Organocatalysis

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Highly Enantioselective Construction of 3-Hydroxy Oxindoles through a Decarboxylative Aldol Addition of Trifluoromethyl α-Fluorinated *gem*-Diols to *N*-Benzyl Isatins**

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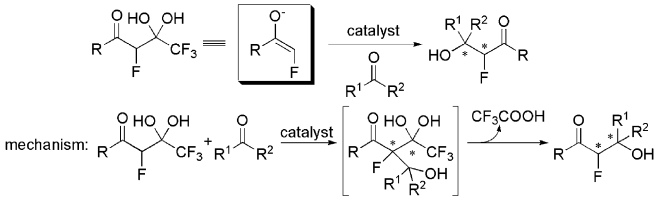
Owing to the stability of carbon–carbon (C–C) bonds their cleavage has long remained a great challenge for organic chemists.[1] Decarboxylation is one of the most prevailing methods to fulfill this purpose because of its efficiency in forming reactive intermediates that successively promote the bond cleavage under mild conditions.[2] Trifluoroacetate is a functional group universally used in many reactions and the release of which is hypothesized to be analogous to decarboxylation. In 1968, the first tactic in which trifluoroacetate was released by elimination of hexafluoroacetone hydrate fragments was reported.[3] Recently, Colby and co-workers have demonstrated that this tactic was also applicable in effectively furnishing α,α-difluoroenolates.[4]

The aldol reaction is among the most important protocols for C–C bond formation. Therefore, many asymmetric syntheses employing this reaction have been developed.[5] A survey of recent literature shows that significant advances in the organocatalytic direct aldol reactions have been made.[6] However, methyl ketones, and particularly, aryl methyl ketones are substrates that are difficult to activate by direct enamine formation[7] owing to the low orbital overlap between the enamine double bond and the nitrogen lone pair.[8] As a result, preactivation, such as the use of silyl enol ethers,[9] of such inert ketones is often required. Recently, Lu and co-workers reported a wise approach of using a β-ketoacid as a surrogate of an aryl methyl ketone enolate.[10] In an attempt to develop an effective approach for reactions involving methyl ketones as aldol donors, we investigate here the possibility of an enolate-mediated aldol reaction where the methyl ketones are sufficiently activated by a trifluoromethyl *gem*-diol group and an α-fluorine atom (Scheme 1).[11]

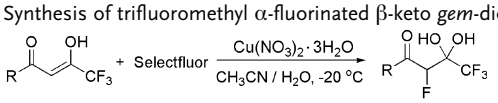


Scheme 1. Activation strategy for methyl ketones in aldol reactions.

The requisite trifluoromethyl α-fluorinated β-keto *gem*-diols **1** that exist exclusively in their keto form[12] were easily prepared with $Cu(NO_3)_2{\cdot}3H_2O$ as catalyst from Selectfluor and trifluoro-1,3-diones obtained by trifluoroacetylation of methyl ketones (Table 1).[13] X-ray analysis in combination with ^{13}C NMR spectroscopic data of crystalline **1a** supported the formation of a *gem*-diol rather than of a ketone and a water molecule.[14]

Asymmetric organocatalysis,[6b,c,15] which uses small molecules as catalyst surrogates of potentially toxic and costly metals, has become a promising strategy in organic synthesis. Therefore, with substrates **1** in hand, we sought to conduct the decarboxylative aldol reaction of trifluoromethyl α-fluori-

Table 1: Synthesis of trifluoromethyl α-fluorinated β-keto *gem*-diols.[a]



1

Entry	R	Product	Yield [%][b]
1	Ph	**1a**	94 (X-ray)
2	3-MeC_6H_4	**1b**	90
3	4-FC_6H_4	**1c**	96
4	3,4-$F_2C_6H_4$	**1d**	87
5	4-$MeOC_6H_4$	**1e**	83
6	2-MeC_6H_4	**1f**	92
7	2-furyl	**1g**	85
8	2-thienyl	**1h**	82
9	4-BrC_6H_4	**1i**	90
10	4-ClC_6H_4	**1j**	91
11	Me	**1k**	62
12	cyclopropyl	**1l**	76

[a] Unless otherwise noted, reactions were performed with 2.5 equiv of Selectfluor. [b] Yields of isolated products.

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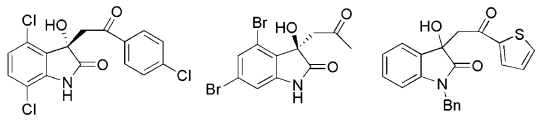
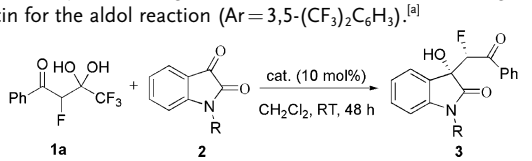
nated β-keto *gem*-diols with isatin derivatives catalyzed by an organic small molecule; the resulting products, 3-hydroxy-3-substituted oxindoles, are a class of important structural motifs in medicinal chemistry (Scheme 2).[16] The results of the catalyst screening and condition optimization are shown in Table 2 and Table 3, respectively.

With dichloromethane as solvent, the reaction catalyzed by a proline derivative (Cat 1) gave the decarboxylated aldol product **3aa** in good yield, but with poor *ee* (Table 2, entry 1). The use of thiourea- and squaramide-based catalysts (Cat 2–Cat 5) led to slightly higher *ee* values, but lower yields (Table 2, entries 2–5). Next, we found that among a series of



Scheme 2. Bioactive 3-hydroxy-3-substituted oxindoles.

Table 2: Catalyst screening and substitution effect of the nitrogen atom of isatin for the aldol reaction (Ar = 3,5-$(CF_3)_2C_6H_3$).[a]



Entry	Catalyst	R	2	3	Yield [%][b]	*ee* [%][c]
1	Cat 1	Bn	**2a**	**3aa**	64	6
2	Cat 2	Bn	**2a**	**3aa**	48	21
3	Cat 3	Bn	**2a**	**3aa**	36	15
4	Cat 4	Bn	**2a**	**3aa**	43	25
5	Cat 5	Bn	**2a**	**3aa**	44	45
6	Cat 6	Bn	**2a**	**3aa**	42	69
7	Cat 7	Bn	**2a**	**3aa**	39	57
8	Cat 8	Bn	**2a**	**3aa**	54	48
9	Cat 9	Bn	**2a**	**3aa**	53	47
10	Cat 10	Bn	**2a**	**3aa**	44	45
11	Cat 11	Bn	**2a**	**3aa**	51	43
12	Cat 6	H	**2j**	**3aj**	39	57
13	Cat 6	Me	**2k**	**3ak**	64	31
14	Cat 6	Boc	**2l**	**3al**	trace	-
15	Cat 6	Ts	**2m**	**3am**	trace	-

[a] Unless otherwise indicated, all reactions were carried out with **2** (0.2 mmol), **1a** (0.3 mmol), and the catalyst (0.02 mmol) in CH_2Cl_2 (2.5 mL) at room temperature. Boc = *tert*-butoxycarbonyl. [b] Yields of isolated products. [c] Determined by HPLC using a chiral stationary phase.

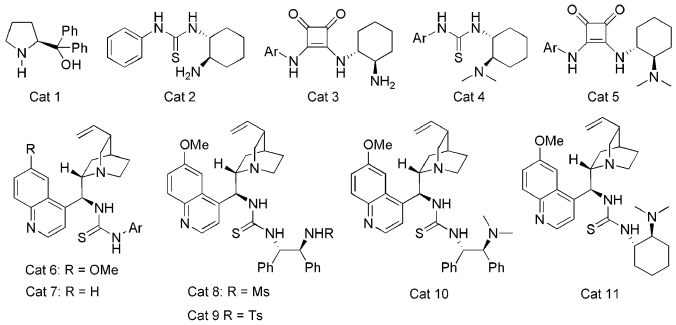
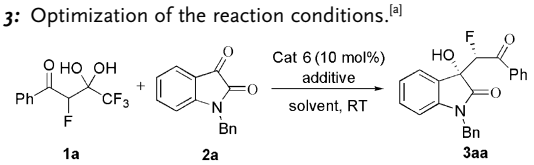


Table 3: Optimization of the reaction conditions.[a]



Entry	Additive (20 mol%)	Solvent	Time [h]	Yield [%][b]	*ee* [%][c]
1		dioxane	48	48	68
2		THF	48	39	66
3		$CHCl_3$	48	54	40
4		DMF	48	59	80
5		DCE	48	53	67
6		MTBE	48	57	78
7		MeOH	3	98	24
8		EtOH	7	95	66
9[d]		*i*PrOH	–	–	–
10		toluene	48	49	54
11		CH_3CN	48	52	54
12	PhCOOH	DMF	48	55	86
13	AcOH	DMF	48	61	89
14	phenol	DMF	48	73	83
15		MeOH/DMF (20:1)	39	84	81
16		H_2O/DMF (20:1)	48	53	69
17		EtOH/DMF (4:1)	20	97	87
18		*i*PrOH/DMF (4:1)	19	98	92
19		*i*PrOH/DMF (1:1)	24	88	88
20		TBA/DMF (4:1)	34	83	94
21[e]		*i*PrOH/DMF (4:1)	38	88	92
22[f]		*i*PrOH/DMF (4:1)	72	86	91
23	AcOH	*i*PrOH/DMF (4:1)	16	99	92
24[g]	AcOH	*i*PrOH/DMF (4:1)	17	99	91
25[f]	AcOH	*i*PrOH/DMF (4:1)	72	85	92

[a] Unless otherwise indicated, all reactions were carried out with **2a** (0.2 mmol), **1a** (0.3 mmol), and Cat 6 (0.02 mmol) in a solvent (2.5 mL) at room temperature. DCE = 1,2-dichloroethane; TBA = *tert*-butyl alcohol. [b] Yields of isolated products. [c] Determined by HPLC using a chiral stationary phase. [d] **2a** not fully dissolvable. [e] The reaction was carried out at 0 °C. [f] 5 mol% of catalyst were used. [g] 40 mol% of acid additive were added.

cinchona alkaloid derived thioureas, the quinine-derived thiourea (Cat 6) was the most promising for the model reaction (Table 2, entry 6). Since the substituent on the nitrogen atom of isatin may sometimes affect the reactivity,[17] we also employed several *N*-substituted isatins for the aldol reaction. With Cat 6, *N*-benzyl isatin (**2a**) gave **3aa** with a higher *ee* value than *N*-H isatin (**2j**) and *N*-methyl isatin (**2k**; Table 2, entries 12–13). However, *N*-Boc (**2l**) and *N*-Ts (**2m**) isatins failed to react with **1a** under the same conditions (Table 2, entries 14–15).

Subsequently, we found that the choice of solvent impacts the yield and enantioselectivity of the model reaction (Table 3). When DMF (dimethyl formamide) and MTBE (methyl *tert*-butyl ether) were used, high enantioselectivities but moderate yields were obtained (Table 3, entries 4 and 6). In contrast, excellent yields but moderate enantioselectivities were obtained in protic solvents (Table 3, entries 7–8), with *i*PrOH (entry 9) as an exception owing to the poor solubility of **2a**.

In the past few years, a number of processes that involved chiral ion pairs have become useful for the design of

organocatalysts.[18] Jacobsen and co-workers recently discovered that the Povarov reaction could be promoted effectively by the combined use of bifunctional urea/thiourea catalysts with a strong Brønsted acid.[19] We thus examined the model reaction in the presence of acid additives (Table 3, entries 12–14). AcOH (20 mol%) appeared to be the most effective additive and gave the product with an excellent 89% *ee* in a moderate yield of 61% (Table 3, entry 13). By screening mixed solvents, we found that a mixture of *i*PrOH with DMF (4:1) afforded **3aa** with excellent yield (98%) and enantioselectivity (92%, Table 3, entry 18). Decreasing the reaction temperature resulted in a slightly decreased yield and prolonged reaction time (Table 3, entry 21). Furthermore, the catalyst loading could be decreased to 5 mol% to afford **3aa** in 86% yield with consistent enantioselectivity, but prolonged reaction time (Table 3, entry 22). Further addition of 20 or 40 mol% of AcOH to the system shortened the reaction time (Table 3, entries 23 and 24), but not in the case where the catalyst loading was lowered to 5 mol% (Table 3, entry 25).

After we established the optimal reaction conditions, the generality of this reaction was probed by using a variety of *gem*-diols **1a**–**1l** as aldol donors (Table 4). In the presence of Cat 6 (10 mol%) and AcOH (20 mol%), the aldol reaction of *N*-benzyl isatin **2a** with aryl-substituted 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-butan-1-ones **1a**–**1h** proceeded smoothly in *i*PrOH/DMF (4:1) at room temperature, giving the desired products **3aa**–**3ha** in admirable yields (91–99%) with excellent diastereoselectivities (99:1) and stereoselectivities (83–98% *ee*), regardless of the positions and electronic nature of the substituents on the phenyl rings (Table 4, entries 1–8). Similar results were also obtained when R^1 was replaced by the heterocyclic 2-furyl and 2-thienyl groups (Table 4, entries 9,10). The reaction could also be carried out with aliphatic *gem*-diols, though more sluggishly, affording the corresponding products in moderate yields, but still with high diastereo- and stereoselectivities (Table 4, entries 11–12). The absolute configuration of the major diastereomer of **3aa** was determined as 3*S*,1′*S* by X-ray analysis (Figure 1).[20]

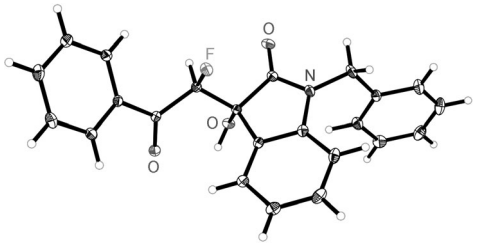
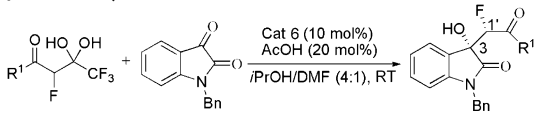


Figure 1. X-ray crystal structure of the major diastereomer of **3aa**. Thermal ellipsoids are set at 30% probability.

Next, we probed the reaction scope with a range of *N*-benzyl isatins **2b**–**2i** as aldol acceptors (Table 5). With **1a** as the substrate, various isatins with different substituents on the aromatic ring, including halogens and electron-donating groups, are suitable for this reaction. Excellent yields (91–99%), high diastereoselectivities (99:1) and stereoselectivities (83–98% *ee*) were obtained (Table 5, entries 1–8). Furthermore, we investigated the reaction of (4-fluorophenyl)-(**1c**) and (4-methoxyphenyl)-3,3-dihydroxybutan-1-one (**1e**) with isatin **2b** and found that the electronic properties of the substituents had a negligible impact on the reactivity (Table 5, entries 9–10).

To study the plausible mechanism of the reaction, we further synthesized two substrates to verify that the asymmetric aldol addition is not a stepwise process in which release

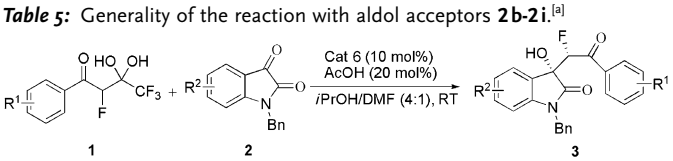
Table 4: Generality of the aldol reaction.[a]



Entry	R^1	Time [h]	Yield [%][b]	d.r. [%][c]	*ee* [%][d]
1	Ph (**1a**)	16	99 (**3aa**)	99:1	92
2	3-MeC_6H_4 (**1b**)	16	97 (**3ba**)	99:1	93
3	4-FC_6H_4 (**1c**)	16	99 (**3ca**)	99:1	91
4	3,4-$F_2C_6H_4$ (**1d**)	16	95 (**3da**)	99:1	83
5	4-MeOC_6H_4 (**1e**)	36	96 (**3ea**)	99:1	95
6	2-MeC_6H_4 (**1f**)	36	91 (**3fa**)	99:1	93
7	4-BrC_6H_4 (**1g**)	20	99 (**3ga**)	99:1	88
8	4-ClC_6H_4 (**1h**)	20	97 (**3ha**)	99:1	91
9	2-furyl (**1i**)	28	99 (**3ia**)	99:1	92
10	2-thienyl (**1j**)	28	99 (**3ja**)	99:1	98
11	Me (**1k**)	60	43 (**3ka**)	99:1	83
12	cyclopropyl (**1l**)	60	67 (**3la**)	99:1	83

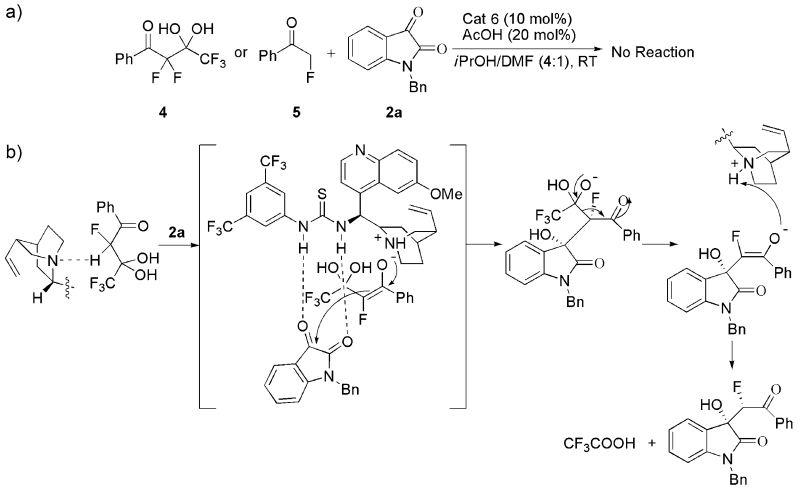
[a] Reactions were performed with **2a** (0.2 mmol) with various substituted 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-butan-1-ones **1a**–**1l** (0.3 mmol) and Cat 6 (0.02 mmol) in *i*PrOH/DMF (4:1, 2.5 mL). [b] Yields of isolated products. [c] Determined by ^{19}F NMR spectroscopic analysis of unpurified reaction products. [d] Determined by HPLC using a chiral stationary phase.

Table 5: Generality of the reaction with aldol acceptors **2b**-**2i**.[a]



Entry	R^1/R^2	Time [h]	Yield [%][b]	d.r. [%][c]	*ee* [%][d]
1	H (**1a**)/5-F (**2b**)	16	99 (**3ab**)	99:1	92
2	H (**1a**)/6-Br (**2c**)	16	99 (**3ac**)	99:1	91
3	H (**1a**)/5-Br (**2d**)	18	99 (**3ad**)	99:1	92
4	H (**1a**)/7-Cl (**2e**)	16	99 (**3ae**)	99:1	86
5	H (**1a**)/5-Me (**2f**)	16	99 (**3af**)	99:1	92
6	H (**1a**)/5-OMe (**2g**)	16	98 (**3ag**)	99:1	98
7	H (**1a**)/4-Br (**2h**)	24	91 (**3ah**)	99:1	91
8	H (**1a**)/5,7-Me_2(**2i**)	24	95 (**3ai**)	99:1	83
9	4-F (**1c**)/5-F (**2b**)	16	98 (**3cb**)	99:1	83
10	4-OMe (**1e**)/5-F (**2b**)	19	99 (**3eb**)	99:1	93

[a] Reactions were performed with various substituted β-nitroolefins **2b**–**2i** (0.2 mmol) with 2,4,4,4-tetrafluoro-3,3-dihydroxy-1-arylbutan-1-one **1** (0.3 mmol) and Cat 6 (0.02 mmol) in *i*PrOH/DMF (4:1, 2.5 mL). [b] Yields of isolated products. [c] Determined by ^{19}F NMR spectroscopic analysis of unpurified reaction products. [d] Determined by HPLC using a chiral stationary phase.



Scheme 3. a) No reaction of **4** or **5** with **2a** was observed under the optimized conditions. b) Plausible mechanism of tandem asymmetric aldol reaction/trifluoroacetate release. The addition of **1a** to **2a** in the presence of Cat 6 is shown.

of trifluoroacetate occurs first, followed by deprotonation of the α-fluoroketone, and then addition to isatin. As expected, the synthesized substrates, namely 2,2,4,4,4-pentafluoro-3,3-dihydroxy-1-phenylbutan-1-one **4** and 2-fluoro-1-phenylethanone **5** did not react with isatin **2a** under the optimized conditions (Scheme 3a). On the basis of the above results, we propose a plausible reaction mechanism, which is shown in Scheme 3b for the addition of **1a** to **2a** in the presence of Cat 6. After the initial formation of a primary asymmetric aldol adduct bearing a 3*R* configuration, the amino group of the catalyst deprives a proton from the addition product, releasing the trifluoroacetate group. Subsequently the enol anion retrieves the proton from the amino group of the catalyst to provide the decarboxylated product **3aa**.

In summary, we have developed a new and efficient direct aldol reaction of *gem*-diols to isatins catalyzed by a bifunctional thiourea derived from a cinchona alkaloid. The key step of this protocol is the release of trifluoroacetate for the cleavage of a C–C bond by making use of *gem*-diols as a synthetic equivalent of fluorinated aryl/alkyl methyl ketone enolates. The resulting decarboxylated products were obtained almost quantitatively with excellent selectivities. We believe that this strategy would complement the existing asymmetric fluorinations, thereby facilitating the synthesis of chiral fluorinated molecules for the development of 3-hydroxy-3-phenacyloxindoles of medicinal interest.

Experimental Section

General procedure for the decarboxylative aldol reaction: To a solution of *N*-benzyl isatin **2** (0.2 mmol) in *i*PrOH/DMF (4:1, 2.5 mL) Cat 6 (0.02 mmol) and trifluoromethyl α-fluorinated β-keto *gem*-diols **1** (0.3 mmol) were added. Upon complete consumption of isatin (monitored by TLC), the reaction mixture was concentrated and purified by column chromatography to afford the adducts.

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Keywords: aldol reaction · carbon–carbon bond cleavage · organocatalysis · reaction mechanisms · trifluoroacetate release

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[20] CCDC 914489 (**3aa**, Figure 1) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

