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Efficient synthesis of (*R*)-3-amino-1,1,1-trifluoropropan-2-ol via a Dakin–West reaction followed by enantioselective reduction

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This paper is respectfully dedicated to Professor Marvin J. Miller on the occasion of his 60th birthday

ABSTRACT

An efficient, chromatography-free asymmetric synthesis of (*R*)-3-amino-1,1,1-trifluoropropan-2-ol was developed for large scale production of a cholesterol ester transfer protein (CETP) inhibitor. The synthesis features a new efficient route to a β-amino trifluoromethylketone involving a modified Dakin–West reaction followed by an asymmetric hydrogenation or an enzymatic reduction of the resulting ketone to the alcohol.

1. Introduction

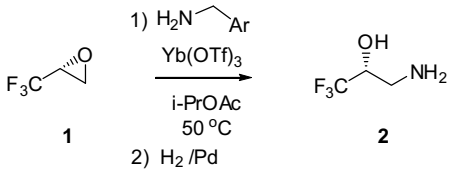
The development of asymmetric routes to enantiomerically pure compounds has become an increasingly important component in the synthesis of complex molecules of pharmaceutical interest. In this context, catalytic asymmetric hydrogenation with an appropriate chiral catalyst or reduction with a suitable biocatalyst has become a valuable tool for more efficient and environmentally friendly industrial processes, and provides the desired substrates with high chemo-, regio- and stereoselectivities.[1,2]

Over the last few decades, fluorinated organic molecules have played a significant role during the development of liquid crystalline materials, agrochemicals and pharmaceuticals due to their unique physicochemical and biological properties.[3] α-Trifluoromethyl alcohols, in particular, have served as precursors to a variety of trifluoromethylated chiral frameworks.[4] Although a number of reports on the enantioselective reduction of ketones to alcohols have appeared in the literature, involving stoichiometric chiral hydride sources,[5] asymmetric hydrogenation,[6] transfer hydrogenation,[7] or enzymatic pathways,[8] the substrate scope of these processes are limited. Any alteration of electronic or steric properties of the molecule often results in a dramatic decline in rate and enantioselectivity of the reaction. To the best of our knowledge, the asymmetric reduction of α-amino or α-amido trifluoromethyl ketone has not been reported in the literature to date. Herein, we report two efficient approaches to (*R*)-3-amino-1,1,1-trifluoropropan-2-ol involving, (1) asymmetric hydrogenation and (2) biocatalytic reduction of the precursor amido-ketone, amenable for large scale production of this key building block.

2. Results and discussion

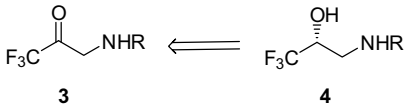
2.1. Dakin–West approach to the amido-ketone

The existing protocol to access to the alcohol relies on the opening of the chiral, commercially available epoxide (Scheme 1) as the chiral pool.



Scheme 1. Epoxide-route to the amino alcohol.

We reasoned that an efficient asymmetric reduction of the precursor ketone would avoid the limitation of using the volatile epoxide in a closed reactor that is difficult to monitor (Scheme 2).



Scheme 2. Ketone reduction.

Although the requisite ketone can be accessed in a variety of ways, the classical Dakin–West reaction[9] proved most promising considering the cost efficiency and operational simplicity of the processes.[10] Thus, *N*-(3,3,3-trifluoro-2-oxopropyl)benzamide could

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be prepared in two steps (Scheme 3) as a crystalline solid from readily available and inexpensive (<$20/kg) *N*-benzoyl glycine (hippuric acid) as shown in Scheme 3, by using a modified Dakin–West reaction.[11,12] To this end, treatment of **5** with trfluoroacetic anhydride gave trifluoroacylated oxazolone **9** in one step. Subsequent hydrolysis and decarboxylation in refluxing water furnished the hydrated trifluoromethyl ketone **6** in good yield.[13] The titled amino alcohol **10** was produced following a reductive debenzoylation protocol. The product amino alcohol showed identical spectroscopic characteristics to that described in the literature.[14,15]

2.2. Asymmetric hydrogenation for the reduction of the ketone

We first investigated asymmetric hydrogenation as the trifluoromethyl group is known to play a significant role in enantiotopic face selection during hydrogenation. A broad screening was performed using the appropriate library of catalysts for ketone reduction. A representative list of catalysts, not all inclusive, has been shown in Table 1. As shown in Table 1, several viable options were apparent after the initial screening. Further optimization of the initial combination of hits was examined using diacetato((*R*)-BINAP) ruthenium (II) as the catalyst. Solvent screening indicated that both toluene and ethyl acetate would serve equally well as solvent, with no differences in either the selectivity or rate of reaction. Furthermore, the enantioselectivity could be enhanced with the addition of 1 M equiv of acid such as trifluoroacetic acid or acetic acid (98% ee, ~99%). The configuration of the products was determined by comparison with authentic samples prepared via the original epoxide route.

The product from the reaction precipitate from toluene and can be purified, if needed, to attain enantiomeric purity. The hydrogenation on a 2 g scale gave a 93% yield of an off-white solid with an enantiomeric purity of 99% ee after a single recrystallization with an initial selectivity of 97% ee.

2.2.1. Representative procedure for hydrogenation

N-(3,3,3-Trifluoro-2-oxo-propyl)-benzamide and diacetato[(*R*)-(+)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]ruthenium(II) (0.015 M equiv) were added to a clean dry reactor and purged five times with nitrogen. Next, 10 volumes of nitrogen-sparged toluene were added to the above followed by 1 equiv of either acetic acid or trifluoroacetic acid. The reaction mixture was heated to 50 °C, after which the temperature was allowed to equilibrate, and maintained at 150 psig under hydrogen for 36 h. The usual work-up after cooling to 30 °C and purging with nitrogen provided a sample for GC–MS and chiral HPLC analysis.

2.2.2. Chiral assay

For the analysis of the benzoyl-(*R*)-3-amino-1,1,1-trifluoropropan-2-ol, the following HPLC method was used (Figs. 1 and 2): Column: Chiralpak OD, 4.6 mm × 250 mm, mobile phase heptane (A): isopropanol + 0.1% DEA (B), A: B (83%:17%), flow rate: 1 mL/min, detection: 220 nm, temp: 25 °C, run time 15 min. Samples were dissolved in heptane/IPA (50/50).

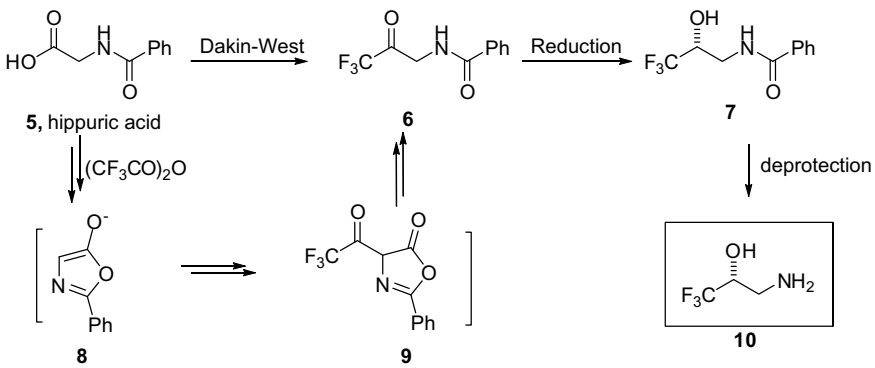
Table 1
Screening results for asymmetric hydrogenation of ketone[a]

Catalyst	Additive	% ee (pdt configuration)	% Conversion
Diacetato[(*R*)-(+)-BINAP]ruthenium(II)		88 (*R*)	92
Diacetato{(*S*)-(−)-dm-segphos}ruthenium(II)		78 (*S*)	73
Dichloro{(*R*)-(+)-dm-Segphos[(1*R*,2*R*)-(+)-1,2-diphenylethylenediamine] ruthenium(II)		66 (*R*)	18
Dimethylammonium dichlorotri (mu-chloro)bis[(*S*)-(−)-Segphos]diruthenate(II)		84 (*S*)	96
Dichloro{(*R*)-(+)-xylBINAP}[(2*R*)-(−)-1, 1-bis(4-methoxyphenyl)-3-methyl-1, 2-butanediamine]ruthenium(II)		78 (*R*)	35
Dichloro{(*R*)-(+)-2xylyl-BINAP}[(1*R*,2*R*)-(+)-1,2-diphenylethylenediamine] ruthenium(II)		80 (*R*)	65
SK-J014-1a		6 (*S*)	33
Diacetato[(*S*)-(+)-BINAP]ruthenium(II)		90 (*S*)	100
Diacetato[(*R*)-(+)-BINAP]ruthenium(II)		90 (*R*)[b]	100
Dimethylammonium dichlorotri(μ-chloro)bis[(*R*)-(−)-Segphos]diruthenate(II)		86 (*R*)	100
Diacetato[(*R*)-(+)-BINAP]ruthenium(II)	Acetic acid	98 (*R*)	100
Diacetato[(*R*)-(+)-BINAP]ruthenium(II)	Trifluoro acetic acid	98 (*R*)	100
Diacetato[(*R*)-(+)-BINAP]ruthenium(II)	Methane sulfonic acid	98 (*R*)	100

[a] All reductions run in toluene unless otherwise stated. Reactions were run at 50 °C, 150 psig for 24–36 h.
[b] Reaction run in EtOAc.

2.3. Biocatalytic reduction of the ketone

The use of enzymes that reduce ketones (ketone reductases or KREDs) is widely accepted in organic chemistry and is rapidly emerging as a useful tool in industry.[16] The following section describes our investigation with regard to the enzymatic reduction of **6** to the corresponding amino alcohol using an enzyme, thus introducing an alternative way to prepare **7**. The enzyme was identified after a screening of several hundred commercial and in-house biocatalysts. Six enzymes showed reasonable to excellent enantioselectivity for the production of the desired (*R*)-enantiomer. The commercially available KRED102 and *Saccharomyces*



Scheme 3. Dakin–West approach to the amido-ketone.

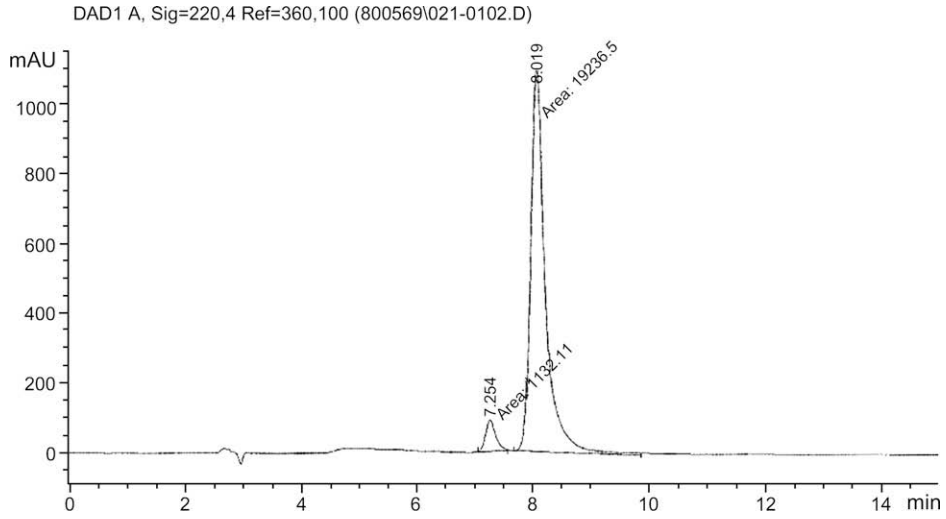


Figure 1. Chiral assay from the asymmetric ketone reduction without any acid additive: 90% ee using Ru(BINAP)diacetate catalyst.

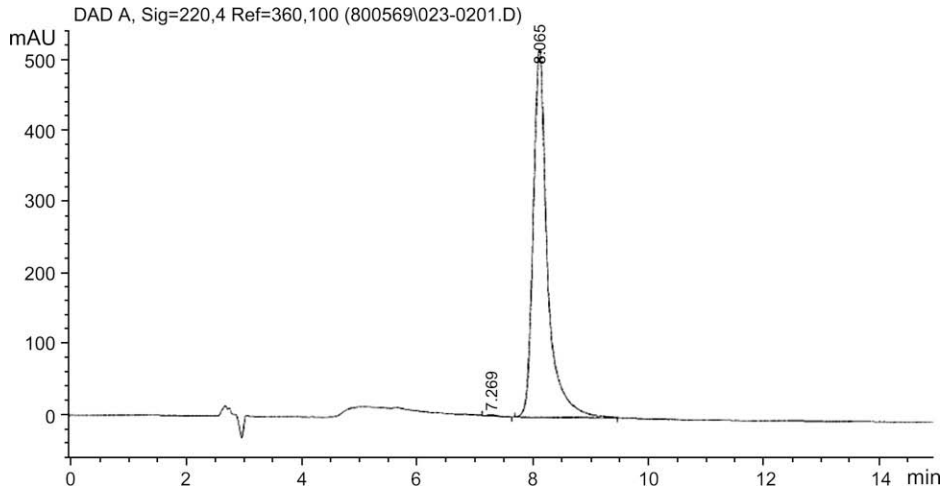


Figure 2. Chiral assay from the asymmetric ketone reduction with 1 equiv of trifluoroacetic acid present: 99% ee.

Table 2
Enzyme hits identified from screening[a]

Hit	Selectivity	% ee
Biocatalytics KRED102	(*R*)	>99
Recombinant in *E. coli S. cerevisiae* aldehyde reductase GCY1	(*R*)	>99
Recombinant in *E. coli K. lactis* aldehyde reductase 2	(*R*)	95
Biocatalytics KRED131	(*R*)	95
Diacel ADH E094	(*R*)	95
Diacel ADH E031	(*R*)	80
IEP-OX 5	(*R*)	80
Recombinant in *E. coli S. salmonicolor* reductase 2	(*S*)	>99
Multiple commercial KREDs	(*S*)	>99

[a] Commercial enzymes were purchased from Biocatalytics Inc. (now part of Codexis Inc.), IEP GmbH and Diacel LTD. Cloned enzymes were produced in house recombinant in *E. coli* and used in a crude form as cell lysates. Biocatalytics KREDs 106, 107, 111–115, 118–121, 123, 124, 128–130 and EXPA1-E, F, I, K, L, N, O, Q, S, T, S, Y, EXPB1-A, E, H, I, K, M, S as well as IEP-OX 25, 28, 56, 58, 59, 66, 76 and Diacel ADH E0-04, 07, 08, 52, 87, 94 all primarily produced the (*S*)-enantiomer in high ee's.

cerevisiae aldehyde reductase GCY1 can be used to produce the (*R*)-enantiomer in >99% ee. More than three dozen commercial enzymes (Table 2) and the *Sporobolomyces Salmonicolor* Aldehyde reductase 2 can be used to produce the (*S*)-enantiomer in >99% ee.

2.3.1. General description of the process

Ketone **6** is reduced to the (*R*)-alcohol **7** using KRED102 and NADPH as the hydride source.[17] A glucose dehydrogenase (GDH-CDX901) is used to convert/recycle $NADP^+$ to NADPH. The glucose is converted to gluconic acid, which is in turn converted to its sodium salt with the addition of 4 M sodium hydroxide. A pH stat is used to maintain the pH of the reaction mixture at about 6.5. The reaction takes place as a slurry mixture. This reaction was performed in a high concentration of **6** (~100 g/L) and 0.1 g KRED 102 and 0.02 g GDH-CDX901 per gram of starting material. The work-up of the reaction and product isolation consists of extraction, phase separation and concentration. The product is obtained as a solid, in good chemical (>95.0%) and very high enantiomeric (>99% ee) purity.

3. Conclusion

Two processes for the asymmetric reduction of α-trifluoromethyl ketoamide using either an efficient asymmetric hydrogenation or using a readily available enzyme are reported. Both processes provide the desired alcohol in high yield and enantioselectivity and give access to the large-scale synthesis of a pharmaceutical intermediate.

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13. Trifluoroacetic anhydride (348 mL, 528 g, 2.51 mol) was added dropwise to a suspension of hippuric acid (150 g, 837 mmol) in dry acetone (1200 mL) at 0 °C. The reaction was stirred at room temperature overnight. Next, most of the acetone and TFAA were evaporated, and the residue was stirred in 3 L of water for 1 h. The solid product was filtered and dried (188 g, 88%). A portion of this solid oxazolone (60 g) was refluxed with water (250 mL) for 2 h. The solid slowly dissolved with emission of carbon dioxide. The hot solution was filtered and cooled. A total of 120 g (71%) of the hydrated ketone was produced following the same process from 188 g of the oxazolone. This material showed identical physical and spectroscopic properties as described in the literature.[12]
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17. *Representative procedure*: A jacketed 0.15 L reactor equipped with a temperature probe, a pH probe (connected to an autotitrator) and a mechanical stirrer was charged with a solution of 9 ml of 0.1 M phosphate buffer, pH 6.5, followed by glucose (794.9 mg 1.02 equiv, 4.4 mmol) and compound **6** (1.0 g, 1.00 equiv; 4.3 mmol). KRED102 (100 mg), GDH-CDX901 (20 mg) and $NADP^+$ (20 mg) were then charged as solids and the jacket temperature is maintained at 35 °C. The titrator (Metrohm Titrando pH autotitrator) is turned on and the reaction mixture is maintained at 6.5 by the addition of 4 M NaOH using the autotitrator. After reaction completion (~18 h), solid KCl (2.0 g) and Celite 545 (1 g) were added to the solution followed by ethyl acetate (11 mL) and the mixture was extracted for 10 min keeping the temperature at 35 °C. The extraction was repeated two more times, and the organic layers were separated and concentrated to a pale yellow solid. The crude material was obtained in high yield (95–98% yield, based on the potency of **6**) and purity (Chiral HPLC).