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Catalytic Asymmetric Synthesis of α,α-Difluoromethylated and α-Fluoromethylated Tertiary Alcohols

Wei-Sheng Huang,[†] Marie-Léonie Delcourt,[†] Xavier Pannecoucke,[†] André B. Charette,[‡] Thomas Poisson,*[,†,§] and Philippe Jubault*[,†]

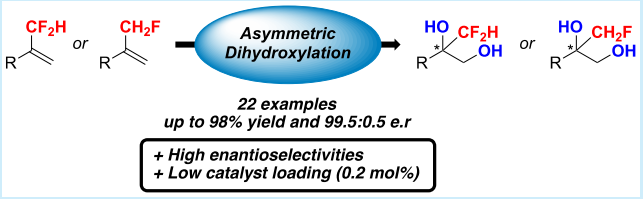
[†]Normandie Université, INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France

[‡]Centre in Green Chemistry and Catalysis, Faculty of Arts and Sciences, Department of Chemistry, Université de Montréal, P.O. Box 6128, Station Downtown, Montréal, Québec H3C 3J7, Canada

[§]Institut Universitaire de France, 1 rue Descartes, 75231 Paris, France

Supporting Information

ABSTRACT: The catalytic asymmetric synthesis of α,α-difluoromethylated tertiary alcohols is described, using an asymmetric dihydroxylation reaction. This protocol using either the AD-mix-α or AD-mix-β allowed an easy access to these valuable fluorinated chiral building blocks, which have been obtained with excellent yields and er. In addition, the reaction was extended to the α-fluoromethylated analogues.



The synthesis of molecules containing one fluorine atom or a fluorinated group has received a significant attention over the past ten years. This interest mainly results from the growing importance of the fluorinated molecules in the drug discovery process, crop science, or material sciences.[1] Indeed, once introduced into a molecule the fluorine atom or the fluorinated group can drastically change the biological and/or the physicochemical properties of the molecules. Hence, impressive efforts were dedicated to the introduction of the fluorine atom or fluorinated groups.[2] Among these groups, the CF_2H one received less attention despite its high potential as an alcohol or thiol bioisoster.[3] Recently, Lippard demonstrated that this motif can carry out H-bonding interactions.[4] Moreover, the stereospecific construction of a chiral center bearing a CF_2H group has been underexplored, in contrast to the formation of F- or CF_3-containing stereogenic centers.[5]

Regarding the catalytic asymmetric formation of α,α-difluoromethyl alcohols, only a handful of straightforward procedures was reported to date (Figure 1). Secondary enantioenriched alcohols can be obtained from the asymmetric reduction of the corresponding ketones (eq 1),[6] an aldol reaction with α,α-difluoroacetaldehyde (eq 2),[7] or the asymmetric allylation of the latter (eq 3).[8] Alternatively, Hu[9] and Leroux[10] reported the diastereoselective addition of difluoromethyl nucleophiles, as surrogates of the HCF_2 anion, prior to their conversion into the enantioenriched α,α-difluoromethyl secondary alcohols (eq 4). Besides, although often restricted to few examples, α,α-difluoromethyl tertiary alcohols were obtained from catalytic asymmetric alkylation,[11] allylation,[12] propargylation,[13] or aldol reactions[14] on α,α-difluoromethylated ketones with moderate to excellent enantioselectivities (eq 5). On the other hand, Mikami described the Pd-catalyzed ene-reaction on α,α-difluoromethylated pyruvates (eq 6),[15] while Hu used a chiral difluoromethylated sulfoximine based reagent to introduce the CF_2H motif on ketones after desulfoximination (eq 7).[16] Finally, in 2019 Lassaletta described the catalytic asymmetric addition of hydrazones onto α,α-difluoromethylated ketones providing the tertiary alcohols with moderate enantioselectivities using chiral squaramide or thiourea catalysts (eq 8).[17] As part of our recent efforts to afford new methods to build up molecules containing the difluoromethyl motif,[18] we aimed at providing a complementary strategy to access enantioenriched α,α-difluoromethyl tertiary alcohols using a chiral catalyst.

The venerable Sharpless asymmetric dihydroxylation reaction (ADR) is a powerful tool to build-up enantioenriched tertiary alcohols, using a chiral catalyst, from olefins.[19] Impressive efforts and contributions led to the development of practical and robust catalytic systems. However, the application of these systems to the synthesis of α-fluorinated alcohols is restricted to a few examples using trifluoromethylated olefins.[20] Hence, we report herein the use of this powerful reaction manifold to access the α,α-difluoromethyl tertiary alcohols with high enantiomeric ratios from the corresponding HCF_2-containing olefins. This practical and efficient method affords a straightforward access to these difficult to build up enantioenriched building blocks.

At the outset of the study, we investigated the ADR of α,α-difluoromethylated styrene **1a** in the presence of AD-mix-α (Table 1). Using AD-mix-α (Os: 0.2 mol %) in a mixture of organic solvent and water (1:1) at 0 °C for 24 h, the asymmetric dihydroxylation of **1a** was optimized. First, alcohols were tested as a cosolvent, and EtOH and *i*PrOH afforded the desired dihydroxylated product **2a** in moderate

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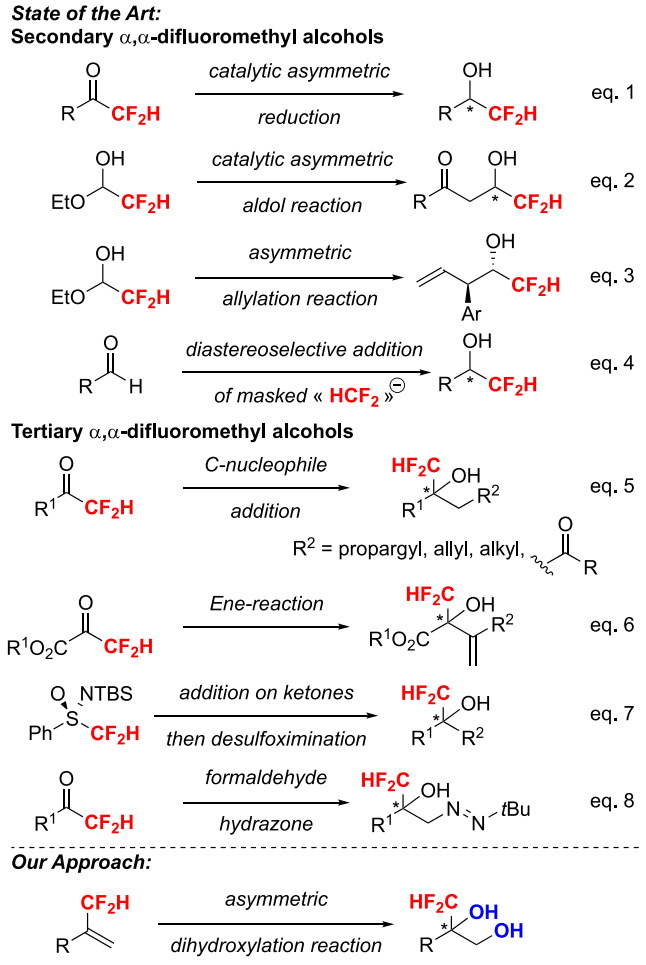
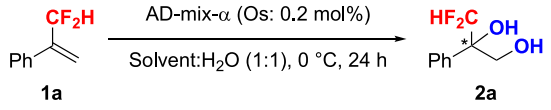


Figure 1. State of the art and present strategy.

Table 1. Optimization of the Asymmetric Dihydroxylation of 1a Using AD-mix-α[a]



1a **2a**

entry	solvent	yield (%)[b]	er[c]
1	EtOH	24	73.5:26.5
2	*i*PrOH	30	76:24
3	amyl alcohol	31	93.5:6.5
4	*t*BuOH	51	96:4
5	ethylene glycol	NR	–
6[d]	*t*BuOH	90	95:5
7[d]	1,4-dioxane	77	94:6
8[d]	Acetone	75	91:9
9[d,e]	*t*BuOH	88	2.5:97.5

[a]Reaction conditions: **1a** (0.1 mmol), AD-mix-α (Os: 0.2 mol %), Solvent:H_2O (1:1, 1 mL), 0 °C, 24 h. [b]Isolated yield is reported. [c]The enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase. [d]72 h instead of 24 h. [e]AD-mix-β was used instead of AD-mix-α. NR: no reaction.

yields (24% and 30%) and modest enantiomeric ratios (er), 73.5:26.5 and 76:24, respectively (entries 1 and 2). Then, amyl alcohol and *t*BuOH were evaluated (entries 3 and 4). Amyl alcohol gave a similar yield as EtOH and *i*PrOH, while the er was increased to 93.5:6.5. Pleasingly, *t*BuOH gave a higher yield (51%) and an excellent 96:4 er. Note that ethylene glycol was inefficient in our reaction (entry 5). In order to get **2a** in a synthetically useful yield, the reaction time was increased to 72 h, and the product **2a** was isolated in 90% yield with a 95:5 er (entry 6). An additional survey of solvent (1,4-dioxane and acetone) did not afford an increase of the yield or the er (entries 7 and 8). Finally, the use of the AD-mix-β, under identical reaction conditions, allowed the access to the other enantiomer of **2a** with a similar yield (88%) and a slightly better er (2.5:97.5, entry 9).

With the optimized conditions set up, we turned our attention to the extension of the scope of the reaction (Scheme 1). First, the scale of the reaction with **1a** was increased to 4 mmol using AD-mix-β and **2a** was isolated in an excellent 98% and a similar 3:97 er, demonstrating the synthetic utility of the method. Then, methyl-substituent on the aromatic ring of the α,α-difluoromethylstyrenes at the *para*, *meta*, and *ortho* position were tested with the two catalysts (AD-mix-α and AD-mix-β). Both *para*- and *meta*-substituted derivatives **2b** and **2c** were obtained in good yield with excellent er (up to 99:1), while the *ortho*-substituted derivative **2d** was obtained in low yields (13% and 14%) and modest er with both catalysts. Surprisingly, the xylyl derivative **1e** gave **2e** with a higher yield and er. A methoxy substituent was also tolerated and the *para*- and *ortho*- substituted derivatives **2f** and **2g** were isolated in moderate yields with good to excellent er. The 1- and 2-naphthyl derivatives **2h** and **2i** were submitted to the dihydroxylation conditions, and the expected products were obtained with very good to excellent er and an excellent yield in the case of **2h**.

Similarly to the *ortho*-substituted derivatives **2d** and **2e**, the *peri*-substitution hampers the efficiency of the process as **2i** was isolated in modest yields (40% and 56%). Halogen substituents were well tolerated since the fluoro, chloro, and bromo substituted α,α-difluoromethyl tertiary alcohols **2j**, **2k**, and **2l** were isolated in excellent yields with excellent er. The thienyl tertiary alcohol **2m** was obtained in good yields and excellent er, showing the compatibility of a sulfur-containing heterocycle. Pleasingly, the methodology was extended to the aliphatic derivative **1n** and the corresponding α,α-difluoromethyl tertiary alcohol **2n** was isolated in decent yields and obtained with moderate to good er. Then, as the monofluoromethyl motif (CH_2F) is important in the drug discovery process, as demonstrated by its presence on the structure of the blockbuster Advair, for instance, we tested α-monofluoromethylated styrene derivatives under our standard conditions. To our delight, the methodology was readily extended to the CH_2F derivatives, which were isolated in excellent yields (70% to 93%). In all cases, the er is excellent (97:3 to 99:1), although a bit lower in the case of **4a** (92:8 with AD-mix-α and 9.5:90.5 with AD-mix-β). The reaction was also tested on other styrene derivatives substituted with a fluorinated group at the α-position. Unfortunately, the CF_2CO_2Et and $CF_2PO(OEt)_2$ derivatives were unreactive under our reaction conditions, whereas the α-CF_2CH_2OTBS substituent was tolerated.[21] The product **6** was isolated in moderate yields with both AD-mix-α and AD-mix-β. In the latter case the er is moderate, while a lower er of 87:13 is obtained with AD-mix-α. Finally, the reaction was extended to β-difluoromethyl and β-trifluoromethyl styrenes **7a** and **7b**. In both cases a very high level of enantioselectivity was observed with the AD-mix-α and -β catalytic systems and **8a** and **8b** were isolated in moderate yields (49−53%).

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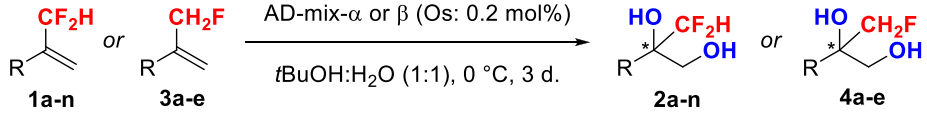
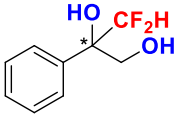
Scheme 1. Scope of the Reaction[d]

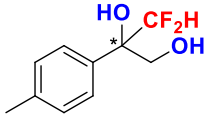


α,α-difluoromethylstyrenes



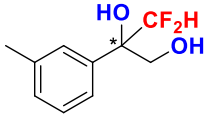
2a

90%, 95:5 er (α)
88%, 2.5:97.5 er (β)
98%,[a] 3:97 er (β)



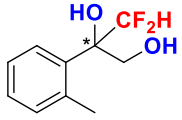
2b

88%, 97.5:2.5 er (α)
82%, 1:99 er (β)



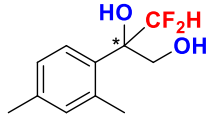
2c

90%, 98:2 er (α)
87%, 2:98 er (β)



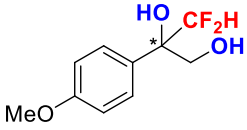
2d

13%, 83.5:16.5 er (α)
14%, 11.5:88.5 er (β)



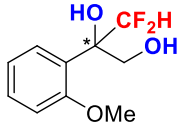
2e

40%, 91:9 er (α)
43%, 6.5:93.5 er (β)



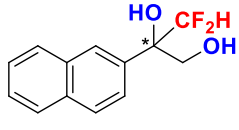
2f

64%, 98:2 er (α)
63%, 1:99 er (β)



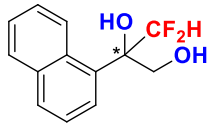
2g

61%, 9:91 er (α)
61%, 94:6 er (β)



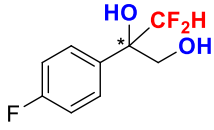
2h

83%, 99:1 er (α)
92%, 0.5:99.5 er (β)



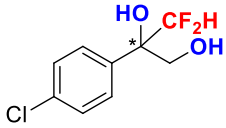
2i

40%, 94:6 er (α)
56%, 3:97 er (β)



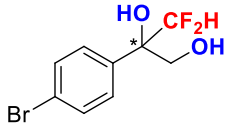
2j

89%, 97.5:2.5 er (α)
80%, 2:98 er (β)



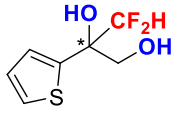
2k

78%, 97:3 er (α)
77%, 1.5:98.5 er (β)



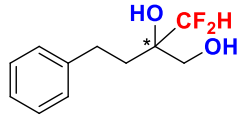
2l

83%, 98:2 er (α)
81%, 1:99 er (β)



2m

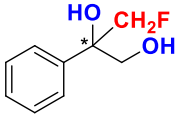
76%, 95:5 er (α)
56%, 4:96 er (β)



2n

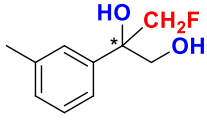
76%, 89:11 er (α)
56%, 6.5:93.5 er (β)

α-monofluoromethylstyrenes



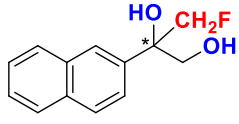
4a

70%, 92:8 er (α)
75%, 9.5:90.5 er (β)



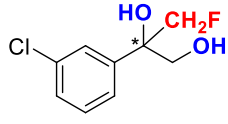
4b

85%, 98.5:1.5 er (α)
76%, 1:99 er (β)



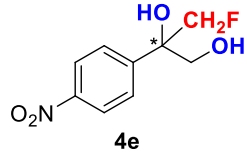
4c

93%, 98.5:1.5 er (α)
90%, 2:98 er (β)



4d

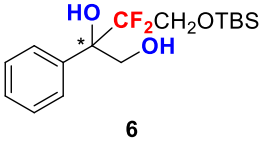
79%, 97:3 er (α)
76%, 2.5:97.5 er (β)



4e

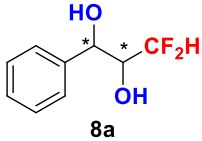
87%, 1:99 er (α)
82%, 2:98 er (β)

Other substrates:



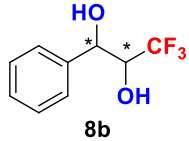
6

46%, 87:13 er (α)
43%, 7.5:92.5 er (β)



8a

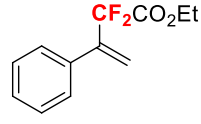
53%, 99:1 er (α)[b]
49%, 0.5:99.5 er (β)[b]

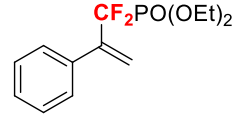


8b

55%, 99:1 er (α)[c]
54%, 0.5:99.5 er (β)[c]

Reluctant substrates:





[a]The reaction was carried out on a 4 mmol scale. [b]Reaction time, 6 days. [c]Reaction was carried out at 20 °C. [d]**1** or **2** (0.25 mmol), AD-mix-*α* or -*β* (Os: 0.2 mol %), *t*BuOH:H_2O (1:1, 2.5 mL), 0 °C, 72 h. Enantiomeric ratio (er) was determined by HPLC analysis on a chiral stationary phase.

Then, we demonstrated the versatility and the synthetic utility of these chiral *α,α*-difluoromethyl tertiary alcohols (Scheme 2).

First, chiral alcohol **2a** was readily converted into the corresponding cyclic sulfate **9** in 75% yield and a similar er. Then, this versatile platform was reduced into the corresponding alcohol **10** in 66% yield and a 4.5:95.5 er. Note that the absolute configuration was determined as *S*, by comparison with the literature data.[17] This finding provides us the clue that the AD reaction of these fluorinated olefins follows the empirical rules for the prediction of the selectivity of the AD reaction using AD-mix-*α* and -*β*.[19b] In the same vein, sulfate **9** was transformed into the corresponding iodo alkane **11** in 75% yield without alteration of the er. Finally, the azide **12** was readily obtained after the reaction of **9** with NaN_3 in 79% yield. A subsequent reduction of the latter followed by a *N*-protection to avoid a tedious purification gave **13** in 68% yield over 2 steps with a 2.5:97.5 er.

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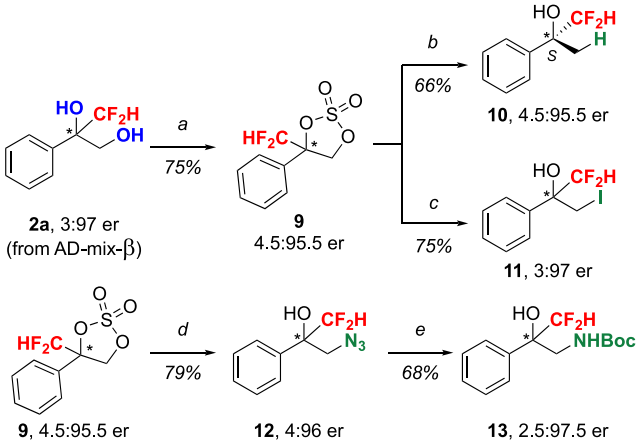
Scheme 2. Synthetic Utility of the α,α-Difluoromethyl Tertiary Alcohol 2a[a]



[a](a) *i.* $SOCl_2$ (1.5 equiv), Et_3N (3 equiv), DCM, 0 °C, 1 h. *ii.* $RuCl_3$ (1 mol %), $NaIO_4$ (2.2 equiv), MeCN/H_2O (1:1), rt, 1 h. (b) $NaBH_4$ (2.8 equiv), DMF, 0 °C, 1 h, then H_2SO_4, H_2O, THF, 0 °C, 1 h. (c) NaI (2 equiv), DMF, rt, 45 min, then H_2SO_4, H_2O, THF, 0 °C, 1 h. (d) NaN_3 (2 equiv), DMF, rt, 1 h, then H_2SO_4, H_2O, THF, 0 °C, 1 h. (e) *i.* H_2, Pd/C, EtOAc, rt, 16 h. *ii.* Boc_2O (2.3 equiv), Et_3N (3.4 equiv), THF, rt, 2 h.

In conclusion, we developed a practical and efficient protocol to access enantioenriched α,α-difluoromethyl tertiary alcohols with good to excellent er and good to excellent yields. Both enantiomers are readily available using either the AD-mix-α or AD-mix-β as the catalyst. Note that in all cases AD-mix-α and AD-mix-β gave very similar results, with a slightly better er. in the case of AD-mix-β. The method was applied to a broad range of substrates. In addition, we extended this reaction to the CH_2F analogues, and the products were obtained in similar yields and er. The scale of the reaction was increased to 4 mmol to highlight the synthetic utility of the reaction. In addition, the versatility of the resulting products was demonstrated through various synthetically useful transformations. We believe that these new building blocks will found application in the synthesis of new bioactive molecules.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02792.

Experimental procedures, compound characterization data, ^1H, ^{13}C, and ^{19}NMR spectra of the products and HPLC traces (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: thomas.poisson@insa-rouen.fr.
*E-mail: philippe.jubault@insa-rouen.fr.

ORCID

Thomas Poisson: 0000-0002-0503-9620
Philippe Jubault: 0000-0002-3295-9326

Notes

The authors declare no competing financial interest.

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