Asymmetric Catalysis

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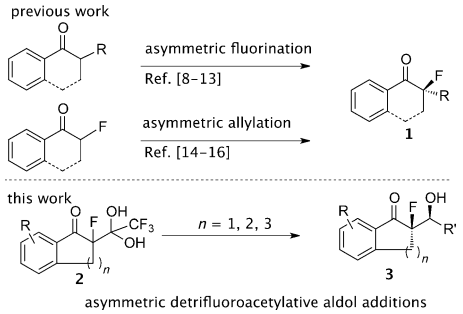
Assembly of Fluorinated Quaternary Stereogenic Centers through Catalytic Enantioselective Detrifluoroacetylative Aldol Reactions**

Chen Xie, Lingmin Wu, Jianlin Han, Vadim A. Soloshonok, and Yi Pan*

Abstract: *A Cu-catalyzed asymmetric detrifluoroacetylative aldol addition reaction of 2-fluoro-1,3-diketones/hydrates to aldehydes in the presence of base and chiral bidentate ligand was developed. The reaction was carried out under convenient conditions and tolerated a wide range of substrates, resulting in fluorinated quaternary stereogenic α-fluoro-β-hydroxy ketone products with good chemical yields, diastereo- and enantioselectivities. This catalytic asymmetric detrifluoroacetylative aldol addition reaction provides a new approach for the preparation of biologically relevant products containing C–F quaternary stereogenic centers.*

Fluorine-containing pharmaceutical agents are usually found among the best performing, most prescribed, and bestselling drugs.[1] Indeed, it is well-established that the introduction of fluorine into biologically active compounds generally leads to an improved efficacy, membrane permeability, and higher stability toward oxidative degradation.[2,3] In fact, the modern pharmaceutical industry critically depends on the new methodological developments in fluorine chemistry, shaping up the future generations of healthcare products.[4] Consequently, the development of new methods for the preparation of fluorine containing compounds has become one of the most active areas of multidisciplinary research.[5] In this context, compounds possessing a quaternary C–F stereogenic center are of high pharmaceutical potential;[1a,b,6] yet, their preparation in enantiomerically pure form presents a continuing methodological challenge.[5a,7] In particular, the asymmetric synthesis of quaternary α-fluoroketone structural unit **1** (Scheme 1) has received enormous attention.[8] However, there is still a very limited number of approaches allowing for catalytic asymmetric synthesis of C–F quaternary carbons. One of them is the catalytic asymmetric "electrophilic" fluorination. Remarkable breakthroughs have been reported by the groups of Togni,[9] Sodeoka,[10] Shibata,[11] Toste,[12] and others[13] during the past fifteen years. The second and significantly less explored approach, is the catalytic asymmetric allylation independently reported by the groups of Stoltz,[14] Nakamura,[15] and Paquin.[16] Despite the intellectual brilliance and reaction ingenuity these two approaches have strict structural requirements for the starting compounds, limiting their widespread application. Thus, the development of novel alternative methods for the preparation of compounds with C–F quaternary stereogenic centers would be highly desirable.



Scheme 1. Catalytic asymmetric synthesis of compounds **1** with C–F quaternary stereogenic centers.

Consistent with our interest in the development of methods for the preparation of fluoroorganic compounds,[17,18] we recently became involved in the detrifluoroacetylative in situ generation of difluoroenolates[19] and their asymmetric Mannich addition reactions.[20] Thus, based on our own experience and drawing inspiration from the work reported by the groups of Wolf[21] and Wu,[22] we speculated that a methodology based on detrifluoroacetylative aldol additions of 2-fluoro-1,3-diketones/hydrates **2** (Scheme 1) would be highly synthetically useful for the preparation of α-fluoro-β-hydroxy ketone products **3**, which contain a chiral fluorinated quaternary stereogenic center. Here we would like to report results on the synthesis of novel compounds **2** from cyclic ketones and their asymmetric Cu-catalyzed reactions with various aldehydes. These aldol additions could take place under convenient conditions,[23] affording products **3** with high diastereo- and enantioselectivities.

The synthesis of *gem*-diols **6** from cyclic ketones is a straightforward two-step process (Table 1). First, the reaction of readily available cyclic ketones **4** with ethyl trifluoroacetate is conducted at ambient temperature in the presence of NaOMe affording the intermediate 1,3-diketo

[*] C. Xie, L. Wu, Dr. J. Han, Dr. Y. Pan
School of Chemistry and Chemical Engineering, State Key Laboratory of Coordination Chemistry, Nanjing University
22 Hankou Road, Nanjing, 210093 (China)
E-mail: hanjl@nju.edu.cn
Prof. Dr. V. A. Soloshonok
Department of Organic Chemistry I, Faculty of Chemistry
University of the Basque Country UPV/EHU
Paseo Manuel Lardizábal 3, 20018 San Sebastián (Spain)
Prof. Dr. V. A. Soloshonok
IKERBASQUE, Basque Foundation for Science Department
Alameda Urquijo 36-5
Plaza Bizkaia, 48011 Bilbao (Spain)

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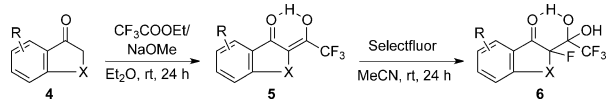
Table 1: Syntheses of *gem*-diols **6**.



4 5 6

Entry	X	R	Product	Yield [%][a]
1	CH_2CH_2	H	**6a**	71
2	CH_2CH_2	7-MeO	**6b**	68
3	CH_2CH_2	7-Br	**6c**	76
4	CH_2	H	**6d**	83
5	CH_2	5-Cl	**6e**	83
6	CH_2	6-F	**6f**	78
7	CH_2	6-Me	**6g**	76
8	$CH_2CH_2CH_2$	H	**6h**	59
9	OCH_2	H	**6i**	67

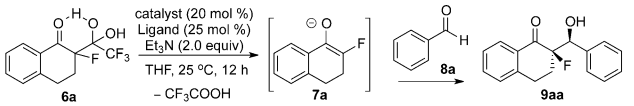
[a] Yields of isolated products.

compounds **5**. The second step consists of fluorination of **5** with Selectfluor in acetonitrile at room temperature giving the target hydrates **6**. The whole procedure is very simple and can be easily reproduced on a 10 gram scale. Taking into account that compounds **6** are novel and relatively complex, we performed a crystallographic analysis (see the Supporting Information, SI) of derivative **6f**, which confirmed the expected structure, featuring a hydrogen bond between one of the hydroxy groups and the carbonyl group. It should be mentioned that this standard procedure is limited to the tetralone-type derivatives as the application of cyclohexanone as a starting compound failed to produce any isolable products.

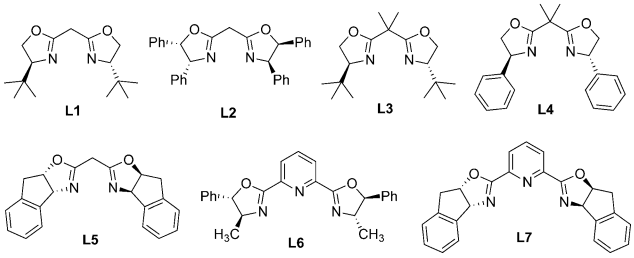
Since the reactivity of precursor **6** as well as the in situ-generated enolates **7** was unknown, an initial study on chiral ligands was carried out with hydrate **6a** and benzaldehyde **8a** as model substrates and $Cu(OTf)_2$ as catalyst in THF at room temperature (Table 2). Interestingly, we found that the stereochemical outcome of this reaction drastically depends on the structure of the chiral ligand used. For example, structurally similar ligands **L1** and **L2** gave product **9aa** with the opposite preference for the major diastereomer (entry 1 versus 2). On the other hand, ligands **L3**–**L5** were rather ineffective in controlling the stereochemistry of product **9aa** (entries 3–5). In sharp contrast, the electronically and structurally different ligands **L6** and **L7** failed to catalyze the reaction (entries 6 and 7), and almost no expected product was obtained. Being intrigued by these results, we tried a series of different trivalent metal salt catalysts in combination with tridentate ligand **L6** (entries 8–12). Indeed, the reactions proceeded quite well and even with good chemical yield (entry 10), however, lower diastereo- and enantioselectivities were observed. Thus, the best result was obtained by using the $Cu(OTf)_2$/ligand **L1** pair (entry 1) to give product **9aa** with 7:93 d.r. and 93% *ee* of the major isomer.

To further improve the reaction conditions, several other bases and solvents were examined (Table 3). Interestingly, a variation of the reaction solvent showed almost no effect on the yield and stereoselectivity of this aldol addition (entries 2–7). For example, the reactions conducted in toluene (entry 2) and DMF (entry 4) gave quite similar results. Ether-type solvents afforded the product **9aa** with 30–43% yields

Table 2: Screening of metal catalysts and chiral ligands.[a]



6a 7a 8a 9aa

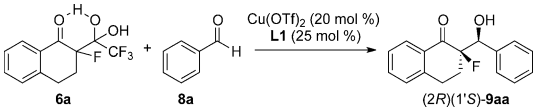


L1 L2 L3 L4 L5 L6 L7

Entry	Catalyst	Ligand	Yield [%][b]	d.r.[c]	*ee* [%][c]
1	$Cu(OTf)_2$	**L1**	41	7:93	11/93
2	$Cu(OTf)_2$	**L2**	77	75:25	22/5
3	$Cu(OTf)_2$	**L3**	23	60:40	4/8
4	$Cu(OTf)_2$	**L4**	56	64:36	53/2
5	$Cu(OTf)_2$	**L5**	65	47:53	13/63
6	$Cu(OTf)_2$	**L6**	< 5	n.d.[d]	n.d.[d]
7	$Cu(OTf)_2$	**L7**	< 5	n.d.[d]	n.d.[d]
8	$Yb(OTf)_3$	**L6**	76	81:19	1/1
9	$Sc(OTf)_3$	**L6**	62	65:35	29/3
10	$Y(OTf)_3$	**L6**	81	81:19	2/3
11	$La(OTf)_3$	**L6**	69	74:26	4/0
12	$Sm(OTf)_3$	**L6**	67	79:21	3/1

[a] Reaction conditions: **6a** (0.2 mmol), aldehyde **8a** (0.4 mmol), catalyst (0.04 mmol, 20 mol%), ligand (0.05 mmol, 25 mol%), and Et_3N (0.4 mmol, 2.0 equiv) in THF (2.0 mL) at 25 °C for 12 h. [b] Yields of isolated products. [c] Determined by chiral HPLC analysis. [d] Not determined.

Table 3: Optimization of the reaction conditions.[a]



6a 8a (2*R*)(1'*S*)-**9aa**

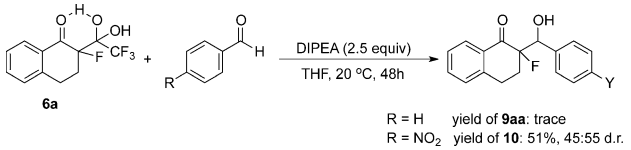
Entry	Base (equiv)	Solvent	*T* [°C]	Yield [%][b]	d.r.[c]	*ee* [%][c]
1	Et_3N (2.0)	THF	25	41	7:93	93
2	Et_3N (2.0)	Toluene	25	48	11:89	86
3	Et_3N (2.0)	Benzene	25	32	12:88	84
4	Et_3N (2.0)	DMF	25	45	8:92	88
5	Et_3N (2.0)	2-Me-THF	25	43	6:94	91
6	Et_3N (2.0)	1,4-dioxane	25	30	6:94	91
7	Et_3N (2.0)	Et_2O	25	38	8:92	92
8	DABCO (2.0)	THF	25	44	7:93	93
9	DIPEA (2.0)	THF	25	73	5:95	93
10	*t*BuOLi (2.0)	THF	25	68	81:19	0
11	nPr_3N (2.0)	THF	25	70	14:86	85
12	nBu_3N (2.0)	THF	25	75	11:89	89
13	iBu_3N (2.0)	THF	25	12	40:60	57
14	DIPEA (2.5)	THF	25	78	4:96	95
15[d]	DIPEA (2.5)	THF	0–20	83	1:99	98
16[e]	DIPEA (2.5)	THF	0–20	84	1:99	98

[a] Reaction conditions: diol **6a** (0.2 mmol), aldehyde **8a** (0.4 mmol), $Cu(OTf)_2$ (0.04 mmol, 20 mol%), ligand **L1** (0.05 mmol, 25 mol%), and base (0.4 mmol, 2.0 equiv) in solvent (2.0 mL) for 12 h. [b] Yields of isolated products. [c] Determined by chiral HPLC analysis. [d] For 24 h. [e] $Cu(OTf)_2$ (0.02 mmol, 10 mol%) and **L1** (0.024 mmol, 12 mol%) were used and the reaction was conducted for 24 h.

and enantiomeric purity comparable to that obtained in THF (entries 5–7 versus 1). On the other hand, variation of base showed an obvious effect on the reaction rate and stereoselectivity. The use of DABCO was as good as Et_3N (entry 8 vs. 1), whereas the use of Hünig's base (DIPEA) resulted in a noticeably improved yield (73%, entry 9). Considering the fact that Et_3N and DIPEA are of about the same basicity but of very different nucleophilicity,[24] we decided to try other inexpensive sterically bulky bases. However, the application of *t*BuOLi (entry 10), nPr_3N (entry 11), nBu_3N (entry 12), and iBu_3N (entry 13) did not lead to the expected improvement. Interestingly, the reaction catalyzed by *t*BuOLi (entry 10), furnished racemic product **9aa** with a preference for the opposite diastereomer. Final optimization was made by using DIPEA as a base. We found that the use of 2.5 equivalents of DIPEA resulted in a noticeable increase of the stereoselectivity (entry 14). Furthermore, initiation of the reaction at 0°C with gradual warming to room temperature (entry 15) and the use of only 10 mol% $Cu(OTf)_2$ and 12 mol% ligand **L1** gave actually excellent results featuring 84% yield and almost complete diastereo- and enantioselectivity (1:99 d.r., 98% *ee*, entry 16).

Then, we applied the optimized conditions to examine the substrate scope of the detrifluoroacetylative aldol addition. First we explored the reaction of unsubstituted hydrate **6a** with different aldehydes **8a**–**z** and the results are summarized in Figure 1. In general, high yields and excellent *ee* values were obtained in most of the reactions, underscoring the synthetic potential of these enantioselective detrifluoroacetylative aldol additions for the construction of fluorinated quaternary stereogenic centers. However, with *o*-substituted substrates, such as **8b**, **8q**, and **8s**, a relatively low control of the configuration of the resulting addition products **9ab**, **9aq**, and **9as** was observed. Also, products **9at** and **9aw**, containing 2-furyl and 2-indolyl groups were obtained with slightly lower stereoselectivity. By contrast, heterocyclic sulfur-containing aldehydes **8u** and **8v** gave the corresponding products **9au** and **9av** with better stereoselectivity. Importantly, the aldol addition tolerates the enolizable (**8y**) and vinyl-type (**8x** and **8z**) substrates affording products **9ax**–**az** with excellent stereoselectivities (93%, 93%, and 94% *ee*, respectively). It should be mentioned that the use of other aliphatic aldehydes resulted in relatively low yields and enantioselectivities.

Another clear trend observed in these reactions is a rather poor stereoselectivity for substrates containing electron-withdrawing groups (**8k**–**n**). The steric effects of the substituents are normal and result from the preferences in corresponding transition states; however, the electronic effects of the substituents, especially of those in *p*-positions, were rather unexpected. Being intrigued by this trend, we performed test-reactions without catalyst (Scheme 2).



Scheme 2. Test reactions.

Interestingly, the reaction of hydrate **6a** with benzaldehyde **8a** gave no product, whereas the application of *p*-nitrobenzaldehyde furnished the aldol product **10** in 51% yield and nearly 1:1 diastereomeric ratio. This outcome clearly indicated that the uncatalyzed background reaction compromised the stereocontrol in the cases of substrates containing electron-withdrawing substituents. This result was rather unfortunate; however, it suggested that reactions with this type of substrates could be optimized to improve the stereoselectivity by controlling the uncatalyzed background pathway.

Then, we decided to explore the substrate scope of the starting hydrates **6** to react with benzaldehyde **8a** (Figure 2). All reactions were conducted under the standard conditions in THF using chiral ligand **L1** (12 mol%), $Cu(OTf)_2$ (10 mol%), and DIPEA (2.5 equiv). The results showed that substrates containing five- (**6d**–**6g**), seven- (**6h**), and substituted six-membered (**6b, 6c**, **6i**) rings also worked well in the reaction resulting in the corresponding products **9** in good to excellent chemical yields and stereoselectivities. Of particular interest is 2,3-dihydrochromen-4-one derivative **9ia**, which was obtained with very high diastereo- and enantioselectivity (98:2 d.r., 95% *ee*). The stereochemistry of the major products **9** was assigned as (1*R*)(1′*S*) by the single-crystal X-ray analysis of product **9ca** (Figure 3).

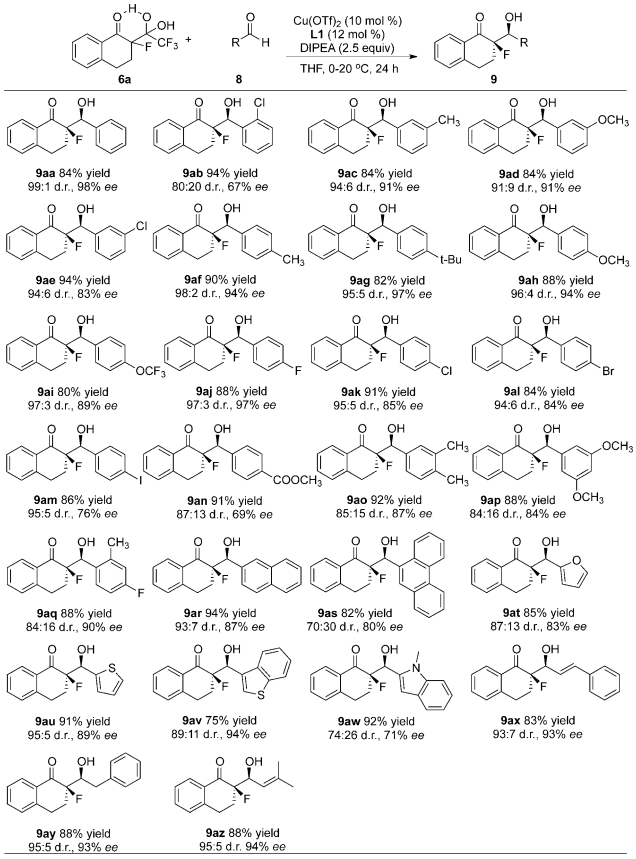


Figure 1. Generality of the aldol reaction using various aldehydes **8**.

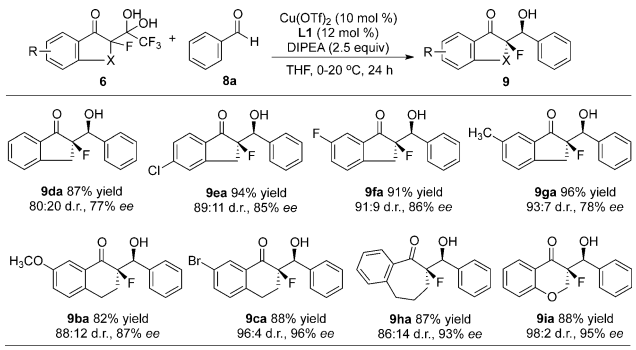


Figure 2. Generality of the aldol reaction using various hydrates **6**.

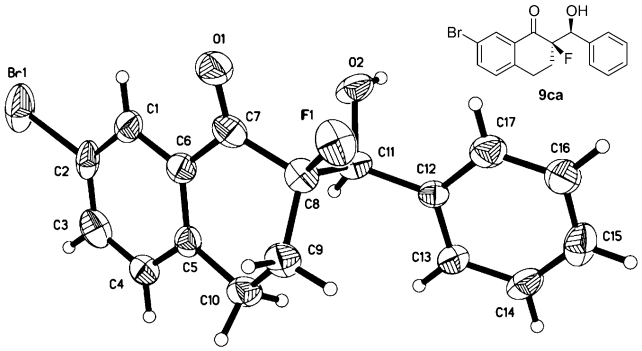


Figure 3. X-ray crystal structure of **9ca**. Ellipsoids are given at 30% probability.

Having determined the absolute configuration of the major products, we can suggest the transition state (TS) **A** (Figure 4) to account for the observed (1*R*)(1′*S*) stereochemical preference. First of all, TS **A** is chair-like and therefore might be the most stereochemically accessible. Second, the

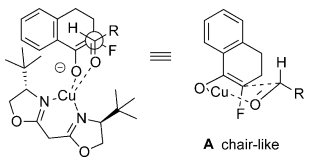


Figure 4. Possible TS **A** in the reactions of 1,3-diketo/hydrates **6** with aldehydes **8**.

relative stereochemistry (diastereoselectivity) in TS **A** is controlled by the favorable position of the stereocontrolling groups R and the enolate moiety in opposite directions, minimizing their steric interactions. Third, the TS **A** allows for minimum charge separation,[25] from the enolate oxygen to the aldehyde oxygen, within the same chelated structure. Finally, the absolute stereochemistry in TS **A** is effectively controlled by the positions of the ligand **L1** *tert*-butyl and the enolate phenyl ring away from each other minimizing stereochemical contacts.

Finally, as it is routinely done in work on catalytic asymmetric synthesis[26] we conducted SDE (self-disproportionation of enantiomers) tests by achiral chromatography[27] and sublimation.[28] Among the products **9**, we selected compound **9al**, which shows high solubility in apolar solvents and a reasonable volatility, as model substrate to carry out the SDE test. Interestingly, the sublimation SDE test was negative, whereas the SDE by achiral chromatography showed noticeable magnitude (see SI). Thus, routine achiral chromatography[29] of product **9al** with initially 84% *ee* resulted in an enantiomerically enriched (88% *ee*) first fraction and enantiodepleted (77% *ee*) last fraction. Accordingly, in the present work the determination of the stereoselectivity was made before any chromatographic purification.

To conclude, a Cu-catalyzed asymmetric detrifluoroacetylative aldol addition reaction of aldehydes with 2-fluoro-1,3-diketones/hydrates derived from cyclic ketones was reported. This reaction provides an efficient method for the preparation of α-fluoro-β-hydroxy ketones containing C–F quaternary stereogenic centers. The reactions were carried out under mild conditions with good yields and stereoselectivities. The data obtained render this approach a synthetically viable and attractive alternative to the well-studied asymmetric fluorination, and can be of immediate use for preparation of C–F compounds.

Keywords: aldol reaction · asymmetric catalysis · C–C bond cleavage · detrifluoroacetylation · fluorinated quaternary stereocenters

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