **I** is possibly due to the generation of a coordinative vacancy in Pd. Compared to the usual stabilization of the corresponding σ -allyl Pd(II) complexes upon coordination with phosphine, in this case, the addition of an additional PPh₃ to the coordination sphere of palladium increases the energy of these σ -allyl Pd(II) complexes. However, in the reaction medium, the vacant coordination site formed after Pd slipping to the η^1 -coordination mode could be occupied. In fact, the coordination of water stabilizes the corresponding σ -allyl Pd(II) complexes (see ESI† for details).

Noticeably, calculations show that starting from each σ -allyl Pd(II) complex, a different reaction pathway is preferred (Scheme 7). From **II**, protodemetalation with water to give **IV** is an almost thermoneutral process ($\Delta G = 3.8$ kcal mol⁻¹) via TS_{II-IV} ($\Delta G^\ddagger = 17.7$ kcal mol⁻¹). In this step, a proton from water bonds to the carbon of the alkene that is further from Pd, forming at the same time a Pd-hydroxide, which remains coordinated to the newly formed double bond. The remaining steps to end the catalytic cycle are both exergonic ($\Delta G = -13.5$ and -11.9 kcal mol⁻¹, respectively). These steps imply the formation of Pd(0) species by a formal reductive elimination of TfOH, which may take place by external water attack on coordinated Tf rather than the direct formation of a S–O bond from **IV**.

In contrast to the evolution of **II**, we were not able to locate a low energy TS for the direct cleavage of the Pd–C bond in **III** with water. However, the β -hydride elimination to form product **4** and palladium hydride **V** was found to be an exergonic process ($\Delta G = -4.7$ kcal mol⁻¹) with a moderately low activation





Scheme 7 Comparison of both possible reaction pathways from π -allyl Pd(II) complex I to form σ -allyl Pd(II) complex II (path A) or III (path B). Reaction free energies and activation energies (kcal mol^{-1}) are calculated at the B3LYP/6-31G(d) (C,H,O,S,F,P,K) and LANL2DZ (Pd) level in the gas phase.

energy ($\Delta G^\ddagger = 12.7 \text{ kcal mol}^{-1}$) (path B, Scheme 7). It is important to note that stabilization of the transition states for both protodemetalation and β -hydrogen elimination is achieved by water coordination along the reaction pathway and, therefore, the calculated activation energies are upper limits and the actual barriers are probably lower. Furthermore, an overall calculation of the reductive elimination step assisted by K_2CO_3 from V to regenerate the Pd(0) catalytically active species shows that the process is, as expected, highly exergonic ($\Delta G = -49.7 \text{ kcal mol}^{-1}$) (Scheme 6).^{11,12} According to these results, path B would be the preferred reaction pathway, since the energy barrier is lower than the alternative path A. Path A would occur in bis(triflyl)cyclobutenes **1** in which the β -hydride elimination process is not attainable.

In summary, a palladium-catalyzed synthesis of (triflyl)-cyclobutenes has been developed through an allylic substitution reaction, taking advantage of the use of water as the hydrogen source. This method can also be used for the preparation of deuterated cyclobutenes with inexpensive D_2O as the deuterium source. Labeling experiments and DFT calculations support the proposal of a possible pathway for this Pd-catalyzed water assisted hydrogen transfer reaction.

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Conflicts of interest

There are no conflicts of interest to declare.

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