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A practical and straightforward access to fluorinated homoallylic alcohols in aqueous media

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ABSTRACT

Herein, a practical and straightforward access to fluorinated homoallylic alcohols is reported. The corresponding products were obtained in good to excellent yield in brine or THF as a solvent using indium(0) and the readily available 3-chloro-2-fluoroprop-1-ene to promote the allylation reaction. This methodology affords an easy access to valuable fluorinated products under mild conditions.

Molecules containing fluorine atoms are of great interest due to the remarkable properties of this intriguing atom.[1] The ability of the fluorine atom to modify the physical and chemical properties of a molecule pushes it at the forefront of the agrochemical and drug discovery.[1] As a result, molecules containing fluorine are found in around 20% of pharmaceuticals and more than 40% of agrochemicals, contrasting with the lack of fluorinated molecules in nature.[2] Therefore, since the discovery of the pioneering Balz–Schiemann reaction[3] the organic chemist community developed several approaches to introduce fluorine in an efficient and practical way.[4] Recently, lots of efforts were devoted to develop and design new and efficient access to fluorinated molecules.[5] These methodologies basically focused on two strategies: (1) the formation of the C–F bond[4] and (2) the functionalization of the readily available fluorinated building blocks.[5,6] Among all these fluorinated molecules, fluoroolefins[7] are pretty interesting and appealing by their use in material science[8] or as a template toward the design of peptidomimetics (Fig. 1).[9]

On the other hand, homoallylic alcohols are considered as a key building block in organic synthesis allowing a huge range of post-functionalization.[10] Thus, taking into account these points and as part of our current research program dealing with the development of valuable fluorinated building blocks,[11] we were interested in the synthesis of secondary and tertiary fluorinated homoallylic alcohols. Surprisingly, only two reports dealing with an access to secondary fluorinated alcohols using either an iridium-catalyzed dehydrogenative C–C forming bond[12a] or an Hosomi–Sakurai reaction with fluorinated allylsilane[12b] have been reported to date. Thus, we report herein a simple, mild, and straightforward access to these new compounds using 3-chloro-2-fluoroprop-1-ene and indium[13] in aqueous media (Fig. 2).

Initially, the first set of reactions was performed in water at room temperature using 1.2 equiv of indium and 1.1 equiv of 3-chloro-2-fluoroprop-1-ene. Pleasingly, the desired product **2a** was obtained in good yield, 72% (entry 1, Table 1). Then 2 equiv of In(0) was used, furnishing a slight improvement of the conversion into **2a** (entry 2). The use of 1.5 equiv of indium along with 1.5 equiv of 3-chloro-2-fluoroprop-1-ene gave a significant enhancement of the conversion, the desired alcohol was obtained in 90% yield (entry 3), while the use of 2 equiv of indium and

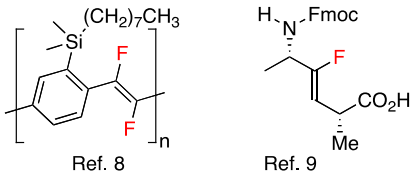

Figure 1. Examples of relevant fluorinated olefins.

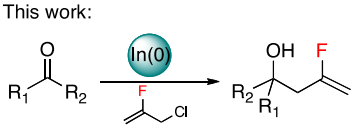

Figure 2. Present work.

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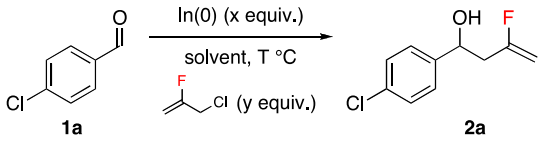
Table 1
Optimization of the reaction conditions



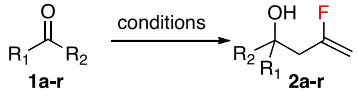
Entry	Solvent	*x* equiv	*y* equiv	Yield[a] (%)
1	H_2O	1.2	1.1	72
2	H_2O	2	1.1	76
3	H_2O	1.5	1.5	90
4	H_2O	2	1.5	89
5	H_2O	2	2	98 (91)[b]
6	Brine	2	2	100 (99)[b]

[a] Determined by ^{19}F NMR and ^{1}H NMR of the crude product using an internal standard.
[b] Isolated yield.

1.5 equiv of the fluorinated starting material did not afford any improvement (entry 4). Finally the use of 2 equiv of In(0) with 2 equiv of fluorinated chloro-allyl species gave the product in 91% isolated yield (entry 5), and the replacement of water by brine[14] gave a complete conversion of the aldehyde and the desired product in quantitative isolated yield (entry 6).

Having these optimized conditions in hands,[15] we next move on to the scope of the reaction (Table 2). First, aromatic aldehydes bearing an electron-withdrawing group were investigated. Pleasingly, an ester moiety was well tolerated under our reaction conditions giving the corresponding homoallylic alcohols **2b** in 88% yield, while benzaldehyde afforded the allylated adduct **2c** in 66% yield (entries 1–3). Electron-rich aromatic aldehyde such as *para*-anisaldehyde **1d** was used giving the fluorinated alcohol **2d** in 99% yield (entry 4). Unprotected phenol **1e** was also suitable for this process affording the desired product **2e** in 73% yield (entry 5), as well as α-substituted-α,β-unsaturated aldehyde **1f** which gave the allylic alcohol **2f** in very good yield (entry 6). Interestingly, valuable heteroaromatic backbones such as thiophene **1g** and pyridine **1h** were also compatible for the allylation reaction (entries 7 and 8). Then, we turned our attention to the aliphatic aldehydes. Hydrocinnamaldehyde **1i** gave the corresponding fluorinated allylic alcohol **2i** in quantitative yield (entry 9), while nonanal **1j** and citronellal **1k** gave lower yield, 60% and 57%, respectively, probably due to their higher volatility (entries 10 and 11). Aldehyde **1l** was used, affording the corresponding fluorinated alcohol **2l** in excellent yield (entry 12). With both citronellal **1k** and aldehyde **1l** as substrates, no significant diastereoselectivities were observed (entries 11 and 12). This methodology was successfully applied to both racemic *trans*- and *cis*-fluorocyclopropane bearing an aldehyde moiety.[11c] The *trans* isomer **1m** furnishes the corresponding difluorinated cyclopropane derivative **2m** in 63% and good 80:20 diastereoisomeric ratio (entry 13), while the *cis* isomer **1n** gave the allylated alcohol **2n** as a single diastereoisomer in 83% yield (entry 14).[16] Finally, ketones were

Table 2
Scope of the reaction[a]



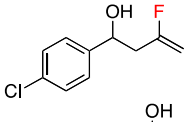
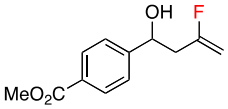
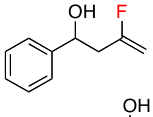
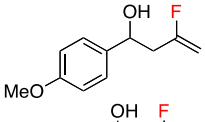
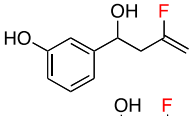
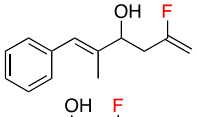
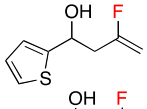
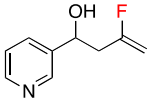
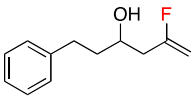
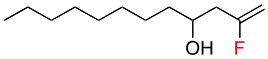
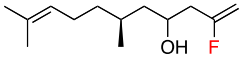
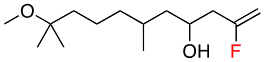
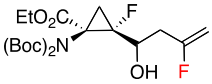
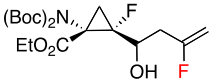
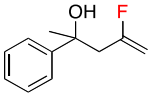
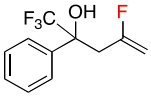
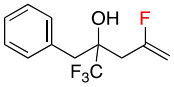
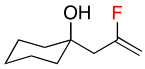
Entry	Starting material	Product		Yield[b] (%)
1	**1a**		**2a**	99
2	**1b**		**2b**	88
3	**1c**		**2c**	66
4[d]	**1d**		**2d**	99
5	**1e**		**2e**	73
6[c]	**1f**		**2f**	87
7	**1g**		**2g**	83
8[c]	**1h**		**2h**	77

Table 2 (*continued*)

Entry	Starting material	Product		Yield[b] (%)
9[d]	**1i**		**2i**	99
10[e]	**1j**		**2j**	60
11[e]	**1k**		**2k**	57 (53:47)[g]
12[e]	**1l**		**2l**	97 (50:50)[g]
13[d]	**1m**		**2m**	63 (80:20)[g]
14[d]	**1n**		**2n**	83 (100:0)[g]
15[d]	**1o**		**2o**	13
16[f]	**1p**		**2p**	99
17[f]	**1q**		**2q**	57
18[f]	**1r**		**2r**	73

[a] Conditions: **1** (1 equiv), 3-chlorofluoropropene (2 equiv), In(0) (2 equiv), brine (1.5 mL), rt, 16 h.
[b] Isolated yield.
[c] 72 h reaction time.
[d] Reaction performed at 40 °C for 72 h.
[e] Reaction performed at 60 °C for 24 h.
[f] Reaction was performed at 60 °C in THF for 24 h.
[g] Diastereoisomeric ratio determined by ^{19}F NMR on the crude reaction mixture.

investigated as substrates in the course of this fluoro-allylation process. Unfortunately, under standard conditions ketone **1o** reacted poorly and gave the desired product **2o** with only 13% yield (entry 15). A survey of temperature and solvents revealed that an increase of temperature from room temperature to 60 °C and the use of THF as a solvent afford quantitatively the desired product **2p** from the highly activated ketone **1p** (entry 16). These reaction conditions were applied to the less activated acetophenone **1o**, unfortunately without any improvement. Then, trifluoroketone **1q** was engaged under these experimental conditions furnishing the corresponding product **2q** in good yield (entry 17). Finally, the unactivated cyclohexanone **1r** was successfully used as a starting material and the corresponding allylated products **2r** were isolated in 73% (entry 18).

In summary, we report herein the first access to fluorinated homoallylic alcohols using a mild and ecofriendly process. This process using indium(0), the readily available 3-chloro-2-fluoroprop-1-ene and brine as a reaction solvent was successfully applied to a broad range of highly functionalized aldehydes. Activated ketones were also successfully converted into the desired tertiary allylic alcohols using THF as a solvent. This approach offers a straightforward access to this new class of compounds. Further studies toward the reactivity and the functionalization of these promising products are currently underway in our laboratory.

Acknowledgments

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References and notes

1. (a) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319; (b) Bégué, J.-P.; Bonnet-Delpon, D. *Bioorganic and Medicinal Chemistry of Fluorine*; John Wiley & Sons, Inc.: Hoboken, NJ, 2008; (c) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004; (d) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1–16.
2. (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886; (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320–330.
3. Balz, G.; Schiemann, G. *Ber.* **1927**, *60B*, 1186–1190.
4. For review on fluorine introduction see: (a) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discov. Dev.* **2008**, *11*, 803–819; (b) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470–477; (c) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929–2942; Selected examples: (d) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094–4097; (e) Rauniyar, V.; Lackner, A. D.; Hamilton, G. L.; Toste, F. D. *Science* **2011**, *334*, 1681–1684.
5. For recent reviews see: (a) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev.* **2011**, *111*, 4475–4520; (b) Leclerc, E.; Pannecoucke, X.; Ethève-Quelquejeu, M.; Sollogoub, M. *Chem. Soc. Rev.* **2013**. http://dx.doi.org/10.1039/c2cs35403a; (c) Zhu, R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2012**, *134*, 12462–12465; (d) Fuchibe, K.; Takahashi, M.; Ichikawa, J. *Angew. Chem., Int. Ed.* **2012**, *51*, 12059–12062.
6. (a) Special Issue on Fluorinated Synthons, *J. Fluorine Chem.* **2004**, *125*, 477–645.; (b) *Fluorine-Containing Synthons*; Soloshonok, V. A., Ed.; American Chemical

Society: Washington, DC, 2005; (c) *Current Fluoroorganic Chemistry: New Synthetic Directions, Technologies, Materials, and Biological Applications*; Soloshonok, V. A., Mikami, K., Yamazaki, T., Welch, J. T., Hoenk, J. F., Eds.; American Chemical Society: Washington, DC, 2007.

7. (a) Landelle, G.; Bergeron, M.; Turcotte-Savard, M.-O.; Paquin, J.-F. *Chem. Soc. Rev.* **2011**, *40*, 2867–2908; (b) Yanai, H.; Taguchi, T. *Eur. J. Org. Chem.* **2011**, 5939–5954; (c) Hara, S. *Top. Curr. Chem.* **2012**, *327*, 59–86.
8. (a) Babudri, F.; Farinola, G. M.; Naso, F.; Ragni, R. *Chem. Commun.* **2007**, 1003–1022; (b) Babudri, F.; Cardone, A.; Farinola, G. M.; Martinelli, C.; Mendichi, R.; Naso, F.; Striccoli, M. *Eur. J. Org. Chem.* **2008**, 1977–1982.
9. Selected examples: (a) Dutheuil, G.; Couve-Bonnaire, S.; Pannecoucke, X. *Angew. Chem., Int. Ed.* **2007**, *46*, 1290–1292; (b) Van der Veken, P.; Senten, K.; Kertèsz, I.; De Meester, I.; Lambeir, A.-M.; Maes, M.-B.; Scharpé, S.; Haemers, A.; Augustyns, K. *J. Med. Chem.* **2005**, *48*, 1768–1780; (c) Zhao, K.; Lim, D. S.; Funaki, T.; Welch, J. T. *Bioorg. Med. Chem.* **2003**, *11*, 207–215; For reviews see: (d) Couve-Bonnaire, S.; Cahard, D.; Pannecoucke, X. *Org. Biomol. Chem.* **2007**, *5*, 1151–1157; (e) Taguchi, T.; Yanai, H. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; Blackwell Publishing Inc., Chichester, 2009; p 257.
10. Selected examples: (a) Makita, N.; Hoshino, Y.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 941–9434; (b) Blanc, A.; Toste, F. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 2096–2099; (c) Malkov, A. V.; Barlóg, M.; Miller-Potuckà; Kabeshov, L. M. A.; Farrugia, L. J.; Kocovsky, P. *Chem. Eur. J.* **2012**, *18*, 6873–6884.
11. (a) Poisson, T.; Belhomme, M.-C.; Pannecoucke, X. *J. Org. Chem.* **2012**, *77*, 9277–9285; (b) Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2012**, *14*, 5130–5133; (c) Milanole, G.; Couve-Bonnaire, S.; Bonfanti, J.-F.; Jubault, P.; Pannecoucke, X. *J. Org. Chem.* **2013**, *78*, 212–223; (d) Lemonnier, G.; Zoute, L.; Quirion, J.-C.; Jubault, P. *Org. Lett.* **2010**, *12*, 844–846; (e) Lemonnier, G.; Zoute, L.; Dupas, G.; Quirion, J.-C.; Jubault, P. *J. Org. Chem.* **2009**, *74*, 4124–4131; (f) David, E.; Milanole, G.; Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Chem. Eur. J.* **2012**, *18*, 14904–14917.
12. (a) Hassan, A.; Montgomery, T. P.; Krische, M. J. *Chem. Commun.* **2012**, *48*, 4692–4694; (b) Hayashi, T.; Usuki, Y.; Iio, H. *J. Fluorine Chem.* **2010**, *131*, 709–713.
13. For reviews dealing with the use of indium(0) in allylation reaction see: (a) Bowyer, W. J.; Singaram, B.; Sessler, A. M. *Tetrahedron* **2011**, *67*, 7449–7460; (b) Augé, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739–1764; (c) Shen, Z.-L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Rev.* **2013**, *113*, 271–401.
14. For the beneficial effect of brine or saturated aqueous solution in indium promoted allylation reaction see: Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259–1262.
15. *Representative procedure:* In a 1.5 mL vial, indium (23 mg, 0.2 mmol), **1a** (14 mg, 0.1 mmol), and brine (1 mL) were added. Then, 3-chloro-2-fluoroprop-1-ene (18 μL, 0.2 mmol) was added and the vial was sealed (screwed cap). The resulting mixture was stirred at rt for 16 h, then DCM was added and the aqueous phase was extracted 2 times. Organic layer was dried over $MgSO_4$ and the residue was purified by flash chromatography (petroleum ether/ethyl acetate mixture) to afford the corresponding fluorinated alcohol **2a** (20 mg, 99% yield). Physical data: Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.23 (d, $^3J_{H,H}$ = 8.7 Hz, 2H), 7.19 (d, $^3J_{H,H}$ = 8.7 Hz, 2H), 4.82 (dd, $^3J_{H,H}$ = 5.8, 7.4 Hz, 1H), 4.55 (dd, $^3J_{H,H}$ = 2.8, $^3J_{H,F}$ = 17.3, 1H), 4.23 (dd, $^3J_{H,H}$ = 2.8, $^3J_{H,F}$ = 50.0, 1H), 2.58–2.38 (m, 2H), 2.34 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 162.8 (d, $^1J_{C,F}$ = 257 Hz), 141.5, 133.5, 128.6 (2C), 127.0 (2C), 93.0 (d, $^2J_{C,F}$ = 19 Hz), 70.2, 42.3 (d, $^2J_{C,F}$ = 26 Hz) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −95.9 (dddd, $^3J_{F,H}$ = 15, 17, 22, 50 Hz) ppm. IR (neat): $\bar{\nu}_{max}$ = 3385, 1675, 1493, 1013, 818 cm^{-1}. Elementary Anal. Calcd for $C_{10}H_{10}ClFO$ (200.64): C, 59.86; H, 5.02. Found: C, 59.90; H, 4.67.
16. So far, we have not been able to determine the stereochemistry of the product.