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Catalytic Asymmetric Mono-Fluorination of α-Keto Esters: Synthesis of Optically Active β-Fluoro-α-Hydroxy and β-Fluoro-α-Amino Acid Derivatives**

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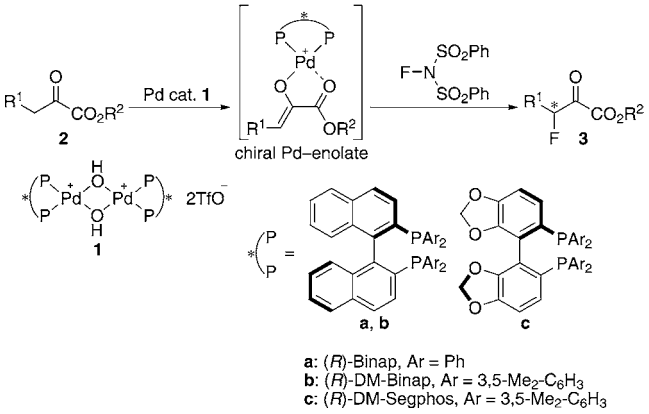
In the field of medicinal chemistry, it is widely recognized that the replacement of a hydrogen atom or a hydroxy group with a fluorine atom often improves the pharmacological activity of the parent compound.[1] Although fluorine substitution on aromatic rings is a common tactic, several drug candidates with fluorine on a stereogenic carbon center have appeared in recent years.[2] Consequently, the development of effective methods for the preparation of optically active fluorinated compounds is attracting considerable attention.[3] We and others have already devised elegant systems for catalytic asymmetric fluorination reactions of carbonyl compounds, including β-keto esters,[4] β-keto phosphonates,[4c,5] α-cyano phosphonates and α-cyano acetates,[6] oxindoles,[4d,7] acid derivatives,[8] and aldehydes.[9]

As an extension of our acid–base catalytic system using late transition metal complexes, we recently reported the first example of catalytic diastereo- and enantioselective conjugate addition of α-keto esters to nitroolefins.[10] Focusing on α-keto esters as useful nucleophiles, we next became interested in asymmetric fluorination (Scheme 1). As the keto group in the product provides a good handle for further transformations, such reactions are expected to be useful for producing medicinally important chiral building blocks. Among them, β-fluoro-α-hydroxy and β-fluoro-α-amino acid derivatives are potentially useful as synthons for obtaining novel bioactive compounds[11] and may contribute to pharmaceutical and chemical biology research. However, to date there is no example of an asymmetric reaction to access these compounds, because it has generally been believed that the monofluorinated products would tend to undergo facile enolization, resulting in the loss of optical purity.[12] Difluorinated compounds might also be formed, albeit with difficulty.[13] Based on our previous results, we envisaged that the use of mildly basic catalysts would permit the asymmetric fluorination of α-keto esters.[10,14] Herein we report the first example of highly enantioselective mono-fluorination of α-keto esters catalyzed by Pd-μ-hydroxo complexes **1**. The resulting fluorinated products were successfully converted into chiral β-fluoro-α-hydroxy esters and β-fluoro-α-amino esters. As there are few generally applicable methods for the preparation of α substituted β-fluoro carboxylic acids,[15] the present procedure is expected to be useful in medicinal chemistry research.



Scheme 1. Enantioselective mono-fluorination of α-keto esters. OTf = trifluoromethanesulfonate.

Initially, we investigated the reaction of commercially available ethyl ester **2a** with *N*-fluorobenzenesulfonimide (NFSI). Though our Pd-catalyzed fluorination reactions of 1,3-dicarbonyl compounds proceeded well in ethanol, no reaction was observed with α-keto ester **2a** in this solvent (Table 1, entry 1). Careful solvent screening resulted in identification of methyl *tert*-butyl ether (MTBE) and cyclopentyl methyl ether (CPME) as the best solvents for the reaction. The yields and enantioselectivities obtained in the two solvents were comparable, but the fluorination reaction at −20 °C reached completion in 12 h in CPME, while it required 22 h in MTBE (Table 1, entries 8 and 9). Thus, CPME became our solvent of choice.[16] As the corresponding fluorinated α-keto ester **3a** was readily converted into the hydrate form during purification, the product was isolated after in situ reduction with diisobutylaluminium hydride (DIBAL-H). The low diastereoselectivity shown in Table 1 was later improved (see below). Furthermore, as the *tert*-butyl

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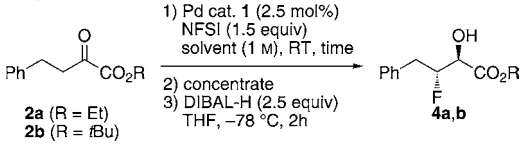
Table 1: Optimization of the reaction conditions.



Entry	2	Solvent	Pd cat. 1	*t* [h]	Yield[a] [%]	*ee*[b] [%]	*syn*/*anti*[c]
1	**2a**	EtOH	**1a**	72	–	–	–
2	**2a**	Et_2O	**1a**	4	63	44	1:3.0
3	**2a**	THF	**1a**	1	92	36	1:2.6
4	**2a**	toluene	**1a**	12	75	50	1:2.7
5	**2a**	MTBE	**1a**	2	73	53	1:2.8
6	**2a**	MTBE	**1b**	6	67	62	1:2.6
7	**2b**	MTBE	**1b**	1	80	73	1:3.2
8[d]	**2b**	MTBE	**1b**	22	81	84	1:3.2
9[d]	**2b**	CPME	**1b**	12	86	85	1:3.1
10[d]	**2b**	CPME	**1c**	16	85	90	1:2.8
11[d,e]	**2b**	CPME	**1c**	20	87	89	1:3.0
12[d,f]	**2b**	CPME	**1c**	22	85	92	1:3.2
13[d,g]	**2b**	CPME	**1c**	36	79	94	1:3.2

[a] Combined yield of isolated product over two steps (major and minor diasteromers). [b] The *ee* of the major *anti* diastereomer was determined by HPLC analysis using a chiral stationary phase. [c] The diasteromeric ratio was determined by ^{19}F NMR and ^{1}H NMR spectroscopy. [d] The reaction was carried out at −20 °C. [e] 0.5 M. [f] 0.2 M. [g] 0.1 M. CPME = cyclopentyl methyl ether, DIBAL-H = diisobutylaluminium hydride, MTBE = methyl *tert*-butyl ether, NFSI = *N*-fluorobenzenesulfonimide.

ester generally gave better enantioselectivity with bulkier catalysts, a catalyst screening was carried out using α-keto ester **2b** as the substrate. In the presence of the palladium catalyst **1b** (2.5 mol%), the desired fluorohydrin **4a** was obtained in 86% yield with 85% *ee* (Table 1, entry 9). Among the catalysts examined, **1c**, which has (*R*)-DM-Segphos as a chiral ligand,[17] was found to be the best. As shown in entry 10, the desired fluorohydrin **4b** was obtained with 90% *ee* when the reaction was performed at −20 °C. In this reaction, the undesired difluorinated compound was not formed, whereas a small amount of the corresponding difluorinated alcohol was isolated after reaction at room temperature. Further optimization revealed that reducing the concentration of the reaction mixture improved the enantioselectivity, albeit at the cost of longer reaction times. An excellent enantioselectivity of 94% was achieved when the reaction was conducted at 0.1 M (Table 1, entry 13). Surprisingly, the initial fluorinated α-keto ester product was stable under the reaction conditions, and its racemization was minimal.

A single recrystallization of *syn*-**4b** or *anti*-**4b** gave the corresponding fluorohydrin with 99% *ee*. Moreover, crystals suitable for X-ray structure determination were obtained, and the relative and absolute configurations of *syn*-**4b** and *anti*-**4b** were unequivocally elucidated (Figure 1).[18] It was thus determined that *syn*-**4b** was obtained as the (2*R*,3*R*) enantiomer and *anti*-**4b** was obtained as the (2*S*,3*R*) enantiomer. The sense of enantioselection in the present fluorination reaction can be explained by assuming the involvement of a square-planar bidentate Pd–enolate structure, as depicted in Figure 2.[19] In this case, the bulky *tert*-butyl ester moiety

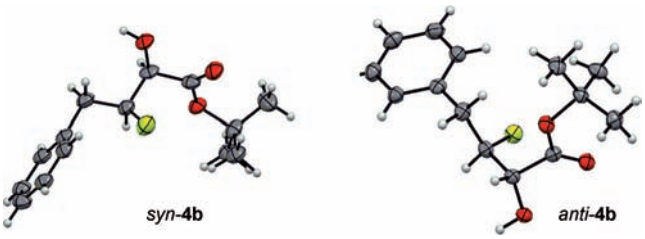


Figure 1. X-ray structure determination of the relative and absolute stereochemistry of fluorohydrins *syn*-**4b** and *anti*-**4b**. Ellipsoids set at 50% probability. Fluorine atoms are shown in yellow, oxygen atoms are shown in red.

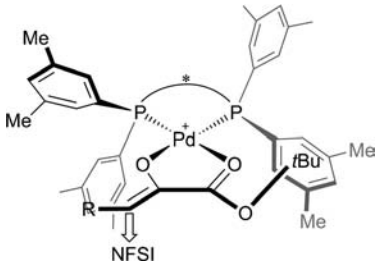
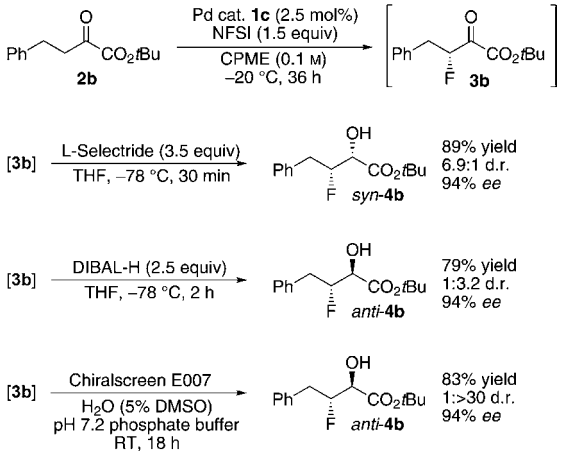


Figure 2. Model for the palladium-catalyzed fluorination of α-keto esters. NFSI = *N*-fluorobenzenesulfonimide.

would be located on one enolate face to avoid steric repulsion with the neighboring equatorial 3,5-dimethylphenyl group of the ligand. Hence, one of the enolate faces would be effectively shielded by the other equatorial aryl group of the ligand and the *tert*-butyl ester moiety. Consequently, NFSI would preferentially approach from the less hindered *re* face of the Pd–enolate.

Having established the optimum reaction conditions for highly enantioselective fluorination and assigned the relative and absolute configurations of *syn*-**4b** and *anti*-**4b**, we next turned our attention to the diastereoselective reduction of the remaining keto group to obtain chiral β-fluoro-α-hydroxy esters[20] (Scheme 2). Various reducing agents, solvents, and

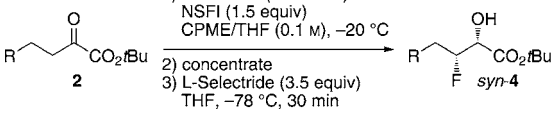


Scheme 2. Stereoselective reduction to give β-fluoro-α-hydroxy esters. CPME = cyclopentyl methyl ether, DIBAL-H = diisobutylaluminium hydride, L-Selectride = lithium tri-sec-butylborohydride, NFSI = *N*-fluorobenzenesulfonimide.

temperatures were examined. The reagent of choice to produce the *syn* diastereomer was found to be lithium tri-sec-butylborohydride (L-Selectride). Thus, after completion of the initial fluorination reaction, the solvent was removed under reduced pressure and the reduction was then carried out in THF at −78 °C. The desired fluorohydrin *syn*-**4b** was isolated in 89% yield (2 steps) with a 6.9:1 diastereomeric ratio. On the other hand, reduction with DIBAL-H was *anti*-selective, and the *anti*-**4b** diastereomer was obtained in 68% yield with modest diastereoselectivity (1:3.2). To improve the *anti* selectivity, we examined enzymatic reduction using DAICEL Chiralscreen OH,[21] expecting that such a reduction would be a good complement to the L-Selectride *syn*-reduction. Among the enzymes examined, E007 was found to give the *anti* product in good yield and with excellent stereoselectivity (1: > 30 d.r.). It should be noted that these reactions proceeded without detectable loss of enantioselectivity.

To probe the generality of the reaction, various α-keto ester substrates were examined (Table 2). In these reactions,

Table 2: Reaction scope.



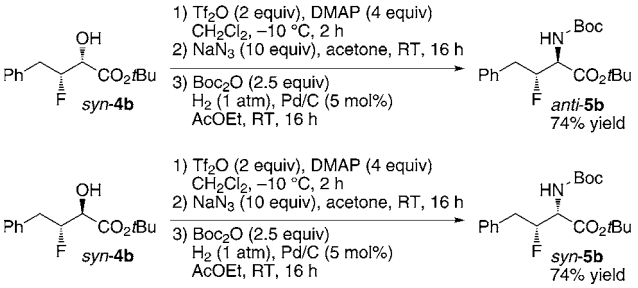
Entry	R	**2**	*t* [h]	Yield[a] [%]	*ee*[b] [%]	*syn*/*anti*[c]
1[d]	Ph	**2b**	36	89	94	6.9:1
2[e]	4-Me-C_6H_4	**2c**	36	83	91	4.6:1
3[e]	4-MeO-C_6H_4	**2d**	30	75	94	4.7:1
4[e]	4-F-C_6H_4	**2e**	24	68	95	6.5:1
5[d]	4-Cl-C_6H_4	**2f**	24	69	95	7.6:1
6[e]	$PhCH_2$	**2g**	34	65	83	4.2:1
7[d,f]	$BnOCH_2$	**2h**	36	66	83	1.4:1

[a] Combined yield of isolated product over two steps (major and minor diasteromers). [b] The *ee* of the major *syn* diastereomer was determined by HPLC analysis using a chiral stationary phase. [c] Diastereomeric ratio of isolated compounds.[22] [d] CPME/THF = 100:0. [e] CPME/THF = 95:5. [f] 0.2 M. Bn = benzyl, CPME = cyclopentyl methyl ether, L-Selectride = lithium tri-sec-butylborohydride, NFSI = *N*-fluorobenzenesulfonimide.

the products were isolated after reduction with L-Selectride and both diastereomers were separated. For less soluble substrates, the addition of a small amount of THF was effective in accelerating the reaction. Substrates variously substituted with methyl, ether, or halogen groups were all available, and the reactions proceeded in a highly enantioselective manner (Table 2, entries 1–5). Also, both a substrate bearing a longer alkyl chain (**2g**) and a benzyloxy-substituted compound (**2h**) underwent the fluorination–reduction sequence, and the desired fluorohydrins were obtained with acceptable enantioselectivities (Table 2, entries 6 and 7).

We considered that our catalytic asymmetric fluorination reaction might provide a convenient entry to optically active β-fluoro-α-amino acids, which have numerous applications owing to their biological activity.[23] Nevertheless, the selective synthesis of β-fluoro-α-amino acid derivatives such as **5b** remains largely unexplored and only a few examples have been reported to date.[24] Therefore, we next focused on the synthesis of β-fluoro-α-amino acids.

In light of the simplicity and selectivity observed during the enzymatic reduction of the β-fluoro-α-keto ester **3b**, we examined the enzymatic reductive amination of **3b** using DAICEL Chiralscreen NH.[21] However, this proved unsuccessful. Therefore, a step-by-step approach from fluorohydrin **4b** was next investigated. Both diastereomers of **4b** were first converted into the corresponding triflates.[25] Nucleophilic substitution with sodium azide, followed by palladium-catalyzed reduction and in situ protection with *tert*-butoxycarbonyl (Boc) gave the desired protected β-fluoro-α-amino esters **5b** in good overall yield in three steps. It is noteworthy that the three-step sequence could be performed without purification of any of the intermediates (Scheme 3). Complete inversion of the α carbon was confirmed by an X-ray structure analysis of racemic *syn*-**5b**.[18]



Scheme 3. Synthesis of β-fluoro-α-amino esters. Boc = *tert*-butoxycarbonyl, DMAP = 4-(dimethylamino)pyridine, Tf = trifluoromethanesulfonyl.

In summary, we have developed the first example of the catalytic enantioselective mono-fluorination of α-keto esters using a chiral palladium μ-hydroxo complex. Surprisingly, racemization of the product was minimal under the optimized reaction conditions. Further transformations afforded β-fluoro-α-hydroxy esters **4** and β-fluoro-α-amino esters **5b** in good yields and with good to excellent stereoselectivities. Moreover, all possible diastereomers were easily accessible by slightly modifying the reaction conditions. These compounds and their derivatives should be of interest in the field of medicinal chemistry. Further studies to improve the reaction efficiency and scope are underway in our laboratory.

Experimental Section

Palladium complex **1c** (50 mg, 0.025 mmol, 2.5 mol%), α-keto ester (1.00 mmol), and NFSI (473.0 mg, 1.50 mmol) were added to a dry round-bottomed flask under argon and cooled to −20 °C. Freshly distilled CPME (10 mL) was then added under argon. The reaction mixture was stirred under argon for 36 h with the strict exclusion of moisture. The resulting mixture was warmed to room temperature and concentrated under reduced pressure. The residue was cooled to −78 °C and dissolved in anhydrous THF (10 mL). L-Selectride (1 M in THF, 3.5 mL, 3.5 mmol) was added dropwise at −78 °C and the reaction mixture was stirred at this temperature for 30 min. Then,

30% aqueous H_2O_2 solution (5 mL) and aqueous NaOH solution (3 M, 5 mL) were added and the reaction mixture was slowly warmed to room temperature. The resulting solution was extracted with ether (3 × 25 mL). The organic layers were combined, washed with brine (3 × 30 mL), filtered through a pad of Celite, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel using n-hexane/ethyl acetate (5:1) as the eluent to give the desired fluorohydrin **4**.

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