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CO_2 and palladium enabled highly chemoselective hydroxylation of *gem*-difluorocyclopropanes†

Xingben Wang, Fang Xiao and Frederic W. Patureau *

The CO_2-mediated hydroxylation of *gem*-difluorocyclopropanes is herein described, under Pd(0) catalysis in the presence of H_2O. The method affords a large series of valuable fluorinated cinnamyl alcohols in high yields and with broad functional group tolerance. It is moreover highly chemoselective, as the double C–O coupled ether side-product could be completely suppressed under the CO_2 atmosphere. The reaction occurs through Pd-catalyzed C–C and C–F bond activation on the one hand, while CO_2 is proposed to activate the weak water nucleophile on the other. This mild synthetic method should impact the fields of medicinal chemistry, organic synthesis, and sustainable processes and advance the concept of CO_2 catalysis.

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Introduction

Carbon dioxide (CO_2) is an increasingly significant part of the atmosphere and is widely accessible, inexpensive, non-toxic, stable, and recyclable.[1–5] In many reports, it is mostly utilized as a convenient C1 source.[6–10] However, its catalytic activity, in particular in cooperation with transition metal co-catalysts, has received relatively sparse attention.[11,12] In the literature, CO_2 catalysis mainly focuses on the activation of substrates with high reactivity and strong nucleophilicity, such as alcohols and amines.[13–24] Other classes of substrates remain far less explored (Fig. 1A). In most prior methods, CO_2 transiently activates the electrophilicity of a substrate through CO_2 adducts associated with starkly altered reactivity. Nevertheless, the use of CO_2 as a catalyst is still underappreciated for the development of innovative synthetic methods, in particular for the activation of nucleophiles. In the present study, we utilized CO_2 catalysis in order to activate one of the weakest and most important nucleophiles in organic synthesis: water (Fig. 1B).[25–29]

The use of H_2O as a nucleophile in Pd-catalyzed cross coupling chemistry remains a daunting challenge, in spite of elegant seminal works on the topic.[30] Another difficulty resides in the fact that most C–OH coupling products tend to be far more nucleophilic than H_2O itself, thus often leading to undesired multiple C–O bond forming escape reactions.[31] This is especially the case in the absence of bulky substituents shielding the reaction site.[31] We hypothesized that CO_2 catalysis might both activate water's nucleophilicity as well as decrease that of the valuable C–OH coupling products.

In this context, we considered *gem*-difluorocyclopropane electrophiles,[32–34] because these are known to readily react with potent nucleophiles under transition metal palladium catalysis.[35–55] However, selectively producing hydroxylated products without further reactions constitutes a considerable

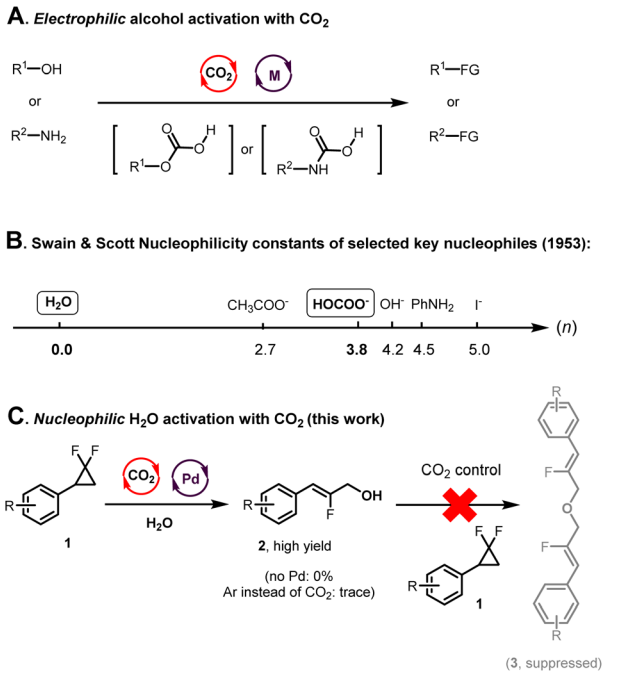

Fig. 1 From CO_2-catalyzed electrophilic activation of alcohols towards CO_2-catalyzed nucleophilic activation of H_2O.

Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany. E-mail: Frederic.Patureau@rwth-aachen.de

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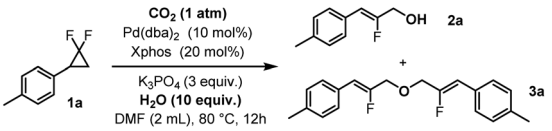
challenge. We thus designed a method for the hydroxylation of *gem*-difluorocyclopropanes, which is enabled by CO_2 and Pd(0)-catalysis, affording a large series of important fluorinated cinnamyl alcohols[56–69] from water. The concept is based on the principle that CO_2 might effectively enhance the poor nucleophilicity of water (n = 0) by generating far more nucleophilic transient carbonates (n = 3.8, Fig. 1B).[25]

Results and discussion

Based on literature precedents,[70–72] we conceived that the Pd(0) active species would first perform the oxidative addition into the strained C–C bond of substrate **1** leading to strained palladacycle intermediate **Int-I** (Fig. 2). This would be followed by β-fluoride elimination,[73] leading to fluoroallyl palladium species **Int-II**. Fluoride-carbonate exchange would then lead to **Int-III**, followed by C–O reductive elimination towards carbonated product **Int-IV** and the regenerated Pd(0) catalyst (Cycle **A**). The former would then release CO_2 towards the final fluoroallyl alcohol product **2**. The released CO_2 would then reform the active carbonate intermediate ($KHCO_3$) in the presence of excess water and K_3PO_4 base, thus closing the CO_2 catalytic cycle (Cycle **B**).

We therefore initially selected 4-methyl-*gem*-difluoro-cyclopropane (**1a**) as a model substrate. Based on a previous report from our group,[70] we serendipitously realized that **1a** produces fluoroallyl alcohol product **2a** in high isolated yield (93%) when exposed to $Pd(dba)_2$ (10 mol%), Xphos (20 mol%), water (10 equiv.), and K_3PO_4 (3 equiv.) in DMF under CO_2 atmosphere (1 atm) at 80 °C for 12 h (Table 1, entry 1). The double C–O bond forming allyl ether byproduct **3a** was not detected under those conditions. Interestingly, utilizing only 10 mol% of Xphos reduced the yield to only 70% (entry 2), presumably due to competing ligand exchange processes. This reaction cannot occur without a palladium precursor (entry 3). Moreover, omitting the addition of water severely reduced the yield (**2a**, 32%, entry 4), suggesting it to be a main hydroxyl source of the reaction. The residual product formation is likely due to traces of water in the other components of the reaction. Likewise, omitting the phosphate base is detrimental to the reaction's efficiency (**2a**, 30%, entry 5). Importantly, CO_2 was found to be essential. Replacing it with an atmosphere of N_2 inert gas almost shuts down the reaction (**2a**, 6%, entry 6), while air did not provide any desired product (entry 7). DMF proved to be an optimal solvent, in contrast for example to DMSO (entries 8–10). Finally, CO_2 could not be replaced by any additives that we tried, whether Lewis or Brønsted acids, or other (entry 11).

Table 1 Reaction conditions[a]



Entry	Deviation from standard conditions[a]	**2a**[b] (%)	**3a**[b] (%)
1	**None**	**98 (93)**[c]	**nd**
2	Only 10 mol% Xphos	70	nd
3	No Pd	nd	nd
4	No H_2O	32	nd
5	No K_3PO_4	30	nd
6	N_2 instead of CO_2	6	<5
7	Air instead of CO_2	nd	nd
8	H_2O instead of DMF	8	<5
9	Toluene instead of DMF	10	nd
10	DMSO instead of DMF	15	nd
11	Additives[d] instead of CO_2	nd	nd

[a] **1a** (0.20 mmol), Pd catalyst precursor (10 mol%), Xphos ligand (20 mol%), K_3PO_4 (3 equiv.), H_2O (10 equiv.), in DMF (2.0 mL) at 80 °C for 12 h. [b] Determined by ^1H NMR, using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield. [d] Selected additives: Ag_2O, $Cu(OAc)_2$, NH_4Cl, $PhCO_2H$, $EtCO_2H$, under N_2.

With the optimized conditions in hand, we then investigated the reaction scope with various *gem*-difluorocyclopropanes. Thus, we tested both electron-donating and withdrawing substituents at *para*-, *meta*- and *ortho*-positions of the arene substituent, providing the corresponding fluoro-cinnamyl alcohols in usually excellent isolated yields (**2a–2zc**, Fig. 3). The functional group tolerance was found outstanding for both electron-poor (R^1 = CF_3) and electron-rich substrates (R^1 = alkyl, *O*-alkyl/aryl, *N*-alkyl), with the notable exception of halides (R^1 = Cl, **2e**). Various heterocycles were moreover very well accommodated such as benzofurane (**2x**), carbazole (**2y**) and benzodioxane (**2w**). Finally, a series of biologically active fragments such as DL-menthol (**2za**), DL-isoborneol (**2zb**) and a protected fructopyranose derivative (**2zc**) could all be tolerated in high yields (79–92%). Unfortunately, however, the alkyl-substituted *gem*-difluorocyclopropane corresponding to target product **2zd** was recovered unreacted, indicating the importance of the aromatic substituent for the strained ring opening step. It should furthermore be noted that we also achieved the hydroxylation reaction of a structurally related geminal difluoroallyl derivative (**4**), which yielded the corresponding cinna-

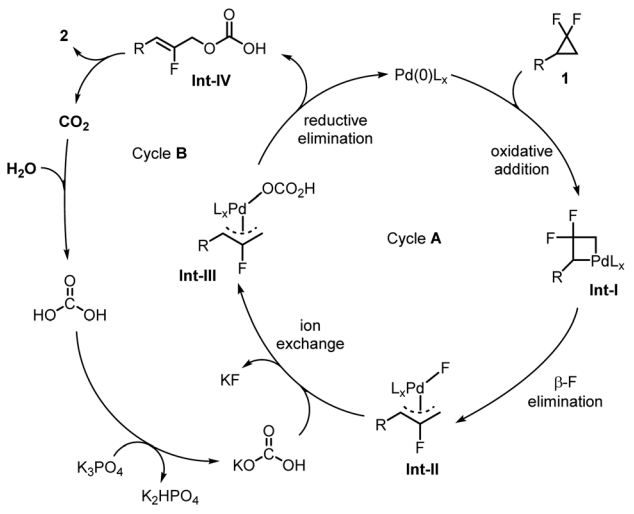


Fig. 2 Proposed mechanism.

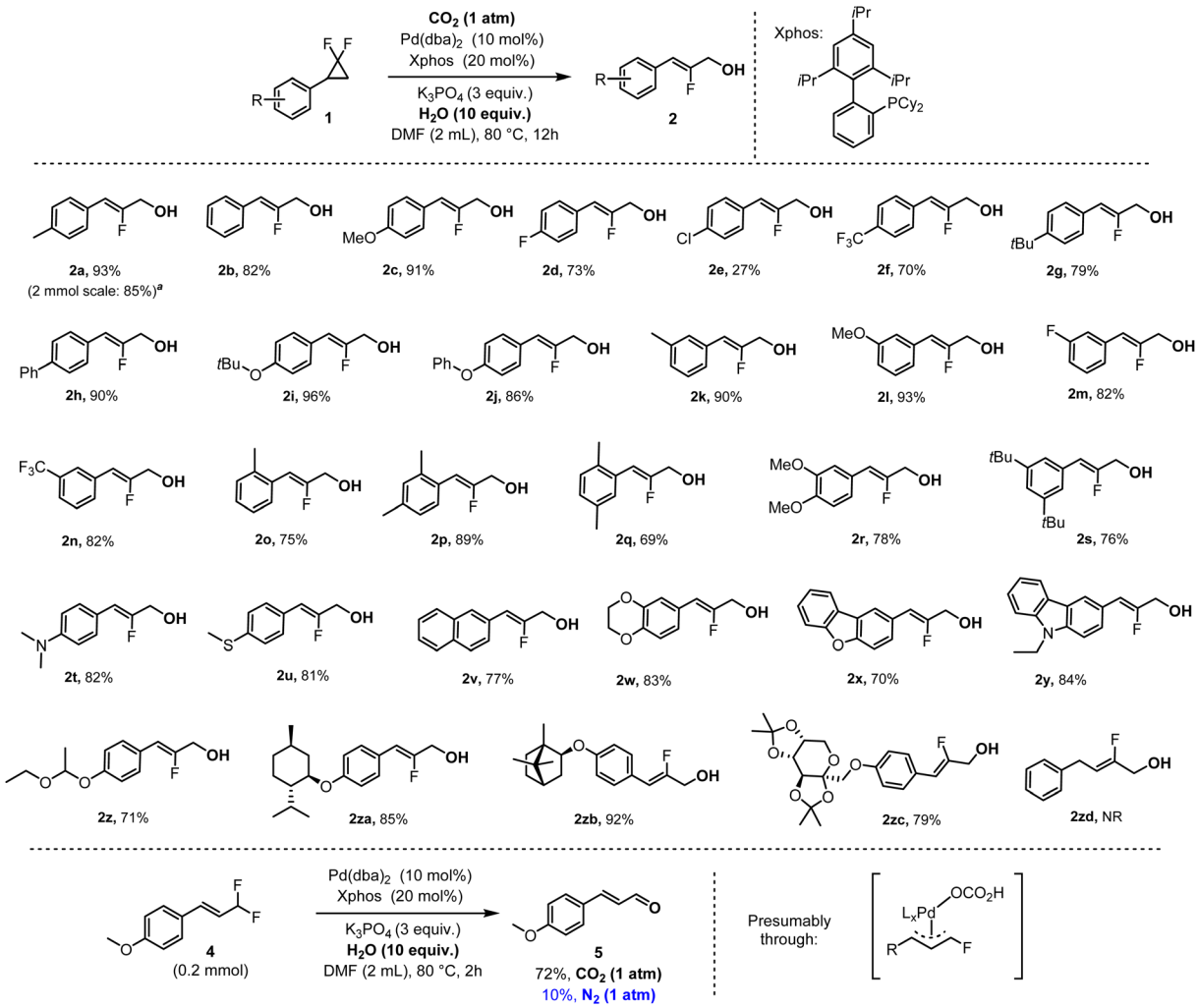


Fig. 3 Substrate scope, isolated yields. Reaction conditions: **1a** (0.20 mmol), Pd catalyst precursor (10 mol%), Xphos ligand (20 mol%), K_3PO_4 (3 equiv.), H_2O (10 equiv.), in DMF (2.0 mL) at 80 °C for 12 h. [a] Large scale (2 mmol): performed in optimized conditions, in 10 mL DMF.

maldehyde (**5**, Fig. 3). There too, CO_2 was found to be essential, as its replacement with an N_2 atmosphere almost shuts down the reaction (Fig. 3). These results confirm the critical water activating role of CO_2.

Next, we investigated whether this reaction could truly proceed under a catalytic loading of CO_2. We therefore replaced CO_2 with catalytic amounts of phenyl isocyanate, which undergoes hydrolysis under the reaction conditions towards the corresponding amine and CO_2, a process known as the Hofmann degradation.[71] This allowed us to carry out the reaction under precise catalytic loading of CO_2 precursor. There too, considerably higher product yields were obtained with only 20 mol% isocyanate loading (**2a**, 58%, Fig. 4, eqn (1)), compared to the complete absence of CO_2 or precursor thereof (**2a**, 6%, Table 1, entry 6). Fluoroallyl amine product **6a** was also observed, however typically as a minor byproduct. These findings are in line with the proposed catalytic role of CO_2 in this reaction. In order to further investigate this matter, we then attempted the reaction in the absence of CO_2, under N_2 inert gas, however in the presence of sur-stoichiometric carbonate salts (Fig. 4, eqn (2)). While the yields are nowhere near optimized conditions with CO_2, at 24–40% depending on the utilized salt, these are still significantly greater than in the absence of both CO_2 and carbonates (6%, Table 1, entry 6). These experiments therefore confirm that transient carbonates are likely essential intermediates in this reaction. However, clearly, CO_2 still outperforms the herein investigated carbonate salts in terms of product yield, suggesting additional not yet well identified enhancing effects of carbon dioxide in the present reaction conditions. It should moreover be noted that the sur-stoichiometric carbonate salt experiment performs less well when water addition is omitted (25% compared to 40%, Fig. 4, eqn (3)), suggesting a potential cooperative role of water with the carbonate intermediate.

In order to further investigate the apparent superiority of CO_2 mediation *versus* carbonate mediation, we performed a final key experiment with catalytic loading of a carbonate salt (20 mol%) under inert N_2 gas, in otherwise standard con-

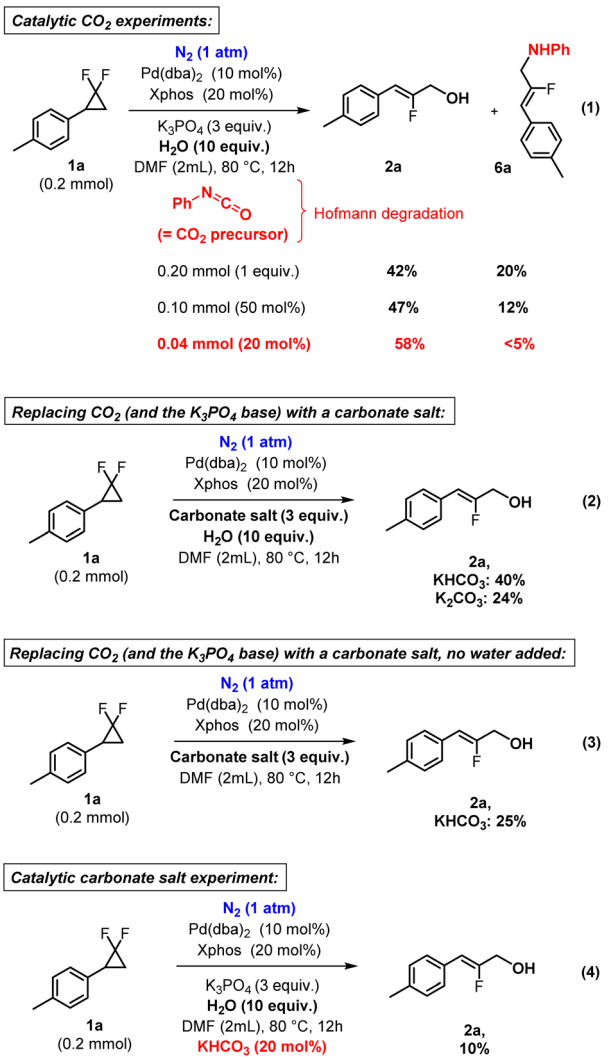


Fig. 4 Mechanistic experiments regarding the catalytic role of CO_2 and the intermediacy of carbonate salts, yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

ditions (Fig. 4, eqn (4)). This led to a severely decreased product yield (**2a**, 10%), thus unambiguously confirming the supposed superiority of CO_2 over carbonates, at least in the current reaction conditions. At this stage, we cannot exclude that a method based solely on carbonate salts, without added CO_2, might eventually also furnish a competent hydroxylation method, especially upon further optimization. However, this remains outside of the scope of this study.

Next, we engaged the reaction with ^{18}O-labelled water (^{18}O label: 97%), in otherwise standard reaction conditions (Fig. 5, eqn (1)). The significant ^{18}O-incorporation into the product (see ESI†) is consistent with water being a hydroxyl source. Interestingly, however, the ^{18}O incorporation is slightly under one third from that of the labelled $H_2(^{18}O)$ reagent, indicating label scrambling with the non-labelled oxygen atoms of CO_2. This is very much consistent with a carbonate intermediate, wherein each of the three resulting oxygen atoms has an equal chance of forming the C–O bond during the reductive elimination event at the Pd(II) center. When employing a catalytic amount of CO_2, however, the ^{18}O content in the product increased dramatically (^{18}O: 77% incorporation, Fig. 5, eqn (2)). This is due to the reduced amount of (non-labelled) CO_2, thus limiting the overall label scrambling within the carbonate intermediate. Both ^{18}O label experiments (eqn (1) & (2)) are thus in excellent agreement with the presumed catalytic role of CO_2 in this reaction.

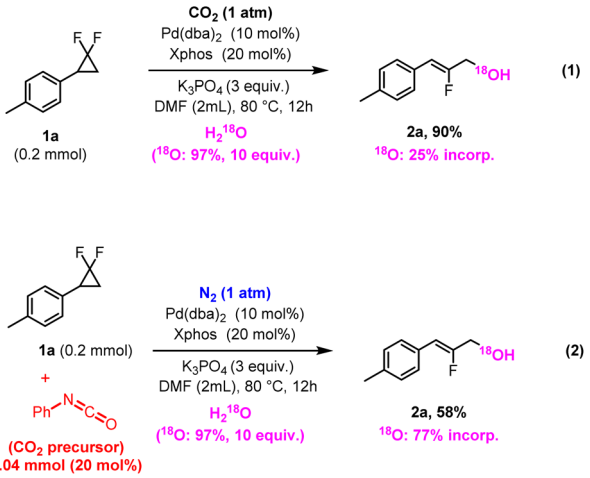


Fig. 5 ^{18}O label experiments, isolated yields.

In order to further explore the synthetic utility of the method, a gram scale reaction was conducted for product **2a**. This target was thus obtained in remarkably preserved 85% isolated yield (2 mmol scale, product **2a**, 0.282 g, Fig. 3). Next, we attempted to force the reaction conditions towards the formation of double C–O coupling product **3a**, in stepwise fashion (Fig. 6). This was carried out under both inert atmo-

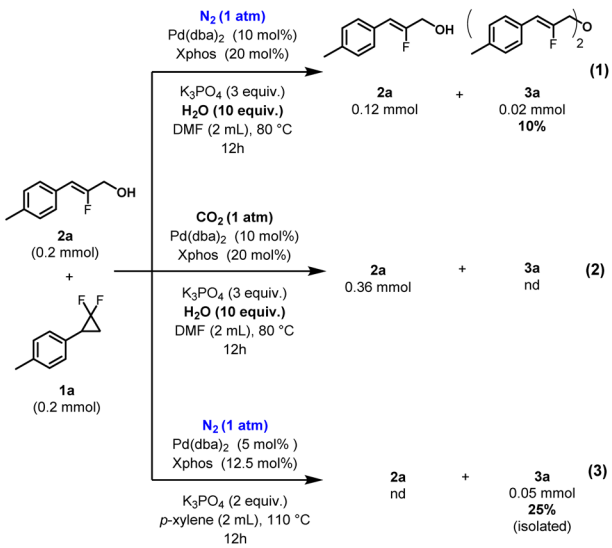


Fig. 6 Pushing towards the ether product **3a**. Unless otherwise stated, yields determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.

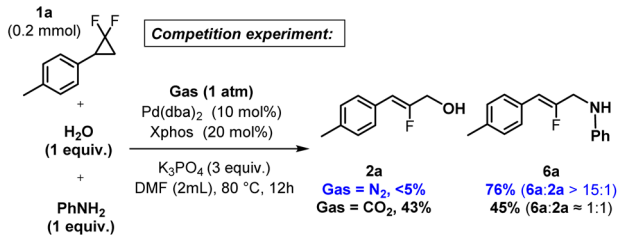


Fig. 7 Nucleophile competition experiment: H_2O *versus* aniline, with and without CO_2, yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

sphere (eqn (1)) as well as under CO_2 (eqn (2)). From these experiments, it can be deduced that CO_2 prevents the formation of double C–O coupling product **3a**, presumably through transient carbonate ester protection, in contrast to N_2. Increasing the temperature further to 110 °C under N_2 atmosphere, along conditions previously reported by us for amines,[70] afforded the double C–O coupling product **3a** in 25% yield (Fig. 6, eqn (3)). Other side products could not be formally identified in these reaction mixtures (Fig. 6).

Finally, we performed a competition experiment between a potent aniline nucleophile (n = 4.5),[25] and poorly nucleophilic water (n = 0),[25] under perfectly identical conditions, either with or without CO_2 atmosphere (Fig. 7). Interestingly, under N_2 inert gas, aniline considerably outperforms water (**6a : 2a** > 15 : 1). Under CO_2 atmosphere, however, water becomes a much more competitive coupling partner compared to aniline (**6a : 2a** ≈ 1 : 1), which is again consistent with the proposed water activation scenario of CO_2.

Conclusions

In conclusion, we developed a CO_2-mediated, Pd(0) catalyzed method for the hydroxylation of *gem*-difluorocyclopropanes from water, affording a large series of valuable fluorinated cinnamyl alcohols in high yields and with broad functional group tolerance, including important bioactive scaffolds. Moreover, we characterized the nucleophile activating role of CO_2 through key mechanistic experiments. The herein presented results should encourage the development of further challenging coupling reactions with weak X–H nucleophiles such as water, by means of CO_2 catalysis,[74–77] and in general the use of CO_2 in synthetic method development.[78]

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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