

# A Journey with Hexafluoroisopropanol

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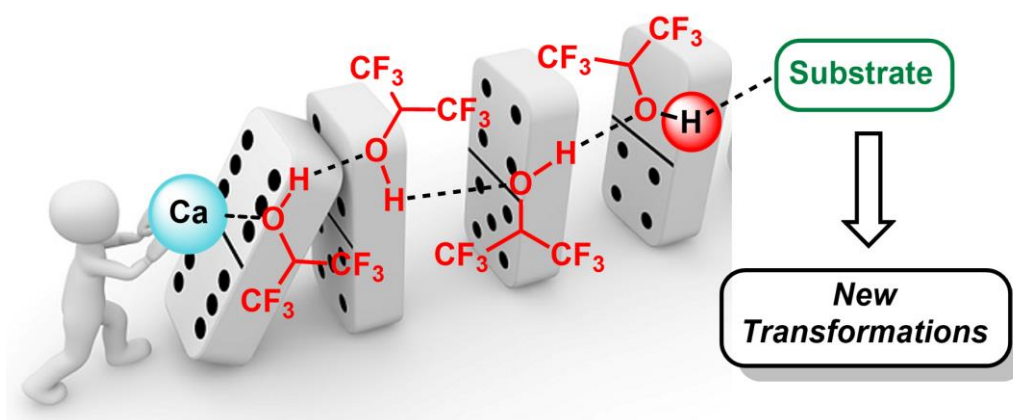
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In recent years, fluorinated alcohol solvents such as hexafluoroisopropanol (HFIP) have become enabling technologies in all areas of organic synthesis, owing to their remarkable intrinsic properties.<sup>1</sup> HFIP can stabilize cationic and radical species. It strongly donates hydrogen bonds and possesses low nucleophilicity, mild acidity and high redox stability. These different facets make it an attractive solvent in all areas of modern catalysis, including transition metal, Lewis and Brønsted acid catalysis as well as photoredox and electrochemical processes, organocatalysis and hypervalent iodine-promoted reactions. As a result, it is now routinely used for the design of new transformations.

Over the past years, we have exploited the unique properties of HFIP to push the limits of Lewis and Brønsted acid-catalyzed reactions that did not take place in traditional solvents.<sup>1b</sup> These reactions are highly user-friendly as they are air- and moisture-tolerant. Based on in-depth mechanistic studies, we demonstrated that the acidity of self-assembled H-bond clusters of HFIP was amplified through coordination to a Lewis acid to promote reactions involving highly deactivated substrates, while the acidity of a Brønsted acid was in turn harnessed by HFIP clusters. By relying on these properties, we showed that the combination acid catalyst/HFIP was a powerful tool to promote hydro- and difunctionalizations of alkenes, alkynes, epoxides, and primary aliphatic alcohols.<sup>2</sup>



**Strong acidity and strong H-bond donating ability**

## References

- [1] For selected reviews on HFIP, see: (a) Colomer, I.; Chamberlain, A. E. R.; Haughey, M. B.; Donohoe, T. J. *Nat. Rev. Chem.* **2017**, *1*, 0088. (b) Pozhydaiev, V.; Power, M.; Gandon, V.; Moran, J.; Lebœuf, D. *Chem. Commun.* **2020**, *56*, 11548. (c) Motiwala, H. F.; Armaly, A. M.; Cacioppo, J. G.; Coombs, T. C.; Koehn, K. R. K.; Norwood IV, V. M.; Aubé, J. *Chem. Rev.* **2022**, *122*, 12544.
- [2] For selected examples: (a) Qi, C.; Gandon, V.; Lebœuf, D. *Angew. Chem. Int. Ed.* **2018**, *57*, 14245. (b) Wang, S.; Force, G.; Carpentier, J.-F.; Sarazin, Y.; Bour, C.; Gandon, V.; Lebœuf, D. *Org. Lett.* **2021**, *23*, 2565. (c) Zhang, S.; Vayer, M.; Noël, F.; Vuković, V. D.; Golushko, A.; Rezajoei, N.; Rowley, C. N.; Lebœuf, D.; Moran, J. *Chem* **2021**, *7*, 3425. (d) Vayer, M.; Zhang, S.; Moran, J.; Lebœuf, D. *ACS Catal.* **2022**, *12*, 3309. (e) Pozhydaiev, V.; Vayer, M.; Fave, C.; Moran, J.; Lebœuf, D. *Angew. Chem. Int. Ed.* **2023**, *62*, e202215257.