Multi-catalytic Enantioselective Synthesis of 1,3-Diols Containing a Tetrasubstituted Fluorinated Stereocenter

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Multi-catalytic Enantioselective Synthesis of 1,3-Diols Containing a Tetrasubstituted Fluorinated Stereocenter

Na Shao,[a] Valérie Monnier,[b] Laurence Charles,[c] Jean Rodriguez,[a] Cyril Bressy,*[a] and Adrien Quintard*[a]

The enantioselective construction of fluorohydrins featuring a tetrasubstituted stereocenter embedded in complex frameworks represents an important challenge. Herein, we report a multicatalytic strategy enabling the stereoselective preparation of a new type of scaffold containing such a challenging fluorohydrin motif. The sequence is based on an organocatalyzed fluorination of α-disubstituted aldehydes followed by a diastereoselective copper-catalyzed decarboxylative aldol reaction. Reduction of the generated β-hydroxy ketone followed by a Lewis base-catalyzed kinetic resolution enables the isolation of original fluorinated 1,3-diols with perfect diastereo- and enantio-control.

Introduction

Tetrasubstituted fluorinated stereocenters are prevalent in a broad range of drugs and bioactive compounds.[1] However, their stereoselective incorporation is particularly challenging due to steric and electronic factors.[2] In bioactive molecules, tetrasubstituted fluorinated stereocenters are often located at the direct vicinity of secondary alcohols as in sofosbuvir or fludrocortisone.[3] Consequently, it is highly desirable to discover concise enantioselective routes towards complex molecules embedding such fluorohydrins of great potential for medicinal chemistry.[4] The new strategies could facilitate the preparation of known fluorinated motifs, but could also unlock access to new fluorinated 1,3-diols especially in the challenging acyclic series. In order to prepare such biologically relevant fluorinated 1,3-diol motifs, the most straightforward routes could imply the catalytic diastereoselective aldol reaction on the corresponding fluorinated carbonyl compounds. However, while a handful number of nucleophilic additions have been reported on α-fluorinated ketones,[5] catalytic enantioselective aldol reaction on parent aldehydes is unknown.[6] As a consequence, discovery of a general enantioselective catalytic transformation would be highly desirable. Besides the inherent difficulty of generating the poorly stable fluorinated aldehydes, the lack of methods is mostly due to the challenge at controlling the diastereoselectivity which implies a selective recognition between poorly distinguishable groups.

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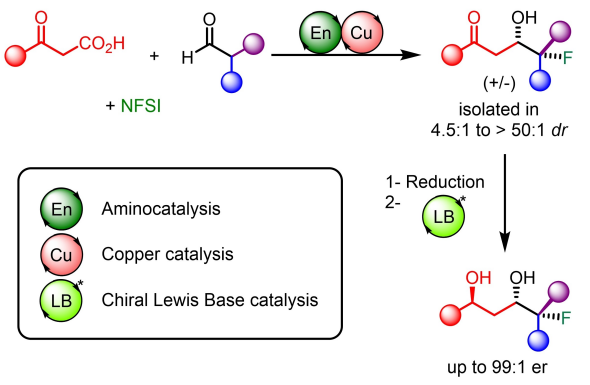
In order to obtain a general method for the preparation of desirable fluorohydrins, we proposed to combine an aminocatalyzed fluorination of α-disubstituted aldehydes[7] with a catalytic diastereoselective decarboxylative aldol reaction (Scheme 1).[8] While enantioselective fluorination of α-disubstituted aldehydes is known,[7] limited accessibility of the catalysts and lack of compatibility between fluorination and aldol reaction systems led us to develop a strategy building at first the racemic aldol product through racemic fluorination, before performing an isothiourea organocatalyzed enantioselective Kinetic Resolution (KR).[9,10] The selectivity of the kinetic resolution could ensure the isolation of the desired adduct in enantiopure form. Overall, this short sequence involving three catalytic transformations enables to generate valuable fluorinated 1,3-diols in excellent diastereo- and enantio-control.

Results and Discussion

In order to develop the desired sequence, we first optimized the organocatalytic racemic α-fluorination of aldehyde **1a** in a polar solvent potentially compatible with the subsequent aldol



Scheme 1. Proposed multi-catalytic synthesis.

reaction.[8] Most notably, the required full conversion was reached after 24 hours with 30 mol% of DL-proline in THF. With these fluorination conditions in hand, we set out to identify proper conditions for the diastereoselective decarboxylative aldol reaction with α-keto-acid **2a** and various catalysts (Table 1).[8,11] First, various organocatalysts did promote the aldol reaction but with moderate diastereocontrol and without noticeable impact of the catalyst chirality over the selectivity (typically 2.4:1 *dr*, entries 1–4).[8,12] Gratifyingly, Lewis acid catalysts improved the reaction efficiency.[13] Applying $Cu(OAc)_2$ or the more sterically congested $Cu(i\text{-}BuCO_2)_2$, slightly improved the diastereoselectivity up to 3.3:1 *dr* (entries 5, 6), while simple acetylacetonate Cu or Fe catalysts proved to be less efficient (entries 7–9). However, more sterically demanding **Cat E** significantly increased the selectivity to 3.8:1 *dr* while keeping a good reactivity (entry 10).

The solvent also considerably impacted both reactivity and selectivity. Using MTBE, another classical solvent for both fluorination and aldol reaction slightly decreased the diastereocontrol of the reaction (entry 11). Non-polar or protic solvents gave only modest reactivity (entries 12, 13) and other polar coordinating solvents such as acetonitrile or DMF did not improve the overall process (entries 14, 15). Finally, we discovered that with 1,4-dioxane, a good reactivity was restored providing full conversion to the aldol product with a good 5.2:1 *dr* (entry 16). Most importantly, upon silica gel chromatography, the fluoro-aldol adduct could be isolated in 59% yield and >50:1 *dr*.

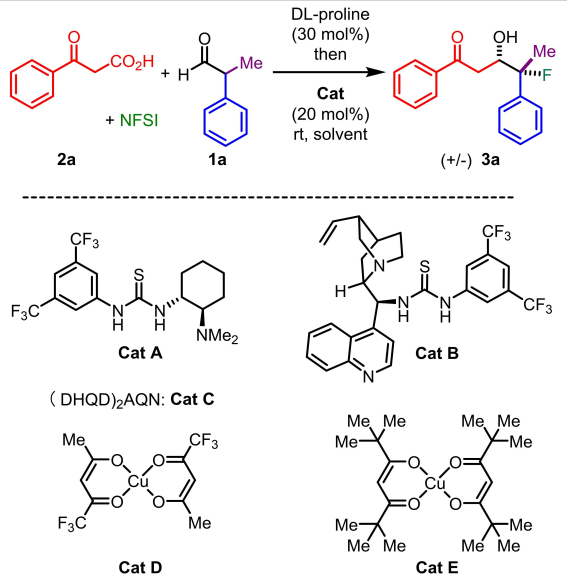
Having optimized the fluorination-aldol reaction sequence, we then scrutinized its scope using various aldehydes and keto-acids (Scheme 2). Using keto-acid **2a**, 11 different fluorohydrins **3a–k** could be synthesized in 38–81% yield and 1.3:1 to 6:1 *dr*. Most importantly, in most cases, the minor diastereomer was easily separable by silica gel chromatography affording the sought-after products in >50:1 *dr*.

Concerning the diastereocontrol, while *para*- and *meta*-substitution of the aromatic lowered the selectivity in **3b–e**, *ortho*-substitution increased the diastereocontrol in **3h–j**. This indicates that the diastereocontrol arises from a differentiation between the methyl and aromatic substituent based on steric repulsion. Replacing the methyl by an ethyl substituent generated **3k** in a lower 2.3:1 *dr* as compared to **3a**. This result confirms that diastereoselection arises from a selective discrimination between a bulky group, here the aromatic, and the smaller aliphatic chain. Modifying the keto-acid with different aromatic substituents or aliphatic chains provided the same reactivity and selectivity in the formation of **3l–p**. Once again, all fluorohydrins could be isolated in >35:1 *dr* and >58% yield, highlighting the excellent synthetic potential of this method.

Single crystal X-Ray analysis of ketol product **3e** confirmed the diastereoselectivity observed during the aldol reaction process (Scheme 2).[14] Given this observed diastereocontrol and the reactivity of both organocatalysts and copper catalysts on other type of substrates,[8d] the postulated mechanistic pathway is described in Scheme 3. From the racemic proline, enamine formation facilitated by the aromatic ring, enables functionalization with the electron-deficient fluorine of NFSI. Subsequent hydrolysis of the resulting iminium ion provides the key intermediate α-fluorinated aldehyde. Of importance, these aldehydes are rather unstable and difficult to isolate highlighting the interest to perform a direct one-pot bi-catalytic process for their interception by aldol reaction with the in situ generated copper enolate of the keto-acid.[7] Dipole-dipole interactions between the aldehyde and the fluorine atom block a conformation while in this class of compound, steric repulsion between the incoming nucleophile and the bulkier aromatic ring generates the observed diastereomer. Decarboxylation followed by exchange with a new incoming keto-acid liberates the final fluoro-aldol product.

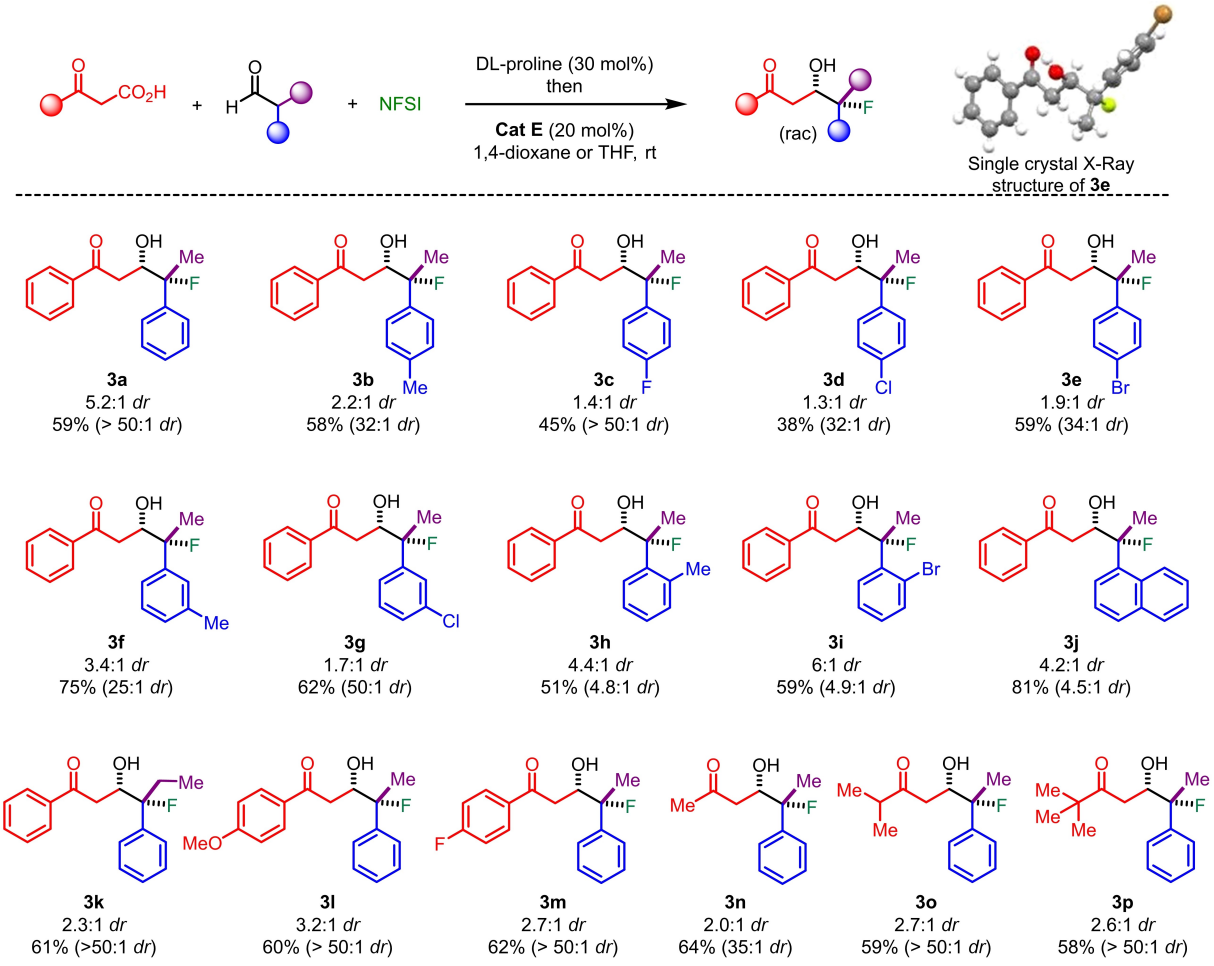
With a rapid and easy access to racemic diastereomerically pure β-keto-fluorohydrins, we then attempted to kinetically

Table 1. Optimization of the fluorination-aldol reaction.[a]



Entry	Cat	Solvent	**2a** conv (isolated yield)	*dr*
1	**Cat A**	THF	95%	2.4:1
2	**Cat B**	THF	96%	2.0:1
3	**Cat C**	THF	85%	2.4:1
4	Quinine	THF	95%	2.4:1
5	$Cu(OAc)_2$	THF	95%	3.2:1
6	$Cu(i\text{-}BuCO_2)_2$	THF	98%	3.3:1
7	$Cu(acac)_2$	THF	99%	2.7:1
8	$Fe(acac)_3$	THF	99%	2.7:1
9	**Cat D**	THF	99%	2.5:1
10	**Cat E**	**THF**	**98%**	**3.8:1**
11	**Cat E**	MTBE	94%	2.0:1
12	**Cat E**	toluene	<5%	–
13	**Cat E**	MeOH	26%[b]	1.8:1
14	**Cat E**	CH_3CN	87%[c]	2.2:1
15	**Cat E**	DMF	32%[d]	2.9:1
16	**Cat E**	**1,4-dioxane**	**98% (59%)**[d]	**5.2:1 (>50:1)**[e]

[a] Reactions run by performing the fluorination over 24 h before adding the keto-acid and the catalyst (**Cat**) and stirring for 18 h. [b] Formation of 60% of non-fluorinated aldol product. [c] Formation of 25% of non-fluorinated aldol product. [d] Isolated yield after fluorination run over 50 h and aldol reaction over 63 h. [e] *dr* of the isolated product.

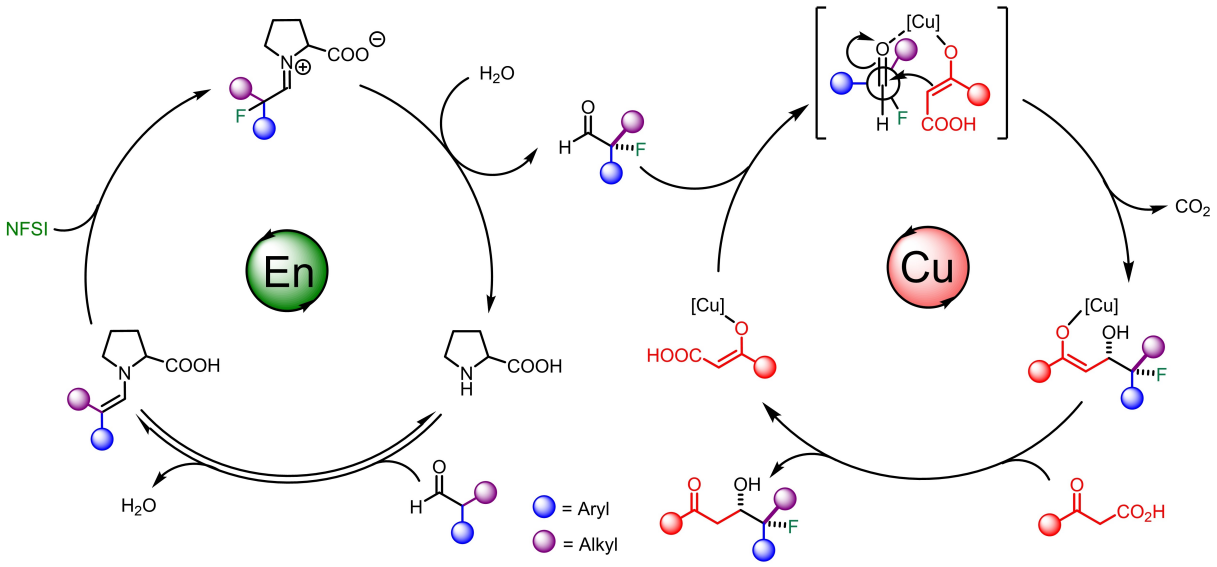


Scheme 2. Scope of the fluorination-aldolization (isolated *dr* in bracket).

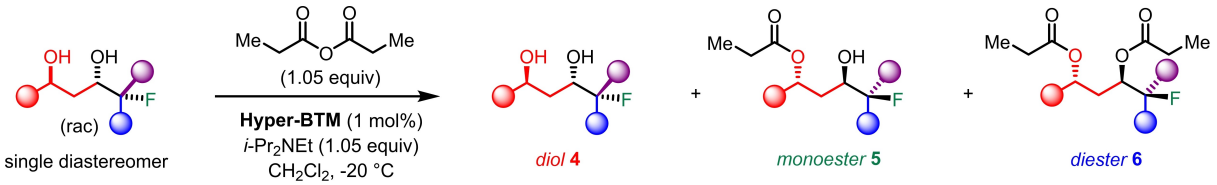
resolve them through organocatalyzed acylation of the corresponding 1,3-diols.[15] Given the increased value for medicinal chemistry of the parent 1,3-diols and their potential reactivity in KR,[16] five representative aldol adducts were reduced to the *anti*-diols **4a,e,f,l,m** prior to acylation (see Supporting Information). While other fluorohydrins have recently been enantioselectively acylated with success,[17] KR of such type of new fluorinated scaffolds was unknown and led us wonder about the reactivity and selectivity using Hyper-BTM as catalyst (Scheme 4).[18]

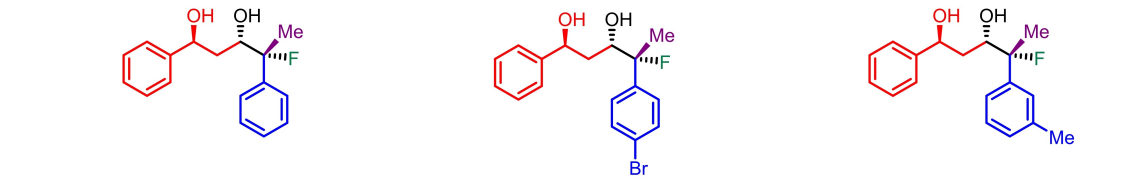
From the first experiments, it appeared that aside from the benzylic hydroxy functions of the (+/−)-fluorinated 1,3-diols **4**, the aliphatic ones also reacted providing a mixture of monoesters **5** and diesters **6** together with the resolved 1,3-diols. As a result, 1.05 equivalents of propionic anhydride in the presence of only 1 mol% of Hyper-BTM were used in order to ensure the recovery of the 1,3-diols in optimized enantioselectivity and yield.

Through this method, diols **4a,e,f,l** could be isolated in 27–38% yield and excellent >98% *ee*. Surprisingly, diol **4m** suffered from a lack of stability and partially decomposed during purification. As a result, it could only be isolated in 10% yield, albeit once again with perfect >98% *ee*. Interestingly, the corresponding diesters **6** were obtained in higher enantiocontrol than the monoesters **5**. For example, diester **6e** was isolated with 93% *ee* while monoester **5e** was obtained in 79% *ee*. This indicates that an amplification of enantioselectivity occurs through selective acylation of the fluorohydrins, suggesting a selective recognition of this motif by the catalyst. Overall, such successive catalytic events known as double catalytic KR (DoCKR)[16] enable to form the diester with improved enantiocontrol.



Scheme 3. Mechanism of the fluorination-aldolization.

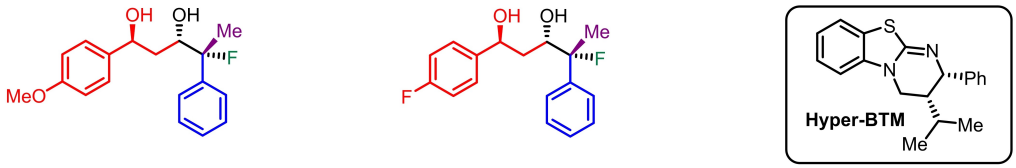




diol **4a**: 38% (> 99:1 *er*)
monoester **5a**: 48% (83.5:16.5 *er*)
diester **6a**: 6% (89:11 *er*)

diol **4e**: 34% (> 99:1 *er*)
monoester **5e**: 40% (89.5:10.5 *er*)
diester **6e**: 10% (96.5:3.5 *er*)

diol **4f**: 27% (> 99:1 *er*)
monoester **5f**: 44% (84:16 *er*)
diester **6f**: 11% (92.5:7.5 *er*)



diol **4l**: 30% (> 99:1 *er*)
monoester **5l**: 51% (89:11 *er*)
diester **6l**: 7% (95.5:4.5 *er*)

diol **4m**: 10% (> 99:1 *er*)
monoester **5m**: 43% (86.5:13.5 *er*)
diester **6m**: 7% (91.5:8.5 *er*)

Scheme 4. Organocatalyzed Kinetic Resolution of fluorinated diols.

Conclusion

To conclude, by combining aminocatalyzed fluorination of α-substituted aldehydes with a catalytic diastereoselective decarboxylative aldol reaction a concise route to original scaffolds containing tetrasubstituted fluorinated stereocenters has been developed. This strategy enables to isolate the challenging fluoro-aldol adducts in 38–81% yield and in most cases as single diastereomers. From these racemic products synthesized in one-pot, ketone reduction followed by organocatalyzed Kinetic Resolution through alcohol acylation enables to obtain the enantiopure fluorinated 1,3-diols of interest in $>98\%$ *ee*. As a result, this approach combining multiple catalysts should be of interest for the incorporation of such organic architectures into bioactive molecules. In addition, it should also inspire the development of other type of multi-catalytic transformations.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Copper catalysis · Enantioselective catalysis · Fluorine · Kinetic Resolution · Organocatalysis

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[14] Deposition Number 2084853 (for **3e**) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

[15] Applying enantiopure L-Proline in the fluorination-aldol reaction only provided the product **3a** in a low 5%*ee*.

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