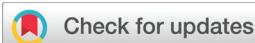


RESEARCH ARTICLE

[View Article Online](#)
[View Journal](#) | [View Issue](#)



Cite this: *Org. Chem. Front.*, 2024, **11**, 2494

Received 18th January 2024,
Accepted 21st February 2024
DOI: 10.1039/d4qo00106k
rsc.li/frontiers-organic

CO₂ and palladium enabled highly chemoselective hydroxylation of gem-difluorocyclopropanes†

Xingben Wang, Fang Xiao and Frederic W. Patureau *

The CO₂-mediated hydroxylation of gem-difluorocyclopropanes is herein described, under Pd(0) catalysis in the presence of H₂O. 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 CO₂ atmosphere. The reaction occurs through Pd-catalyzed C–C and C–F bond activation on the one hand, while CO₂ 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 CO₂ catalysis.

Introduction

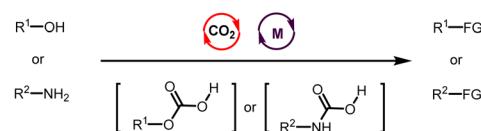
Carbon dioxide (CO₂) is an increasingly significant part of the atmosphere and is widely accessible, inexpensive, non-toxic, stable, and recyclable.^{1–5} In many reports, it is mostly utilized as a convenient C1 source.^{6–10} However, its catalytic activity, in particular in cooperation with transition metal co-catalysts, has received relatively sparse attention.^{11,12} In the literature, CO₂ 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, CO₂ transiently activates the electrophilicity of a substrate through CO₂ adducts associated with starkly altered reactivity. Nevertheless, the use of CO₂ 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 CO₂ catalysis in order to activate one of the weakest and most important nucleophiles in organic synthesis: water (Fig. 1B).^{25–29}

The use of H₂O 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 H₂O 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 CO₂ cataly-

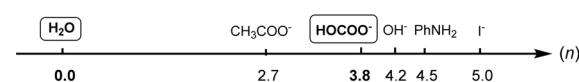
sis might both activate water's nucleophilicity as well as decrease that of the valuable C–OH coupling products.

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

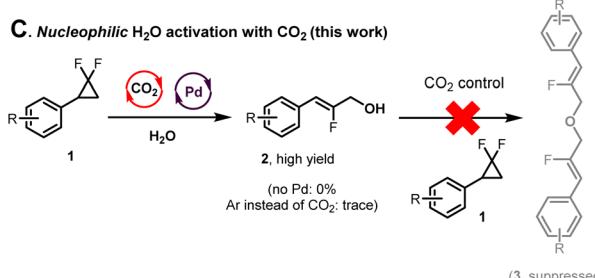
A. Electrophilic alcohol activation with CO₂



B. Swain & Scott Nucleophilicity constants of selected key nucleophiles (1953):



C. Nucleophilic H₂O activation with CO₂ (this work)



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

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d4qo00106k>

Fig. 1 From CO₂-catalyzed electrophilic activation of alcohols towards CO₂-catalyzed nucleophilic activation of H₂O.



challenge. We thus designed a method for the hydroxylation of *gem*-difluorocyclopropanes, which is enabled by CO_2 and $\text{Pd}(0)$ -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 $\text{Pd}(0)$ 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 $\text{Pd}(0)$ 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 $\text{Pd}(\text{dba})_2$ (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

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 , $\text{Cu}(\text{OAc})_2$, NH_4Cl , PhCO_2H , EtCO_2H , under N_2 .

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).

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**–**2ze**, Fig. 3). The functional group tolerance was found outstanding for both electron-poor ($\text{R}^1 = \text{CF}_3$) and electron-rich substrates ($\text{R}^1 = \text{alkyl, O-alkyl/aryl, N-alkyl}$), with the notable exception of halides ($\text{R}^1 = \text{Cl}$, **2e**). Various heterocycles were moreover very well accommodated such as benzofuran (**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 cinnamyl

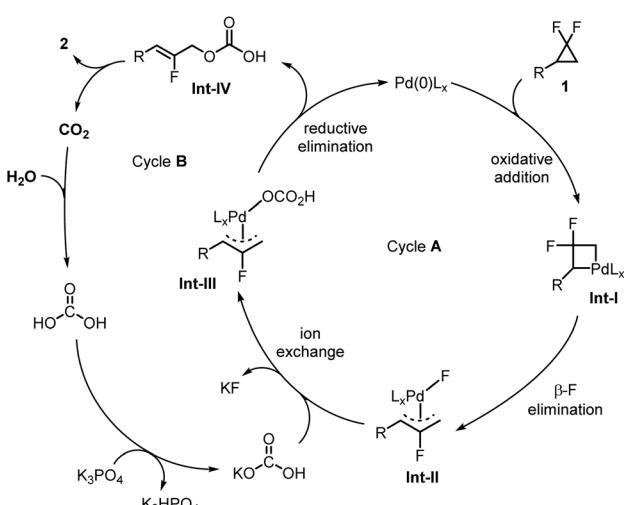


Fig. 2 Proposed mechanism.



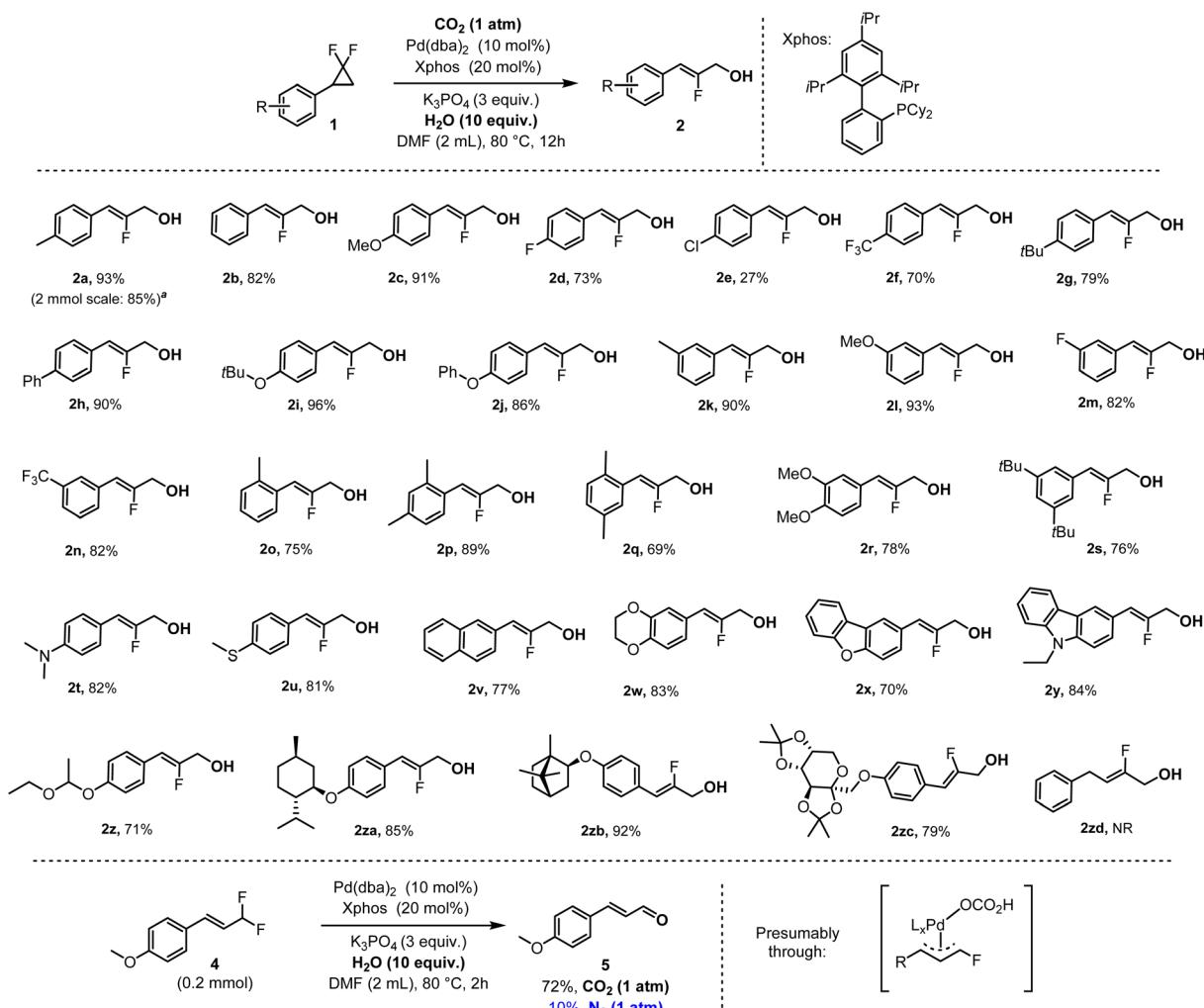


Fig. 3 Substrate scope, isolated yields. Reaction conditions: **1a** (0.20 mmol), Pd catalyst precursor (10 mol%), Xphos ligand (20 mol%), K_3PO_4 (3 equiv.), H_2O (10 equiv.), in DMF (2.0 mL) at 80 °C for 12 h. ^a Large scale (2 mmol): performed in optimized conditions, in 10 mL DMF.

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-



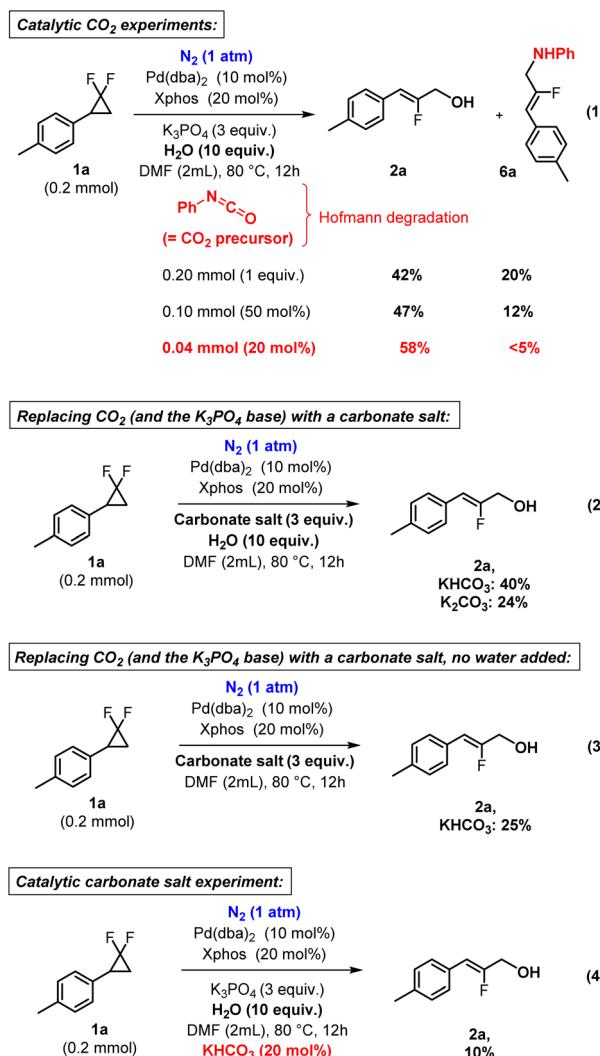


Fig. 4 Mechanistic experiments regarding the catalytic role of CO_2 and the intermediacy of carbonate salts, yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.

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 $\text{H}_2(^{18}\text{O})$ 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 elimin-

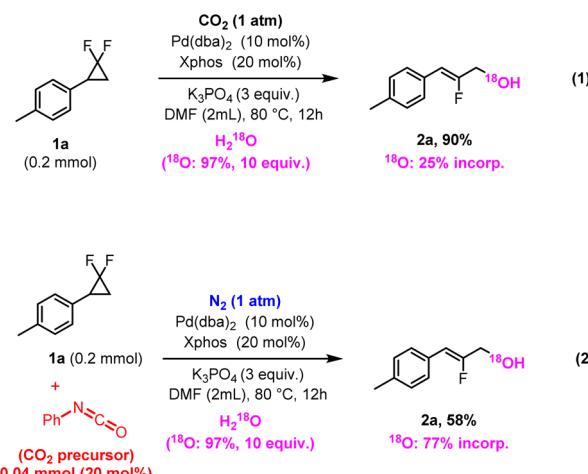


Fig. 5 ^{18}O label experiments, isolated yields.

ation event at the $\text{Pd}(\text{II})$ 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.

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-

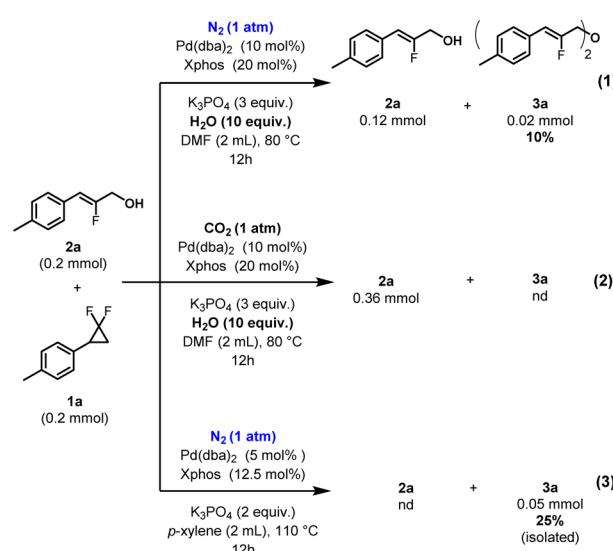


Fig. 6 Pushing towards the ether product 3a. Unless otherwise stated, yields determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard.



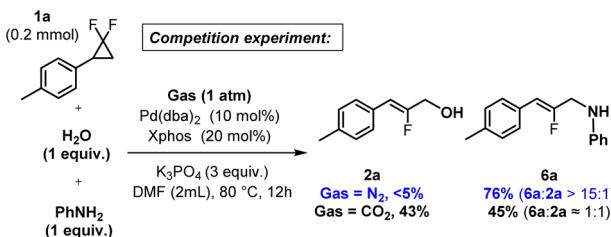


Fig. 7 Nucleophile competition experiment: H₂O versus aniline, with and without CO₂, yields determined by ¹H NMR using 1,3,5-trimethoxybenzene as an internal standard.

sphere (eqn (1)) as well as under CO₂ (eqn (2)). From these experiments, it can be deduced that CO₂ prevents the formation of double C–O coupling product 3a, presumably through transient carbonate ester protection, in contrast to N₂. Increasing the temperature further to 110 °C under N₂ 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 CO₂ atmosphere (Fig. 7). Interestingly, under N₂ inert gas, aniline considerably outperforms water (6a : 2a > 15 : 1). Under CO₂ 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 CO₂.

Conclusions

In conclusion, we developed a CO₂-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 CO₂ 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 CO₂ catalysis,^{74–77} and in general the use of CO₂ in synthetic method development.⁷⁸

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

DFG-funded Transregional Collaborative Research Center SFB/TRR 88 “Cooperative effects in homo and heterometallic com-

plexes” (<https://3MET.de>), and the CSC (XW and FX, grants no. 202008330337 and 202208430011, respectively) are acknowledged for generous financial support.

Notes and references

- J. Artz, T. E. Müller, K. Thenert, J. Kleinekorte, R. Meys, A. Sternberg, A. Bardow and W. Leitner, Sustainable Conversion of Carbon Dioxide: An Integrated Review of Catalysis and Life Cycle Assessment, *Chem. Rev.*, 2018, **118**, 434.
- Y. Yao, K. Ivanovski, J. Inekwe and R. Smyth, Human capital and CO₂ emissions in the long run, *Energy Econ.*, 2020, **91**, 104907.
- K. Huang, C. L. Sun and Z. J. Shi, Transition-metal-catalyzed C–C bond formation through the fixation of carbon dioxide, *Chem. Soc. Rev.*, 2011, **40**, 2435.
- M. D. Burkart, N. Hazari, C. L. Twy and E. L. Zeitler, Opportunities and Challenges for Catalysis in Carbon Dioxide Utilization, *ACS Catal.*, 2019, **9**, 7937.
- J.-H. Ye, T. Ju, H. Huang, L.-L. Liao and D.-G. Yu, Radical Carboxylative Cyclizations and Carboxylations with CO₂, *Acc. Chem. Res.*, 2021, **54**, 2518.
- Z. Zhang, J.-H. Ye, T. Ju, L.-L. Liao, H. Huang, Y.-Y. Gui, W.-J. Zhou and D.-G. Yu, Visible-Light-Driven Catalytic Reductive Carboxylation with CO₂, *ACS Catal.*, 2020, **10**, 10871.
- Y. Zhang, T. Zhang and S. Das, Catalytic transformation of CO₂ into C1 chemicals using hydrosilanes as a reducing agent, *Green Chem.*, 2020, **22**, 1800.
- B. Limburg, À. Cristòfol, F. Della Monica and A. W. Kleij, Unlocking the Potential of Substrate-Directed CO₂ Activation and Conversion: Pushing the Boundaries of Catalytic Cyclic Carbonate and Carbamate Formation, *ChemSusChem*, 2020, **13**, 6056.
- Q. Liu, L. Wu, R. Jackstell and M. Beller, Using carbon dioxide as a building block in organic synthesis, *Nat. Commun.*, 2015, **6**, 5933.
- M. Aresta, A. Dibenedetto and A. Angelini, Catalysis for the Valorization of Exhaust Carbon: from CO₂ to Chemicals, Materials, and Fuels. Technological Use of CO₂, *Chem. Rev.*, 2014, **114**, 1709.
- P. K. Sahoo, Y. Zhang and S. Das, CO₂-Promoted Reactions: An Emerging Concept for the Synthesis of Fine Chemicals and Pharmaceuticals, *ACS Catal.*, 2021, **11**, 3414.
- C. Park and J. Lee, Recent achievements in CO₂-assisted and CO₂-catalyzed biomass conversion reactions, *Green Chem.*, 2020, **22**, 2628.
- M. Sakamoto, I. Shimizu and A. Yamamoto, Activation of C–O and C–N Bonds in Allylic Alcohols and Amines by Palladium Complexes Promoted by CO₂. Synthetic Applications to Allylation of Nucleophiles, Carbonylation, and Allylamine Disproportionation, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 1065.
- S. Minakata, Y. Yoneda, Y. Oderaotoshi and M. Komatsu, Unprecedented CO₂-Promoted Aminochlorination of Olefins with Chloramine-T, *Org. Lett.*, 2006, **8**, 967.



15 S. B. Lang, T. M. Locascio and J. A. Tunge, Activation of Alcohols with Carbon Dioxide: Intermolecular Allylation of Weakly Acidic Pronucleophiles, *Org. Lett.*, 2014, **16**, 4308.

16 Y. Wang, J. Zhang, J. Liu, C. Zhang, Z. Zhang, J. Xu, S. Xu, F. Wang and F. Wang, C–N and N–H Bond Metathesis Reactions Mediated by Carbon Dioxide, *ChemSusChem*, 2015, **8**, 2066.

17 P. Hirapara, D. Riemer, N. Hazra, J. Gajera, M. Finger and S. Das, CO₂-assisted synthesis of non-symmetric α -diketones directly from aldehydes via C–C bond formation, *Green Chem.*, 2017, **19**, 5356.

18 M. Kapoor, P. Chand-Thakuri and M. C. Young, Carbon Dioxide-Mediated C(sp²)-H Arylation of Primary and Secondary Benzylamines, *J. Am. Chem. Soc.*, 2019, **141**, 7980.

19 J. Ye, I. Kalvet, F. Schoenebeck and T. Rovis, Direct α -alkylation of primary aliphatic amines enabled by CO₂ and electrostatics, *Nat. Chem.*, 2018, **10**, 1037.

20 G. Pupo, R. Properzi and B. List, Asymmetric Catalysis with CO₂: The Direct α -Allylation of Ketones, *Angew. Chem., Int. Ed.*, 2016, **55**, 6099.

21 D. Riemer, B. Mandaviya, W. Schilling, A. C. Götz, T. Kühl, M. Finger and S. Das, CO₂-Catalyzed Oxidation of Benzyllic and Allylic Alcohols with DMSO, *ACS Catal.*, 2018, **8**, 3030.

22 M. Kapoor, D. Liu and M. C. Young, Carbon Dioxide-Mediated C(sp³)-H Arylation of Amine Substrates, *J. Am. Chem. Soc.*, 2018, **140**, 6818.

23 T. Roy, M. J. Kim, Y. Yang, S. Kim, G. Kang, X. Ren, A. Kadziola, H. Y. Lee, M. H. Baik and J. W. Lee, Carbon Dioxide-Catalyzed Stereoselective Cyanation Reaction, *ACS Catal.*, 2019, **9**, 6006.

24 Y. Yang, J. Liu, F. S. Kamounah, G. Ciancaleoni and J.-W. Lee, A CO₂-Catalyzed Transamidation Reaction, *J. Org. Chem.*, 2021, **86**, 16867.

25 C. G. Swain and C. B. Scott, Quantitative Correlation of Relative Rates. Comparison of Hydroxide Ion with Other Nucleophilic Reagents toward Alkyl Halides, Esters, Epoxides and Acyl Halides, *J. Am. Chem. Soc.*, 1953, **75**, 141.

26 H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov and H. Schimmel, Reference Scales for the Characterization of Cationic Electrophiles and Neutral Nucleophiles, *J. Am. Chem. Soc.*, 2001, **123**, 9500.

27 R. Lucius, R. Loos and H. Mayr, Kinetic Studies of Carbocation–Carbanion Combinations: Key to a General Concept of Polar Organic Reactivity, *Angew. Chem., Int. Ed.*, 2002, **41**, 91.

28 H. Mayr and A. R. Ofial, Kinetics of electrophile-nucleophile combinations: A general approach to polar organic reactivity, *Pure Appl. Chem.*, 2005, **77**, 1807.

29 H. Mayr and A. R. Ofial, Do general nucleophilicity scales exist?, *J. Phys. Org. Chem.*, 2008, **21**, 584.

30 S. Enthaler and A. Company, Palladium-catalysed hydroxylation and alkoxylation, *Chem. Soc. Rev.*, 2011, **40**, 4912.

31 For an early representative example see: K. W. Anderson, T. Ikawa, R. E. Tundel and S. L. Buchwald, The Selective Reaction of Aryl Halides with KOH: Synthesis of Phenols, Aromatic Ethers, and Benzofurans, *J. Am. Chem. Soc.*, 2006, **128**, 10694.

32 D. Seyferth, H. Dertouzos, R. Suzuki and J. Y. P. Mui, Halomethyl-metal compounds. XIII. Preparation of gem-difluorocyclopropanes by iodide ion-induced CF₂ transfer from trimethyl(trifluoromethyl)tin, *J. Org. Chem.*, 1967, **32**, 2980.

33 A. P. Thankachan, K. S. Sindhu, K. K. Krishnan and G. Anilkumar, Recent advances in the syntheses, transformations and applications of 1,1-dihalocyclopropanes, *Org. Biomol. Chem.*, 2015, **13**, 8780.

34 D. M. Volochnyuk and O. O. Grygorenko, in *Emerging Fluorinated Motifs: Synthesis, Properties, and Applications*, ed. D. Cahard and J.-A. Ma, Wiley, 2020, vol. 1, p. 135.

35 J. Xu, E. A. Ahmed, B. Xiao, Q. Q. Lu, Y. L. Wang, C. G. Yu and Y. Fu, Pd-Catalyzed Regioselective Activation of gem-Difluorinated Cyclopropanes: A Highly Efficient Approach to 2-Fluorinated Allylic Scaffolds, *Angew. Chem., Int. Ed.*, 2015, **54**, 8231.

36 L. Lv, H. Qian, Y. Ma, S. Huang, X. Yan and Z. Li, Ligand-controlled regioselective and chemodivergent defluorinating functionalization of gem-difluorocyclopropanes with simple ketones, *Chem. Sci.*, 2021, **12**, 15511.

37 J. Wenz, C. A. Rettenmeier, H. Wadeohl and L. H. Gade, Catalytic C–F bond activation of geminal difluorocyclopropanes by nickel(I) complexes via a radical mechanism, *Chem. Commun.*, 2016, **52**, 202.

38 E. A. M. A. Ahmed, A. M. Y. Suliman, T. J. Gong and Y. Fu, Palladium-Catalyzed Stereoselective Defluorination Arylation/Alkenylation/Alkylation of gem-Difluorinated Cyclopropanes, *Org. Lett.*, 2019, **21**, 5645.

39 E. A. M. A. Ahmed, A. M. Y. Suliman, T. J. Gong and Y. Fu, Access to Divergent Fluorinated Enynes and Arenes via Palladium-Catalyzed Ring-Opening Alkynylation of gem-Difluorinated Cyclopropanes, *Org. Lett.*, 2020, **22**, 1414.

40 A. M. Y. Suliman, E. A. M. A. Ahmed, T. J. Gong and Y. Fu, Cu/Pd-Catalyzed cis-Borylfluoroallylation of Alkynes for the Synthesis of Boryl-Substituted Monofluoroalkenes, *Org. Lett.*, 2021, **23**, 3259.

41 P. X. Zhou, X. Yang, J. Wang, C. Ge, W. Feng, Y. M. Liang and Y. Zhang, Palladium-Catalyzed C–H Allylation of Electron-Deficient Polyfluoroarenes with gem-Difluorinated Cyclopropanes, *Org. Lett.*, 2021, **23**, 4920.

42 A. M. Y. Suliman, E. A. M. A. Ahmed, T. J. Gong and Y. Fu, Three-component reaction of gem-difluorinated cyclopropanes with alkenes and B₂pin₂ for the synthesis of mono-fluoroalkenes, *Chem. Commun.*, 2021, **57**, 6400.

43 L. Lv and C. J. Li, Palladium-Catalyzed Defluorinating Alkylation of gem-Difluorocyclopropanes: Switching Regioselectivity via Simple Hydrazones, *Angew. Chem., Int. Ed.*, 2021, **60**, 13098.

44 Z. Fu, J. Zhu, S. Guo and A. Lin, Palladium-catalyzed allylic alkylation dearomatization of β -naphthols and indoles with gem-difluorinated cyclopropanes, *Chem. Commun.*, 2021, **57**, 1262.



45 B. Xiong, X. Chen, J. Liu, X. Zhang, Y. Xia and Z. Lian, Stereoselective gem-Difluorovinylation of gem-Difluorinated Cyclopropanes Enabled by Ni/Pd Cooperative Catalysis, *ACS Catal.*, 2021, **11**, 11960.

46 Z. T. Jiang, J. Huang, Y. Zeng, F. Hu and Y. Xia, Rhodium Catalyzed Regioselective C–H Allylation of Simple Arenes via C–C Bond Activation of Gem-difluorinated Cyclopropanes, *Angew. Chem., Int. Ed.*, 2021, **60**, 10626.

47 L. Lv, H. Qian, A. B. Crowell, S. Chen and Z. Li, Pd/NHC-Controlled Regiodivergent Defluorinative Allylation of gem-Difluorocyclopropanes with Allylboronates, *ACS Catal.*, 2022, **12**, 6495.

48 Y. Zeng, H. Gao, Y. Zhu, Z.-T. Jiang, G. Lu and Y. Xia, Site-Divergent Alkenyl C–H Fluoroallylation of Olefins Enabled by Tunable Rhodium Catalysis, *ACS Catal.*, 2022, **12**, 8857.

49 Y. Ai, H. Yang, C. Duan, X. Li and S. Yu, Cobalt-Catalyzed Fluoroallylation of Carbonyls via C–C Activation of gem-Difluorocyclopropanes, *Org. Lett.*, 2022, **24**, 5051.

50 Z.-T. Jiang, Z. Chen, Y. Zeng, J.-L. Shi and Y. Xia, Enantioselective Formation of All-Carbon Quaternary Stereocenters in gem-Difluorinated Cyclopropanes via Rhodium-Catalyzed Stereoablative Kinetic Resolution, *Org. Lett.*, 2022, **24**, 6176.

51 Y. Zeng, H. Yang, J. Du, Q. Huang, G. Huang and Y. Xia, Rh-catalyzed regio-switchable cross-coupling of gem-difluorinated cyclopropanes with allylboronates to structurally diverse fluorinated dienes, *Chem. Sci.*, 2022, **13**, 12419.

52 X. Wu, Y. Zeng, Z.-T. Jiang, Y. Zhu, L. Xie and Y. Xia, Lewis Acid-Catalyzed Ring-Opening Cross-Coupling Reaction of gem-Difluorinated Cyclopropanes Enabled by C–F Bond Activation, *Org. Lett.*, 2022, **24**, 8429.

53 Y.-R. Zhao, Z.-Y. Ma, L. Liu, P. Gao, X.-H. Duan and M. Hu, Synthesis of α -Difluoromethylene Ethers via Photoredox-Induced Hyperconjugative Ring Opening of gem-Difluorocyclopropanes, *J. Org. Chem.*, 2023, **88**, 3787.

54 H. Qian, H. D. Nguyen, L. Lv, S. Chen and Z. Li, Chemo-, Stereo- and Regioselective Fluoroallylation/Annulation of Hydrazones with gem-Difluorocyclopropanes via Tunable Palladium/NHC Catalysis, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303271.

55 Y. Zeng and Y. Xia, Rhodium-Catalyzed Regio- and Diastereoselective [3+2] Cycloaddition of gem-Difluorinated Cyclopropanes with Internal Olefins, *Angew. Chem., Int. Ed.*, 2023, **62**, e202307129.

56 Selected synthetic routes: T. Dubuffet, C. Bidon, P. Martinet, R. Sauvretre and J. F. Normant, Préparation d’alcools allyliques fluorés, *J. Organomet. Chem.*, 1990, **393**, 161.

57 T. Hanamoto, K. Nishiyama, H. Tateishi and M. Kondo, New Route for the Synthesis of Mono-fluorinated Allyl Alcohols Using the Stereoselective Wittig Olefination via Reaction of (α -fluorovinyl)triphenylphosphonium Triflate, *Synlett*, 2001, 1320.

58 R. Zemmouri, M. Kajjout, Y. Castanet, S. Eddarir and C. Rolando, Palladium-Catalyzed Stereoconvergent Formylation of (E/Z)- β -Bromo- β -fluorostyrenes: Straightforward Access to (Z)- α -Fluorocinnamic Aldehydes and (Z)- β -Fluorocinnamic Alcohols, *J. Org. Chem.*, 2011, **76**, 7691.

59 M. A. Novikov, N. V. Volchkov, M. B. Lipkind and O. M. Nefedov, Copper(I)-catalyzed solvolysis of gem-chloro- and gem-bromofluorocyclopropanes. Preparation of 2-fluoroallylic ethers, esters and alcohols, *J. Fluor. Chem.*, 2015, **180**, 131.

60 X.-Y. Lu, M.-T. Gao, L.-J. Yu, H.-Y. Pan, X. Zhang, R. Huang, K. Yang, F.-Y. Shui, Y.-W. Song and G.-X. Yang, Synthesis of fluorinated allylic alcohols via photoinduced decarboxylative cross-coupling of α -fluoroacrylic acids and alcohols, *Org. Chem. Front.*, 2023, **10**, 1788.

61 Importance of cinnamyl alcohols as intermediates for the synthesis of drug molecules, flavors, and fungicides, selected references: R. Zhu, H. Liu, C. Liu, L. Wang, R. Ma, B. Chen, L. Li, J. Niu, M. Fu, D. Zhang and S. Gao, Cinnamaldehyde in diabetes: A review of pharmacology, pharmacokinetics and safety, *Pharmacol. Res.*, 2017, **122**, 78.

62 S. Shreaz, W. A. Wani, J. M. Behbehani, V. Raja, M. Irshad, M. Karched, I. Ali, W. A. Siddiqi and L. T. Hun, Cinnamaldehyde and its derivatives, a novel class of anti-fungal agents, *Fitoterapia*, 2016, **112**, 116.

63 P. S. Babu, S. Prabuseenivasan and S. Ignacimuthu, Cinnamaldehyde—A potential antidiabetic agent, *Phytomedicine*, 2007, **14**, 15.

64 S. C. Ho, K. S. Chang and P. W. Chang, Inhibition of neuroinflammation by cinnamon and its main components, *Food Chem.*, 2013, **138**, 2275.

65 Importance of fluorine containing drugs, selected references: H. Mei, J. Han, S. Fuster, M. Medio-Simon, D. M. Sedgwick, C. Santi, R. Ruzziconi and V. A. Soloshonok, Fluorine-Containing Drugs Approved by the FDA in 2018, *Chem. – Eur. J.*, 2019, **25**, 11797.

66 H. Chen, S. Viel, F. Ziarelli and L. Peng, ^{19}F NMR: a valuable tool for studying biological events, *Chem. Soc. Rev.*, 2013, **42**, 7971.

67 N. C. Yoder and K. Kumar, Fluorinated amino acids in protein design and engineering, *Chem. Soc. Rev.*, 2002, **31**, 335.

68 M. Salwiczek, E. K. Nyakatura, U. I. Gerling, S. Ye and B. Koksch, Fluorinated amino acids: compatibility with native protein structures and effects on protein–protein interactions, *Chem. Soc. Rev.*, 2012, **41**, 2135.

69 E. N. G. Marsh, Fluorinated Proteins: From Design and Synthesis to Structure and Stability, *Acc. Chem. Res.*, 2014, **47**, 2878.

70 X. Wang and F. W. Patureau, Pd-catalyzed access to mono- and di-fluoroallylic amines from primary anilines, *Chem. Commun.*, 2023, **59**, 486.

71 E. S. Wallis and J. F. Lane, The Hofmann Reaction, *Org. React.*, 1946, **3**, 267.



72 J. Piera, A. Persson, X. Caldentey and J.-E. Bäckvall, Water as Nucleophile in Palladium-Catalyzed Oxidative Carbohydroxylation of Allene-Substituted Conjugated Dienes, *J. Am. Chem. Soc.*, 2007, **129**, 14120.

73 T. Fujita, K. Fuchibe and J. Ichikawa, Transition-Metal-Mediated and -Catalyzed C–F Bond Activation by Fluorine Elimination, *Angew. Chem., Int. Ed.*, 2019, **58**, 390.

74 For selected recent works, see: Y. Zhao, X. Guo, S. Li, Y. Fan, G.-C. Ji, M. Jiang, Y. Yang and Y.-Y. Jiang, Transient Stabilization Effect of CO₂ in the Electrochemical Hydrogenation of Azo Compounds and the Reductive Coupling of α -Ketoesters, *Angew. Chem., Int. Ed.*, 2022, **61**, e202213636.

75 S. Okumura, T. Takahashi, K. Torii and Y. Uozumi, Photocatalytic Cross-Pinacol Coupling Promoted by Carbon Dioxide, *Chem. – Eur. J.*, 2023, **29**, e202300840.

76 S. Chen and C. Xi, CO₂ promoted photoredox/Ni-catalyzed semi-reduction of alkynes with H₂O, *Green Chem.*, 2023, **25**, 7978.

77 J. Yang, W.-H. Li, H.-T. Tang, Y.-M. Pan, D. Wang and Y. Li, CO₂-mediated organocatalytic chlorine evolution under industrial conditions, *Nature*, 2023, **617**, 519.

78 For a selected recent review, see: C.-K. Ran, H.-Z. Xiao, L.-L. Liao, T. Ju, W. Zhang and D.-G. Yu, Progress and challenges in dicarboxylation with CO₂, *Natl. Sci. Open*, 2023, **2**, 20220024.

