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2,2-Difluoro-1,3-diketones as *gem*-Difluoroenolate Precusors for Asymmetric Aldol Addition with *N*-Benzylisatins

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Abstract: 2,2-Difluoro-1,3-diketones are introduced as *gem*-difluoroenolate precursors for the first example of an organocatalytic asymmetric aldol addition with *N*-benzylisatins to form 3-difluoroalkyl-3-hydroxyoxindoles.

Keywords: difluoroalkylation; 2,2-difluoro-1,3-diketones; difluoroenolates; enantioselectivity; organocatalysis

Special chemical and biological properties associated with fluorinated molecules have encouraged chemists to develop new fluorination reactions, especially in an asymmetric fashion.[1] The carbonyl α-position is an important place for fluorine insertion.[2] Shown in Figure 1 are representative biologically active oxindoles bearing hydroxy and alkyl groups at the C-3 position.[3] Mono- and difluorination of the carbonyl α-position of such compounds is a topic of current interest.[4–6]

Compared to using α-fluorinated ketones as nucleophiles,[7] aldol additions using α,α-difluoroenoxysilanes[6a,b] or α,α-difluoroenolates as nucleophiles to assemble 2,2-difluoro-3-hydroxy ketones **I** have attracted more attention. α,α-Difluoroketones **IIa**,[8] α,α,α-trifluoro-ketones **IIb**,[9] α,α-difluoro-β-ketone-*gem*-diols **IIc**,[10] α,α-difluoro-α-(trimethylsilylacet)amides **IId**,[11] and α,α-difluoro-β-ketoesters **IIe**[12] have been developed as precursors for α,α-difluoroenolates **III** (Scheme 1). The α,α-difluoromethylsulfone anion ($RSO_2CF_2^-$) derived from $PhSO_2CF_2TMS$ or $PhSO_2CF_2H$ has also been reported for nucleophilic additions.[13] Asymmetric nucleophilic additions of α,α-difluoroenoxysilanes or α,α-difluoroenolates with isatins **1** to prepare 3-hydroxy-3-difluoroalkyl-substituted oxindoles **3** have been documented (Scheme 2). But so far only the organocatalytic reaction of difluoroenol silyl ether **IV** reported by Zhou's group is successful.[6] The Fang and Wu groups developed an organocatalytic aldol reaction of α-monofluoro-β-ketone-*gem*-diols **IIc′** for monofluorinated oxindoles **3′**.[4a] But this failed for the reaction of **IIc** to afford difluorinated oxindoles **3**. We have recently reported the deacylation of 2-fluoro-1,3-dicarbonyls for making α-fluoro-α,β-unsaturated carbonyl compounds.[14] We

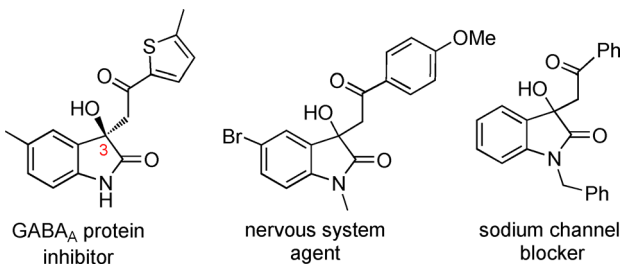
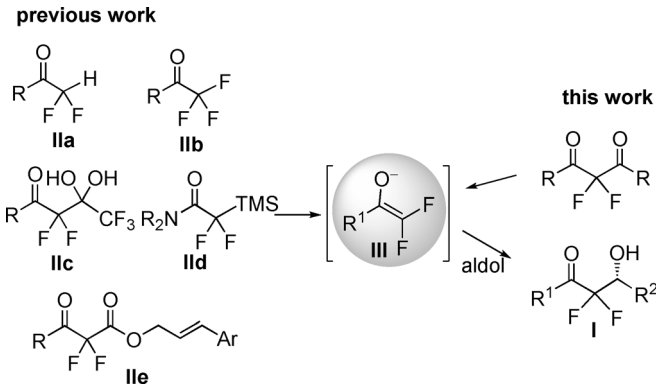
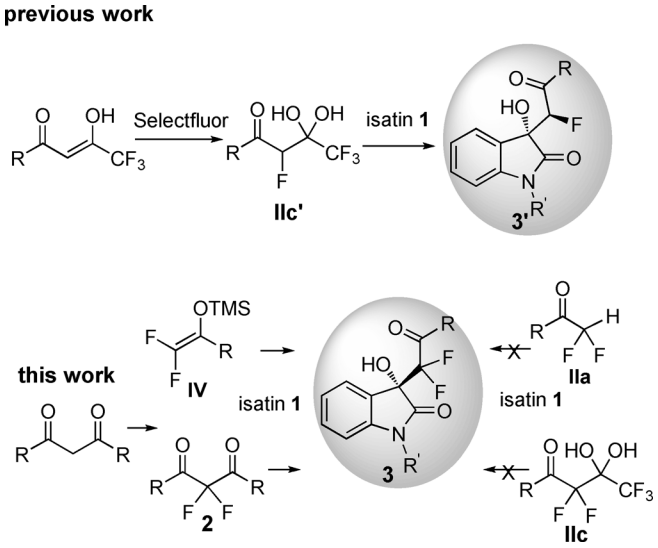


Figure 1. Bioactive 3-hydroxy-3-alkyloxindoles.



Scheme 1. Methods for the preparation of α,α-difluoroenolates **III**.



Scheme 2. Asymmetric aldol additions towards fluorinated oxindoles **3**.

also found that readily available 2,2-difluoro-1,3-diketones **2** could be deacylated under basic conditions to form α,α-difluoroenolates **III**.[15] We envisioned that difluoro-1,3-diketones **2** could be a new synthon for organocatalytic aldol reactions.

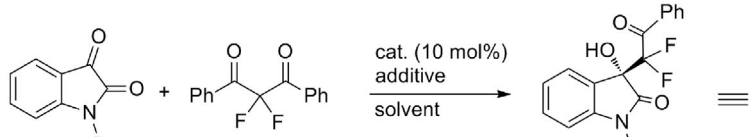
Results obtained from the initial reactions of *N*-benzylisatin **1a** with 2,2-difluoro-1,3-diones **2a** in the presence of different *Cinchona* alkaloid-thiourea organocatalysts **C-1** to **C-5** are shown in Table 1.[16] Using CH_2Cl_2 as a solvent at room temperature reactions catalyzed with **C-1** and using AcOH or benzoic acid as an additive[4a] only gave a trace amount of product **3aa** after 72 h (Table 1, entries 1 and 2). When the additive was changed from acids to a base (NH_3), the reaction occurred at room temperature, but had a poor *ee* (entry 3). Reactions at lower temperature and for longer reaction time did not increase the *ee*, but significantly decreased the yields (entries 4 and 5). To our surprise, an acceptable yield (78%) and *ee* (55%) were obtained from a reaction without using an additive (entry 6). Screening of different catalysts **C1–C4** revealed that **C-3** is the winner (entries 6–9). Further optimization of the conditions by variation of solvent, reaction temperature and time showed that the **C-3** catalyzed reaction in MeOH for 48 h at room temperature could afford **3aa** in 91% yield and 92% *ee* (entry 15). The reaction with a fluorous organocatalyst **C-5** gave a similar result as that with **C-3** (entry 16).[17] Recyclable **C-5** could be easily isolated from the reaction mixture by fluorous solid-phase extraction (F-SPE).[18] To evaluate the effect of MeOH on the catalysis process, reactions using MeOH as an additive or a co-solvent were conducted (entries 17–19). These reactions gave good yields and *ee*, albeit slightly lower than that from the reaction using MeOH as a solvent (entry 15). No improvements in yield and *ee* were obtained by running the reactions in MeOH at lower temperature but with increased time (entries 20–22). A 7.7 mmol (2 g)-scale reaction of **2a** gave a similar yield and *ee* as the 0.2 mmol-scale reaction, which demonstrates the scale up capability of this reaction (entry 23). The absolute configuration of product **3aa** was determined by comparison with literature data and also by X-ray crystallographic analysis (Table 1).[4a,6a]

With the optimized reaction conditions in hand, we investigated the substrate generality using different *N*-substituted isatins **1a–k** and 2,2-difluoro-1,3-diketones **2a–j** (Table 2). Reactions of *N*-benzylisatin **1a** with **2a–j** afford the corresponding products **3aa–aj** in good to excellent yields (82–95%) and *ee* (66–92%) (Table 2, entries 1–9). The position and electronic property of the substituents on the phenyl rings have no significant impact on the yield. The reaction of **2h**, which has a 2-fluorophenyl as R^3, gave **3ah** with a decreased *ee* (66%) (entry 8). The reaction of **2k**, which has Me instead of Ar as R^3, gave **3ak** in low yiled (42%) and decreased *ee* (63%) (entry 11). The configuration of **3ak** was confirmed by comparison with the literature data.[4a,19] Reactions of **2a** with *N*-substituted isatins **1a–k** were also conducted. Substitutions such as halogen atoms and electron-donating MeO group on the aromatic ring of **1** are tolerated to give products **3** in excellent yields (82–93%) with good *ee* (62–98%) (Table 2, entries 12–19). Reactions of *N*-methylisatin **1j** and *N*-phenylisatin **1k** also gave the corresponding compounds **3ja** and **3ka** in good yields (79% and 58%), but slightly low *ee* (79% and 58%) (entries 20 and 21).

Two control reactions were conducted to gain mechanistic insights of the aldol reaction of difluoroenolates. The first one is a reaction of isatin **1a** with monofluoro-1,3-diketone **4** under **C-3** catalysis. Compound **5** was obtained in 97% yield, but with neither diastereoselectivity nor enantioselectivity (Scheme 3, A). This may suggest that the asymmetric aldol reactions of α-fluoro-1,3-diketones take a different pathway from that of α-flourinated-β-ketone-*gem*-diols reported in Fang and Wu's work.[4a] The second control reaction of difluoro-1,3-dione **2l** which has two different substitution groups on the phenyl rings was conducted to verify if two enolates could be generated from the deacylation of **2l**. Indeed, the reaction of 1.5 equiv. of **2l** with **1a** generated **3af** and **3ad** in 46% and 43% yields, and 80% and 76% *ee*, respectively (Scheme 3, B).

Monitoring the reaction of **1a** and **2g** (Table 2, entry 7) by ^{19}F NMR allowed us to observe the process of deacylation of **2g** to form difluoroenolate **6g**, as well as methyl 4-fluorobenzoate by-product (see the Supporting Information). Based on our experimental results and literature information,[6] a mechanism for the organocatalytic aldol addition involving

Table 1. Optimization of the reaction conditions.[a]



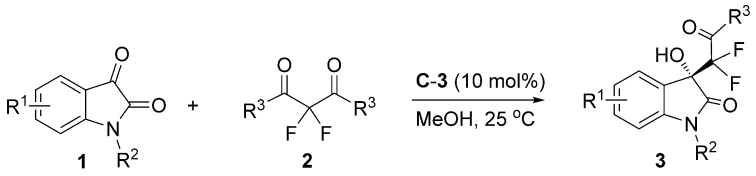
Entry	Catalyst [10 mol%]	Additive [20 mol%]	Solvent	Temperature [°C]	Time [h]	**3aa** [%][b]	*ee* [%][c]
1	**C-1**	AcOH	CH_2Cl_2	25	72	trace	–
2	**C-1**	PhCOOH	CH_2Cl_2	25	72	trace	–
3	**C-1**	NH_3	CH_2Cl_2	25	24	83	5
4	**C-1**	NH_3	CH_2Cl_2	0	72	32	40
5	**C-1**	NH_3	CH_2Cl_2	−20	72	trace	–
6	**C-1**	–	CH_2Cl_2	25	72	78	55
7	**C-2**	–	CH_2Cl_2	25	72	79	49
8	**C-3**	–	CH_2Cl_2	25	72	89	75
9	**C-4**	–	CH_2Cl_2	25	72	80	62
10	**C-3**	–	THF	25	72	81	73
11	**C-3**	–	PhMe	25	72	66	58
12	**C-3**	–	MeOH	25	72	93	89
13	**C-3**	–	DMF	25	72	90	71
14	**C-3**	–	*i*PrOH	25	72	67	82
15	**C-3**	**–**	**MeOH**	**25**	**48**	**91**	**92**
16	**C-5**	–	MeOH	25	48	87	90
17	**C-3**	MeOH 50 mol%	CH_2Cl_2	25	72	87	77
18	**C-3**	MeOH 300 mol%	CH_2Cl_2	25	72	89	81
19	**C-3**	–	CH_2Cl_2/MeOH = 1/1	25	48	83	84
20	**C-3**	–	MeOH	25	24	76	88
21	**C-3**	–	MeOH	0	72	trace	–
22	**C-3**	NH_3	MeOH	0	72	46	40
23[d]	**C-3**	–	MeOH	25	48	93	90

[a] Reaction of **1a** (0.2 mmol), **2a** (0.3 mmol) and catalyst (0.02 mmol).
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Scale-up reaction with a 2 g scale of **1a**.

difluoroenolate is proposed in Scheme 4. The deacylation of **2a** catalyzed with **C-3** results in difluoroenlate **6a**.[20] It is then paired with the bridgehead amino group of **C-3**. The aldol reaction is activated by the hydrogen bonds between two hydrogens in the thiourea and two carbonyls in isatin. The transition state of the complex is arranged in a way where the unfavorable interaction between the isatin benzene ring and the enolate could be avoided. Attack of the difluoroenolate from the favorable *Re* face of isatin affords the (*S*)-enantiomer as the aldol addition product.[6,21]

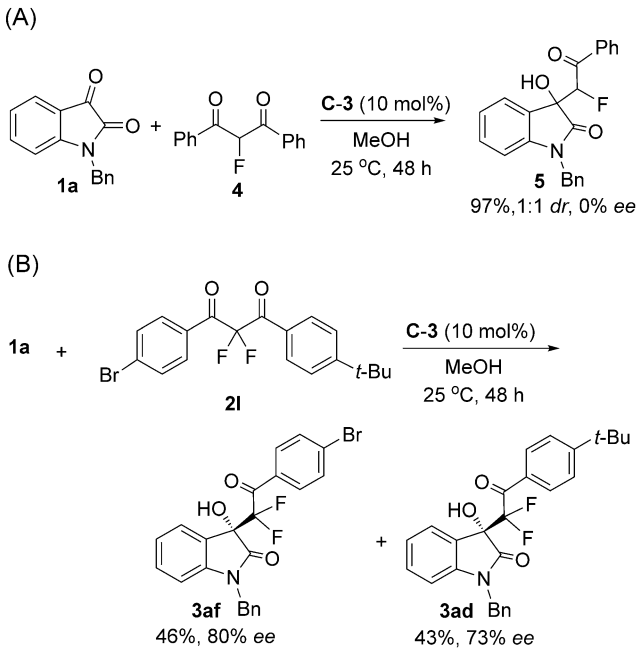
In conclusion, the first example of aldol addition of difluoroenlates derived from 2,2-difluoro-1,3-diketones with isatins is introduced. The reactions are promoted with a *Cinchona* alkaloid-thiourea bifunctional organocatalyst to afford various 3-hydroxy-3-difluoroalkylated oxindoles in good yields and enantioselectivities. Readily available difluoroenlate precursors

Table 2. Scope of the reactions with isatins **1** and **2**.[a]

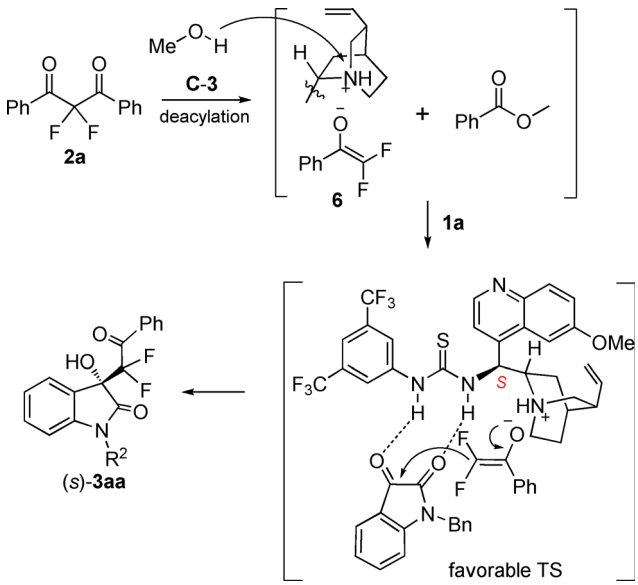


Entry	R^1/R^2	R^3	Time [h]	Yield [%][b]	*ee* [%][c]
1	H/Bn (**1a**)	Ph (**2a**)	48	91 (**3aa**)	92
2	H/Bn (**1a**)	4-MeC_6H_4 (**2b**)	48	87 (**3ab**)	75
3	H/Bn (**1a**)	3-MeC_6H_4 (**2c**)	48	82 (**3ac**)	88
4	H/Bn (**1a**)	4-*t*-BuC_6H_4 (**2d**)	48	80 (**3ad**)	74
5	H/Bn (**1a**)	4-ClC_6H_4 (**2e**)	36	89 (**3ae**)	86
6	H/Bn (**1a**)	4-BrC_6H_4 (**2f**)	48	95 (**3af**)	82
7	H/Bn (**1a**)	4-FC_6H_4 (**2g**)	36	91 (**3ag**)	79
8	H/Bn (**1a**)	2-FC_6H_4 (**2h**)	36	88 (**3ah**)	66
9	H/Bn (**1a**)	4-$CF_3C_6H_4$ (**2i**)	36	93 (**3ai**)	88
10	H/Bn (**1a**)	2-thienyl (**2j**)	36	85 (**3aj**)	77
11	H/Bn (**1a**)	Me (**2k**)	36	42 (**3ak**)	63
12	4-Br/Bn (**1b**)	Ph (**2a**)	48	85 (**3ba**)	70
13	5-Me/Bn (**1c**)	Ph (**2a**)	48	89 (**3ca**)	89
14	5-OMe/Bn (**1d**)	Ph (**2a**)	48	87 (**3da**)	70
15	5-Cl/Bn (**1e**)	Ph (**2a**)	48	85 (**3ea**)	84
16	5-F/Bn (**1f**)	Ph (**2a**)	48	82 (**3fa**)	98
17	6-Cl/Bn (**1g**)	Ph (**2a**)	48	90 (**3ga**)	90
18	6-Br/Bn (**1h**)	Ph (**2a**)	48	88 (**3ha**)	92
19	7-F/Bn (**1i**)	Ph (**2a**)	48	89 (**3ia**)	62
20	H/Me (**1j**)	Ph (**2a**)	48	87 (**3ja**)	79
21	H/Ph (**1k**)	Ph (**2a**)	48	93 (**3ka**)	58

[a] Reaction of **1a** (0.2 mmol), **2** (0.3 mmol, **C-3** (0.02 mmol) in MeOH (1.5 mL).
[b] Isolated yield.
[c] Determined by HPLC.



Scheme 3. Control reactions.



Scheme 4. A proposed mechanism.

and scalability of the reaction make it a feasible method for asymmetrical introduction of difluoromethene and hydroxy groups through the aldol addition.

Experimental Section

General Information

All reactions were run using flame-dried glassware and magnetic stirring. Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H, ^{19}F and ^{13}C NMR spectra were recorded on a 500 MHz Bruker DRX 500 and tetramethylsilane (TMS) was used as a reference. Chemical shifts are reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform $\delta = 7.26$, acetone $\delta = 2.09$, DMSO $\delta = 2.50$), carbon (chloroform $\delta = 77.0$, acetone $\delta = 205.87, 30.60$, DMSO $\delta = 40.45$). GC-MS were performed on an ISQ Trace 1300 (electrospray ionization: EI). For thin-layer chromatography (TLC), Sorbent silica gel XHL TLC plates (130815) were used, and compounds were visualized with a UV light at 254 nm. Melting points were measured on a melting point apparatus and are uncorrected. Mass spectra were recorded on the Waters Q-Tof micro™ (electrospray ionization: ESI). HPLC analysis was performed on an Agilent1200 instrument with a Daicel Chiralpak AD-H column.

Synthesis of 2,2-Difluoro-1,3-diones 2

Step A: To a suspension of ketone (10 mmol) in THF (40 mL) was added NaH (0.8 g, 20 mmol, 60%). After the reaction mixture was stirred at 0 °C for about 1 h, the ester was added dropwise at the same temperature. Then the mixture was stirred at room temperature until TLC indicated the total consumption of the ketone. The reaction mixture was poured into ice-water (100 mL), acidified with aqueous HCl (3 M) to pH 2–3 and extracted with EtOAc (100 mL × 3). The combined organic layer was dried over sodium sulfate and evaporated under reduced pressure. The 1,3-diketone obtained was used for the next step without further purification.

Step B: The 1,3-diketone (10 mmol) was added to a solution of Selectfluor™ (7.187 g, 21 mmol) in CH_3CN (30 mLwith 3 mL water). This mixture was stirred at room temperature for 24–36 h until TLC indicated the total consumption of the 1,3-diketone. The solvent was removed by rotary evaporation to provide the raw products. The residue was then extracted with CH_2Cl_2, dried over Na_2SO_4. The solvent was removed under reduced pressure to yield corresponding 2,2-difluoro-1,3-diketones.

General Procedure for Asymmetric Synthesis of 3-Hydroxy-3-substituted Oxindoles

A solution of *N*-substituted isatin (0.200 mmol) and **C-3** (10 mol%) in MeOH (2.5 mL) was stirred for 20 min at room temperature, then the 2,2-difluoro-1.3-dione (0.300 mmol) was added. Upon consumption of N-substituted isatin (monitored by TLC), the reaction mixture was concentrated and purified by column chromatography to afford the decarboxylative aldol products **3**.

Acknowledgements

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