Tetrahedron 70 (2014) 3239–3242

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Continuous flow whole cell bioreduction of fluorinated acetophenone

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ARTICLE INFO

Article history:
Received 21 October 2013
Received in revised form 5 December 2013
Accepted 11 December 2013
Available online 28 December 2013

Keywords:
Continuous flow
Bioreduction
Chiral trifluoromethyl alcohols

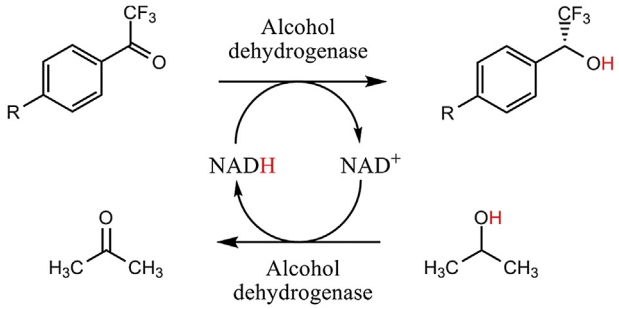
ABSTRACT

Several microorganism strains were used to reduce 2,2,2-trifluoroacetophenone (**1**) and 4′-Br-2,2,2-trifluoroacetophenone (**3**). Immobilized cells of *Geotrichum candidum* in calcium alginate led to conversion and enantiomeric excess higher than 99%. By using immobilized *G. candidum* cells under continuous flow conditions, the same conversion and enantiomeric excess were achieved in 90 min of residence time.

1. Introduction

Chiral trifluoromethyl alcohols play an important role in pharmaceutical, veterinary, agrochemical, and material sciences based on the influence of fluorine's unique properties. Of particular relevance is the emergence of drug candidates featuring fluorine atoms, which often present a favorable therapeutic profile.[1] Chiral trifluoromethyl alcohols can be produced by asymmetric hydrogenation of trifluoromethyl ketones catalyzed by organoboranes,[2–5] (*S*)-binap,[6] chiral organomagnesium amides,[7] chiral rhodium-(I)-complexes[8] or chiral ruthenium-complexes.[9,10] However, some chemical catalysts led to insufficient levels of enantioselectivity and low catalytic efficiencies.

On the other hand, chiral trifluoromethyl alcohols can also be produced by biocatalytic processes.[11–17] Biocatalysis often offers advantages over chemical synthesis, mainly due to higher enantioselectivity, milder and safer reaction conditions and lower environmental impact. Biocatalysts for reduction can be isolated enzymes and whole cells microorganisms, animals or plants. To exhibit catalytic activities, the enzymes require a coenzyme, such as NADH or NADPH from which a hydride is transferred to the substrate carbonyl carbon. Hydrogen sources, as ethanol, 2-propanol, glucose, formic acid or dihydrogen, are necessary to perform the reduction reaction. The reduction of the substrate accompanies the oxidation of the coenzyme from NADH to NAD^+. Then, the coenzyme has to be reduced to NADH, which can be driven by different hydrogen sources. After that, the next cycle of the ketone can occur (Scheme 1).[18–20]



Scheme 1. The cycle of asymmetric reduction of ketone to alcohol by alcohol dehydrogenase, the coenzyme (NADH) and cofactor regeneration (2-propanol).

In comparison to isolated enzymes, the whole cell methodology has distinct characteristics. Enzymes used as whole cells are stable once they are used in their natural environment. Furthermore, the cells have internal coenzyme and cofactor regeneration, so that the addition of cheap glucose is sufficient to drive the reaction.[21–25]

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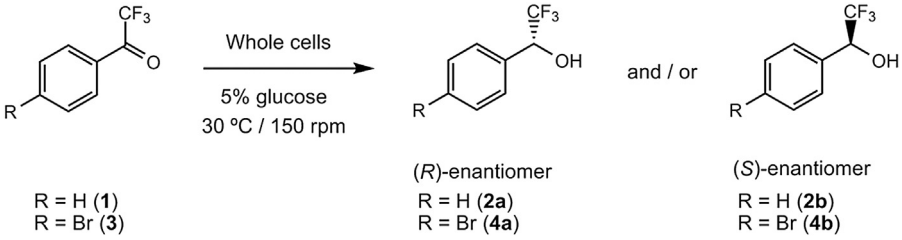
0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.12.036

In this work, we report the use of eight different microorganisms (six yeasts strains and two filamentous fungi strains) for the asymmetric reduction of 2,2,2-trifluoroacetophenone (**1**) and 4′-Br-2,2,2-trifluoroacetophenone (**3**) (Scheme 2). Different concentrations of substrate were studied using free cells and immobilized cells (only yeasts strains) under batch and continuous flow conditions.



Scheme 2. Reduction of 2,2,2-trifluoroacetophenone (**1**) and 4′-Br-2,2,2-trifluoroacetophenone (**3**) using whole cells microorganisms.

2. Results and discussion

In the first step of this work, we tested eight different microorganisms (six yeasts strains and two filamentous fungi strains) for the asymmetric reduction of 2,2,2-trifluoroacetophenone (**1**) and 4′-Br-2,2,2-trifluoroacetophenone (**3**) using free cells and substrate concentrations of 7.2 and 14.4 mM (final concentration in 5% glucose solution). According to the results showed in Table 1, all microorganisms were able to reduce completely 2,2,2-trifluoroacetophenone (**1**), and some microorganisms, such as *Geotrichum candidum* and *Aspergillus niger* provided the *S*-enantiomer (**2b**) in enantiomeric excess higher than 90%. *Kluyveromyces marxianus* and *Rhodotorula minuta* were able to produce the *S*-enantiomer (**2b**) in 50% and 45% ee, respectively, while lower ee were obtained with *Hansenula* sp. (24%) and *Candida* sp. (29%). *Mucor ramannianus* and *Rhodotorula rubra* furnished the *R*-enantiomer (**2a**) in 13% and 45% ee, respectively. Interestingly, for some microorganisms the switch from hydrogen to bromine in the 4′ position leads to decreased conversions compared to the 2,2,2-trifluoroacetophenone (**1**). *G. candidum*, *R. minuta*, and *R. rubra* were able to reduce completely 4′-Br-2,2,2-trifluoroacetophenone (**3**). *G. candidum* provided the *S*-enantiomer in 96% ee, while *R. minuta* and *R. rubra* provided the *S*-enantiomer and *R*-enantiomer in 50% and 35% ee, respectively. All reactions were carried out for 24 h at 30 °C under orbital shaking speed of 150 rpm in the orbital shaker.

In order to improve the method, yeasts were immobilized in calcium alginate spheres and tested for the reduction of acetophenone **1** and **3**.[21–25] The immobilization can influence enantiomeric excess and conversion level,[26] however according to the results showed in Table 3, immobilized *Candida* sp., *G. candidum*, *R. minuta*, and *R. rubra* were able to completely reduce 2,2,2-trifluoroacetophenone (**1**). On the other hand, reduction with immobilized *Hansenula* sp. and *K. marxianus* presented lower conversions in comparison to free whole cells.

Considering the 4′-Br-2,2,2-trifluoroacetophenone (**3**), immobilized *Candida* sp., *G. candidum*, *R. minuta*, and *R. rubra* were able to reduce it preserving the same conversion achieved by using free whole cells. Immobilized *Hansenula* sp. and *K. marxianus* increased conversions compared with whole cells. All immobilized microorganisms preserved the enantiomeric excess achieved by using of free whole cells.

Based on Table 3, high ee were achieved for the reduction of 2,2,2-trifluoroacetophenone (**1**) and 4′-Br-2,2,2-trifluoroacetophenone (**3**) by using immobilized cells of *G. candidum*. Then, we decided to increase the substrate concentration to 14.4 mM for this microorganism. The immobilized cells of *G. candidum* were able to reduce the acetophenone **1** with high conversions and enantiomeric excess while for the reduction of acetophenone **3**, the conversion decreased to 56%.

Based on the results obtained on the bioreduction of acetophenones under bath conditions by using immobilized *G. candidum*

Table 1
Bioreduction of 2,2,2-trifluoroacetophenone (**1**) and 4′-Br-2,2,2-trifluoroacetophenone (**3**) by using free cells (with substrates in a 7.2 mM final concentration)

Microorganism	2,2,2-Trifluoroacetophenone (**1**)			4′-Br-2,2,2-trifluoroacetophenone (**3**)		
	Conversion (%)	ee (%)	Space-time yield [g/(L d)]	Conversion (%)	ee (%)	Space-time yield [g/(L d)]
A. niger	>99	90 (*S*)	127	79	94 (*S*)	145
Candida sp.	>99	29 (*S*)	127	62	1 (*S*)	114
G. candidum	>99	91 (*S*)	127	>99	96 (*S*)	183
Hansenula sp.	>99	24 (*S*)	127	39	74 (*S*)	72
K. marxianus	>99	50 (*S*)	127	68	18 (*S*)	125
M. ramannianus	>99	13 (*R*)	127	91	1 (*R*)	167
R. minuta	>99	45 (*S*)	127	>99	50 (*S*)	183
R. rubra	>99	28 (*R*)	127	>99	35 (*R*)	183

Reaction condition: Substrates were previously dissolved in 1 mL of ethanol and added to a mixture of microorganisms and 5% glucose solution to give 50 mL of a solution with final substrate concentration of 7.2 mM. Reactions were carried out for 24 h at 30 °C under a shaking speed of 150 rpm in the orbital shaker. Products were analyzed by (chiral) gas chromatography (GC).

Based on the table above, higher ee were achieved for the reduction of 2,2,2-trifluoroacetophenone (**1**) and 4′-Br-2,2,2-trifluoroacetophenone (**3**) by using *G. candidum* and *A. niger*. Then, in order to enhance the productivity of the reduction with and based on previous results obtained by our group on the bioreduction of ketones in continuous flow with immobilized cells, we decided to move forward towards a continuous flow methodology for such transformation. For such, cells of *G. candidum* immobilized

Table 2
Bioreduction of 2,2,2-trifluoroacetophenone (**1**) and 4′-Br-2,2,2-trifluoroacetophenone (**3**) by using free cells (with substrates in a 14.4 mM final concentration)

Microorganism	2,2,2-Trifluoroacetophenone (**1**)			4′-Br-2,2,2-trifluoroacetophenone (**3**)		
	Conversion (%)	ee (%)	Space-time yield [g/(L d)]	Conversion (%)	ee (%)	Space-time yield [g/(L d)]
A. niger	96	91 (*S*)	243	8	96 (*S*)	29
G. candidum	>99	95 (*S*)	253	56	91 (*S*)	206

Reaction condition: Substrates were previously dissolved in 1 mL of ethanol and added to a mixture of microorganisms and 5% glucose solution to give 50 mL of a solution with final substrate concentration of 14.4 mM. Reactions were carried out for 24 h at 30 °C under a shaking speed of 150 rpm in the orbital shaker. Products were analyzed by (chiral) gas chromatography (GC).

Table 3
Bioreduction of 2,2,2-trifluoroacetophenone (**1**) and 4′-Br-2,2,2-trifluoroacetophenone (**3**) by immobilized cells (with substrates in a 7.2 mM final concentration)

Microorganism	2,2,2-Trifluoroacetophenone (**1**)			4′-Br-2,2,2-trifluoroacetophenone (**3**)		
	Conversion (%)	ee (%)	Space-time yield [g/(L d)]	Conversion (%)	ee (%)	Space-time yield [g/(L d)]
Candida sp.	>99	8 (*S*)	127	62	20 (*S*)	114
G. candidum	>99	96 (*S*)	127	>99	93 (*S*)	183
Hansenula sp.	68	43 (*S*)	86	76	12 (*S*)	140
K. marxianus	65	75 (*S*)	82	97	4 (*S*)	178
R. minuta	>99	20 (*S*)	127	97	61 (*S*)	178
R. rubra	>99	43 (*R*)	127	98	42 (*R*)	180

Reaction condition: Substrates were previously dissolved in 1 mL of ethanol and added to a mixture of microorganisms and 5% glucose solution to give 50 mL of a solution with final substrate concentration of 7.2 mM. Reactions were carried out for 24 h at 30 °C under a shaking speed of 150 rpm in the orbital shaker. Products were analyzed by (chiral) gas chromatography (GC).

in calcium alginate were packed in a glass column (Omnifit column; volume: 12.3 mL) for the bioreduction of acetophenone **3** under continuous flow conditions. We evaluated the substrate concentration (7.2 and 14.4 mM) and different residence time on the bioreduction of 4′-Br-2,2,2-trifluoroacetophenone (**3**). We decided for acetophenone **3** instead of acetophenone **1**, due to its potential as a building block for the interesting intermediates for the pharmaceutical industry and cascade cross-coupling reactions. According to the results showed on Table 4, using lower concentration of substrate (7.2 mM) at 60 min of residence time and flow rate of 45 μL/min, the *S*-enantiomer was achieved in 97% conversion and enantiomeric excess higher than 99%. Using higher concentration of substrate (14.4 mM) at 90 min of residence time and flow rate of 30 μL/min, conversion and enantiomeric excess were up to 99%.

Table 4
Bioreduction of 4′-Br-2,2,2-trifluoroacetophenone (**3**) in continuous flow by using immobilized cells of *G. candidum*

Final concentration of substrate (mM)	Residence time (min)	Flow rate (μL/min)	Conversion (%)	ee (%)	Space-time yield [g/(L d)]
7.2	30	90	88	>99 (*S*)	7695
	60	45	97	>99 (*S*)	4241
14.4	30	90	47	>99 (*S*)	8219
	90	30	>99	>99 (*S*)	5870

Reaction condition: Substrates were previously dissolved in 1 mL of ethanol and added to a mixture of microorganisms and 5% glucose solution to give a solution with final substrate concentration of 7.2 mM or 14.4. Immobilized cells of *G. candidum* were used to fill the column (Omnifit column; volume: 12.3 mL), which was heated at 30 °C. Products were analyzed by (chiral) gas chromatography (GC).

3. Conclusion

In conclusion we presented a highly efficient whole cell biocatalyzed reduction of trifluoroacetophenone **1** and **3**. In the reaction systems studied high conversion and good to excellent enantiomeric excess (>99%) for the reduction of **1** were observed for the *S*-enantiomer after 24 h using *G. candidum*, *A. niger* cells. In the case of **3**, only *G. candidum* presented high conversion and excellent enantiomeric excess. Upon immobilization *G. candidum* cells were essayed under continuous flow conditions and the same conversion and enantiomeric excesses could be observed with the decrease in reaction time for 90 min.

4. Experimental

4.1. Materials

2,2,2-Trifluoroacetophenone, 4′-Br-2,2,2-trifluoroacetophenone, and (*R*)-2,2,2-trifluoro-1-phenylethanol were purchased from Sigma Aldrich and racemates were obtained via $NaBH_4$ reduction. The products were analyzed by ^1H and ^{13}C NMR.

*4.1.1. rac-2,2,2-Trifluoro-1-phenylethanol (**2**).* ^1H NMR (300 MHz, $CDCl_3$, TMS) δ (ppm): 2.83 (s, 1H, O*H*); 4.98–5.05 (q, 1H, *J*=6.7 Hz, H1); 7.40–7.50 (m, 5H, H2′, H3′, H4′, H5′, H6′).

^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ (ppm): 72.4, 72.8, 73.2, 73.7 (q, *J*=31.9 Hz, *C*OH); 122.6 and 126.4 (d, *J*=279.7 Hz, *C*F_3); 127.7 (C2′ and C6′); 128.9 (C4′); 129.8 (C3′ and C5′); 134.3 (s, C1′).

*4.1.2. rac-1-(4-Bromophenyl)-2,2,2-trifluoroethanol (**4**).* ^1H NMR (300 MHz, $CDCl_3$, TMS) δ (ppm): 2.78 (s, 1H, O*H*); 5.00 (q, 1H, *J*=6 Hz, H1); 7.37 (d, 2H, *J*=9 Hz, H3′ and H5′); 7.56 (m, 2H, H2′ and H6′).

^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ (ppm): 72.5 (q, *J*=31.5 Hz, *C*OH); 118.6, 122.3, 126.0 and 129.8 (q, *J*=280.5 Hz, *C*F_3); 128.0 (C4′); 129.3 (C2′ and C6′); 132.1 (C3′ and C5′); 133 (d, C1′).

Mp=52.5–53.6 °C (Stuart™ melting point apparatus SMP3) (mp=55–56 °C).[2]

4.2. Microorganisms, media, growth conditions, and biotransformation

K. marxianus, *Hansenula* sp., *G. candidum*, *Candida* sp., *R. rubra*, *R. minuta*, and filamentous fungi, *A. niger*, *Trichoderma harzianum*, and *M. ramannianus*, belong to the collection of the 'Departamento de Engenharia Bioquímica, Escola de Química, UFRJ'. Cells were allowed to grow for 48 h at 30 °C under a shaking speed of 150 rpm in the orbital shaker in a medium containing 1% glucose, 0.5% yeast extract, 0.5% peptone, 0.1% $(NH_4)_2SO_4$, and 0.1% $MgSO_4 \cdot 7H_2O$. After

that period, they were harvested by centrifugation, re-suspended in distilled water and used for the reaction. After centrifugation, the cells (12 g/L, dried weight) were added to the 250 mL Erlenmeyer containing: 5% glucose in a final volume of 50 mL distilled water. After 30 min of addition of the microorganisms, the substrate (previously dissolved in 1 mL of ethanol) was added to the 50 mL of the mixture to give a final solution with substrate concentration of 7.2 mM or 14.4 mM. The reaction was carried out for 24 h at 30 °C under a shaking speed of 150 rpm in the orbital shaker. After 24 h, the mixture was centrifuged to separate the cells and the liquid phase was extracted with ethyl acetate. The organic phase was dried (anhydrous Na_2SO_4), filtered, and concentrated under vacuum. Products were analyzed by (chiral) gas chromatography (GC).

4.3. Immobilized cells

After the growing process described above, the cells (12 g/L, dry weight) were centrifuged and the precipitate was re-suspended in 3 mL of distilled water to obtain a cell-suspension. Then, a 1.5% w/v sodium alginate aqueous solution in distilled water (final volume of 20 mL) was added to the cell-suspension, and the mixture (cell-suspension and sodium alginate aqueous solution) was dropped into a $CaCl_2$ aqueous solution (0.1 M), forming calcium alginate spheres. Spheres were filtered and washed with distilled water. After that, the spheres were added to the 250 mL Erlenmeyer containing 50 mL of a 5% glucose solution with substrate concentration of 7.2 or 14.4 mM (substrates were previously dissolved in 1 mL of ethanol before they were added to the 5% glucose solution). The reaction was carried out for 24 h at 30 °C under a shaking speed of 150 rpm in the orbital shaker. After 24 h, the mixture was filtered to separate the cells and the liquid phase was extracted with ethyl acetate. The organic phase was dried (anhydrous Na_2SO_4), filtered, and concentrated under vacuum. Products were analyzed by (chiral) gas chromatography (GC).

4.4. Continuous flow (Asia flow reactor)

after the immobilization, the *G. candidum* spheres (6 g/L, dry weight) were used to fill the column (Omnifit column; volume: 12.3 mL) heated at 30 °C and a 5% glucose solution was pumped through it. After that, a 5% glucose solution with substrate concentration of 7.2 or 14.4 mM were pumped through the column at different flow rates (flow rates: 30, 45, and 90 μL/min; which correspond to 90, 60, and 30 min residence times, respectively). The complete reaction mixture was collected and extracted with ethyl acetate. The organic phase was dried (anhydrous Na_2SO_4), filtered, and concentrated under vacuum. Products were analyzed by (chiral) gas chromatography (GC).

4.5. GC-FID Analysis

Products were analyzed by (chiral) gas chromatography (GC) on column CYCLODEXB (29 m×0.25 mm×0.25 μm).

2,2,2-Trifluoroacetophenone (**1**): after 5 min at 100 °C the temperature was increase in 5 °C/min to 120 °C and kept at 120 °C for 9 min. The elution order for 2,2,2-trifluoroacetophenone (**1**) was: 2,2,2-trifluoroacetophenone (**1**) (t_R=2.6 min), (*S*)-enantiomer (**2b**) (t_R=15.0 min) and (*R*)-enantiomer (**2a**) (t_R=15.5 min).

4′-Br-2,2,2-trifluoroacetophenone (**3**): after 5 min at 100 °C the temperature was increase in 40 °C/min to 140 °C and kept 140 °C for 24 min. The elution order for 4′-Br-2,2,2-trifluoroacetophenone (**3**) was: 2,2,2-trifluoroacetophenone (**3**) (t_R=6.5 min), (*S*)-enantiomer (**4b**) (t_R=25.9 min) and (*R*)-enantiomer (**4a**) (t_R=27.0 min).

4.6. Polarimeter

(*R*)-1-(4-Bromophenyl)-2,2,2-trifluoroethanol (**4a**): $[\alpha]_D^{23}$ −37.4° (*c* 1.06 Ethanol) (literature $[\alpha]_D^{20}$ −27.5°).[2] Optical rotations were measured from $CHCl_3$ solutions using a JASCO DIP-370 polarimeter at the sodium D line (589 nm) operating at room temperature and compared to literature.

Acknowledgements

Financial support from FAPERJ, FINEP, CAPES, and CNPq is acknowledged.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.12.036.

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