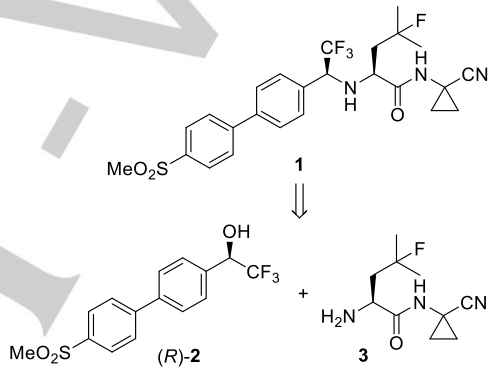
Chemoenzymatic synthesis of an Odanacatib precursor through a Suzuki-Miyaura cross coupling and bioreduction sequence

Daniel González-Martínez,[a] Vicente Gotor[a] and Vicente Gotor-Fernández*[a]

Abstract: A series of 1-aryl-2,2,2-trifluoroethanones has been chemically synthesized to later study their bioreduction using stereocomplementary alcohol dehydrogenases (ADHs). Satisfyingly, (*R*)-alcohols were obtained in high conversions and selectivities using the ADH from *Ralstonia* species and the one from *Rhodococcus ruber*, while the (*S*)-enantiomers were independently produced using the ADH from *Lactobacillus brevis* and the commercially available evo-1.1.200. In the search for a stereoselective route towards the Odanacatib, an orally bioavailable and selective inhibitor of Cathepsin K, the development of a sequential methodology combining a palladium-catalyzed cross coupling between 1-(4-bromophenyl)-2,2,2-trifluoroethanone and 4-(methylsulfonyl)phenylboronic acid in aqueous medium with the bioreduction of the resulting 2,2,2-trifluoro-1-(4'-(methylsulfonyl)-[1,1'-biphenyl]-4-yl)ethanone has been extensively studied. Finally, the desired (*R*)-2,2,2-trifluoro-1-(4′-(methylsulfonyl)-[1,1′-biphenyl]-4-yl)ethanol was obtained in enantiomerically pure form and 85% yield with a 128 g L^{-1} d^{-1} productivity following a sequential approach.

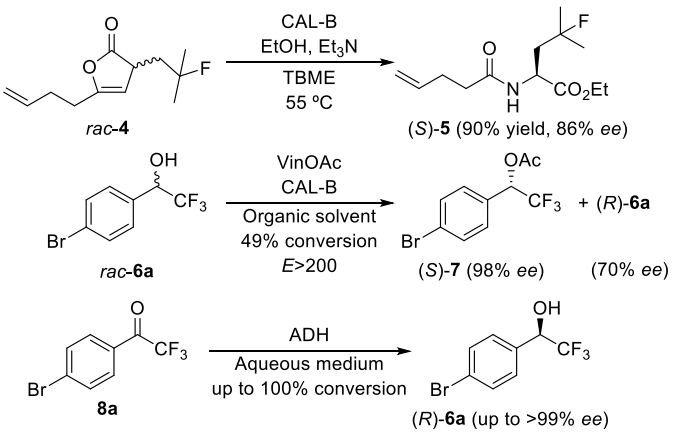
Introduction

Odanacatib (MK-0822, **1**, Scheme 1) is an orally bioavailable and selective inhibitor of Cathepsin K, a cysteine protease abundantly expressed in osteoclasts that are the cells responsible for bone resorption.[1] Nowadays the correct expression of Cathepsin K is considered a central therapeutic target for the treatment of osteoporosis. Odanacatib was developed by Merck and Co., and its potential was demonstrated by significantly reducing risks of hip and spine fractures. Its application and safety has been largely studied,[2] and after analysis of major adverse cardiovascular events, it was concluded that the drug increases the risk of strokes among patients. Therefore, the company decided in 2016 to discontinue its development and deny seeking the regulatory approval for its use. However, the search for new Odanacatib applications such as anti-hookworm drug,[3] and the synthesis of Odanacatib analogues for the development of improved Cathepsin K inhibitors[4] continues nowadays attracting research interests.
Different studies have disclosed the total synthesis of Odanacatib,[5] but mainly the preparation of adequate precursors has been extensively reported. From the latest, enzyme catalysis plays a key role for the preparation of (*R*)-2,2,2-trifluoro-1-[4′-(methylsulfonyl)-(1,1′-biphenyl)-4-yl]ethanol (**2**) and aminoamide **3**, which are valuable Odanacatib fragments (Scheme 1). For instance, an elegant dynamic kinetic resolution of azlactone **4** has been reported for the large-scale production of the key fluoroleucine intermediate (*S*)-**5** in 90% yield and 86% *ee*, using a column reactor process (Scheme 2 top).[6] Further optimization of the biocatalyst and the reaction conditions has allowed the isolation of the product in 95% yield and 88% *ee* when attempting the reaction at a 100 kg scale.[7]



Scheme 1. Structure of and general retrosynthetic analysis of Odanacatib.

Years later, Porto and coworkers reported the classical kinetic resolution of 1-(4-bromophenyl)-2,2,2-trifluoroethanol through an acetylation procedure under shaking or microwave irradiation conditions using vinyl acetate (VinOAc) as acyl donor in toluene (Scheme 2 middle).[8] However, the selective bioreduction of 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**) has focused the interest of different research groups by using different alcohol dehydrogenases (ADHs, Scheme 2 bottom).[9]



Scheme 2. Biocatalytic reactions for the production of Odanacatib fragments by using lipases or ADHs.

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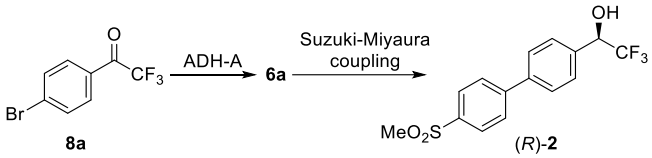
In recent years, the combination of metal- or enzyme-catalyzed carbon-carbon bond formation reactions with biotransformations have opened up new possibilities for the development of sequential stereoselective processes.[10] In this context, the organocatalytic aldol reaction is nowadays fully expanded and its combination with ADH-mediated reactions has been probed.[11] In this context, palladium-catalyzed reactions have attracted great attention for the development of chemoenzymatic strategies giving access to a wide variety of products by considering Suzuki,[12] Heck[13] or Wacker processes,[14] among others.[15] In fact, de Souza and co-workers have reported the bioreduction of 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**) catalyzed by the ADH from *Rhodococcus ruber* (ADH-A) and a later Suzuki-Miyaura cross coupling in continuous flow for the synthesis of the Odanacatib precursor (*R*)-2,2,2-trifluoro-1-(4′-(methylsulfonyl)-[1,1′-biphenyl]-4-yl)ethanol (**2**) that was recovered with excellent stereoselectivity and 73% crude yield (Scheme 2).[16]



Scheme 2. Biocatalytic reactions for the production of Odanacatib fragments by using lipases and ADHs.

Herein, we have focused our efforts in the exploration of new synthetic possibilities towards (*R*)-2,2,2-trifluoro-1-(4′-(methylsulfonyl)-[1,1′-biphenyl]-4-yl)ethanol (**2**). Initially, different ADHs will be screened for the asymmetric synthesis of 1-(4-bromophenyl)-2,2,2-trifluoroethanol (**6a**), extending later the study to other 1-aryl-2,2,2-trifluoroethanones to demonstrate their ability to produce valuable organofluorinated chiral alcohols. Next, the Suzuki-Miyaura cross coupling between 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**) and the corresponding boronic acid will be studied in order to obtain a ketone precursor suitable to be stereoselective reduced towards (*R*)-**2**. Finally, both chemical coupling and enzymatic-catalyzed reduction will be exhaustively analyzed and optimized trying to develop a cascade strategy for the synthesis the target Odanacatib precursor.

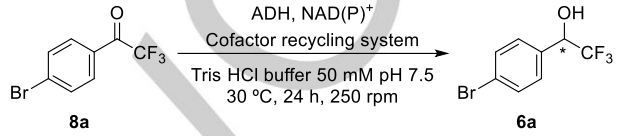
Results and Discussion

Bioreduction of 1-(4-bromophenyl)-2,2,2-trifluoroethanone

1-(4-Bromophenyl)-2,2,2-trifluoroethanone (**8a**) was selected as model substrate to study the behavior of a representative panel of ADHs (Table 1), most of them over-expressed in *E. coli* and employed as freeze-dried whole cells such as the ones from *Rhodococcus* species (ADH-A),[17] *Thermoanaerobacter* species (ADH-T),[18] *Thermoanaerobacter ethanolicus* (TeS-ADH)[19] and *Ralstonia* species (Ras-ADH),[20] which act with Prelog selectivity, while the ones from *Lactobacillus brevis* (Lb-ADH)[21] and *Sphingobium yanoikuyae* (Sy-ADH)[22] were used as anti-Prelog enzymes, including also in the screening the commercially available evo-1.1.200.[23]

Five out of the seven enzymes led to the desired alcohol **6a** with optical purities >95% *ee* (entries 1, 2, 4, 5 and 7), including the ADH-A already reported in the literature for this bioreduction.[16] Therefore, ADHs from *Rhodococcus ruber*, *Thermoanaerobacter* species, *Ralstonia* species, *Lactobacillus brevis* and evo-1.1.200 were selected to monitor the reaction progress over the time, finding quantitative conversions and total selectivities when using ADH-A, ADH-T, Ras-ADH and evo-1.1.200 after only 1 h.

Table 1. Enzymatic reductions of 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**) using different ADHs after 24 h at 30 ºC and 250 rpm.[a]



Entry	ADH	*c* (%)[b]	*ee* (%)[b,c]
1	*E. coli*/ADH-A	>99	99 (*R*)
2	*E. coli*/ADH-T	>99	>99 (*R*)
3	*E. coli*/TeS-ADH	40	72 (*R*)
4	*E. coli*/Ras-ADH	>99	>99 (*R*)
5	*E. coli*/Lb-ADH	>99	96 (*S*)
6	*E. coli*/Sy-ADH	12	69 (*S*)
7	evo-1.1.200	>99	>99 (*S*)

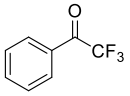
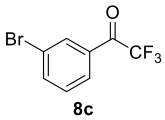
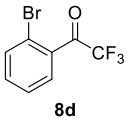
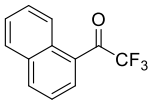
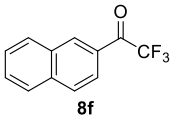
[a] Reaction conditions: Ketone **8a** (0.010 mmol, 2.5 mg), ADH (15 mg for *E. coli* overexpressed ADHs or 0.06 mg for evo-1.1.200), $NAD(P)^+$ (1 mM), isopropanol (25 µL) except for Ras-ADH [glucose (60 mM) and GDH (5 U)] as cofactor regeneration system in Tris·HCl buffer (50 mM, pH 7.5, 600 µL) for 24 h at 30 ºC and 250 rpm. [b] Conversion and enantiomeric excess values measured by GC (see Supporting Information for additional information). [c] Absolute configuration of the alcohol appears in brackets.

Table 2. Bioreductions of 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**) for the production of alcohol enantiopure (*R*)-**6a** without external addition of nicotinamide cofactors.[a]

Entry	ADH	t (h)	[**8a**] (mM)	*c* (%)[b]
1	*E. coli*/ADH-A	1	20	76
2	*E. coli*/ADH-A	16	20	>99
3	*E. coli*/Ras-ADH	1	20	74
4	*E. coli*/Ras-ADH	16	20	82
5	*E. coli*/ADH-A	0.5	100	50
6	*E. coli*/ADH-A	1	100	60
7	*E. coli*/ADH-A	16	100	85

[a] Reaction conditions: Ketone **8a** (20 or 100 mM), ADH (1:1 w/w enzyme:ketone ratio), isopropanol (25 µL) for ADH-A or glucose (60 mM) and GDH (5 U) for Ras-ADH in Tris·HCl buffer (50 mM, pH 7.5, 600 µL) at 30 ºC and 250 rpm. [b] Conversion values measured by GC (see Supporting Information for additional information).

Table 3. ADH-catalyzed reductions of ketones **8b**-**f** (20 mM) at 30 ºC and 250 rpm.[a]

Entry	Ketone	ADH	External cofactor	t (h)	c (%)[b]	*ee* (%)[b,c]
1	 **8b**	ADH-A	----	16	92	>99 (*R*)
2		ADH-T	----	16	69	>99 (*R*)
3		Ras-ADH	----	16	>99	97 (*R*)
4		Lb-ADH	----	16	>99	>99 (*S*)
5		evo-1.1.200	NAD^+	16	>99	>99 (*S*)
6	 **8c**	ADH-A	----	1	79	>99 (*R*)
7		Ras-ADH	----	1	54	>99 (*R*)
8		Lb-ADH	----	1	26	10 (*S*)
9		evo-1.1.200	NAD^+	1	74	>99 (*S*)
10	 **8d**	ADH-A	----	17	97	>99 (*R*)
11		Ras-ADH	----	17	>99	>99 (*R*)
12		Lb-ADH	----	17	>99	94 (*R*)
13		evo-1.1.200	NAD^+	17	96	>99 (*S*)
14	 **8e**	ADH-A	----	24	>99	>99 (*R*)
15		Ras-ADH	----	24	>99	99 (*R*)
16		Lb-ADH	----	24	19	71 (*R*)
17		evo-1.1.200	NAD^+	24	>99	>99 (*S*)
18	 **8f**	ADH-A	----	24	>99	98 (*R*)
19		Ras-ADH	----	24	>99	92 (*R*)
20		Lb-ADH	----	24	19	92 (*S*)
21		evo-1.1.200	NAD^+	24	>99	>99 (*S*)

[a] Reaction conditions: Ketone **8b**-**f** (0.012 mmol), ADH (6 mg for *E. coli* overexpressed ADHs or 0.02 mg for evo-1.1.200), NAD^+ (1 mM for evo-1.1200), isopropanol (25 µL) except for Ras-ADH [glucose (60 mM) and GDH (5 U)] as cofactor regeneration system in Tris·HCl buffer (50 mM, pH 7.5, 600 µL at 30 ºC and 250 rpm. [b] Conversion and enantiomeric excess values measured by GC and/or HPLC (see Supporting Information). [c] Absolute configurations of **6b**-**f** in brackets.

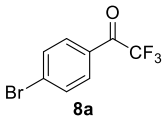
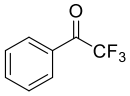
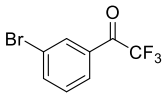
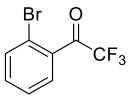
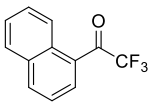
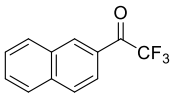
A key issue in the development of redox biotransformations is the external addition of nicotinamide cofactors, which can be avoided by using lyophilized whole cells of a host such as *E. coli* that contains the overexpressed enzyme.[24] For that reason, bioreductions were attempted without the addition of NAD^+ or $NADP^+$ using two ADHs that employed different cofactor regeneration systems: ADH-A and Ras-ADH (Table 2). In this case, the reaction at 20 mM substrate concentration went to completion after 16 h for ADH-A (entries 1 and 2), while an 82% conversion was attained for Ras-ADH (entries 3 and 4). Trying to improve the productivity of the system, the ADH-A catalyzed reaction was run at 100 mM substrate concentration, reaching 85% conversion of the alcohol (*R*)-**4a** after 16 h, fact that made advisable the external addition of nicotinamide cofactors when developing the asymmetric reduction at high substrate concentrations.

Bioreduction of 1-aryl-2,2,2-trifluoroethanones

At this point, the versatility of the ADHs was tested in the reduction of other trifluoroethanones **8b**-**f** in order to explore the substrate scope of the selected redox enzymes (Table 3). High to excellent selectivities were found for the production of the corresponding (*R*)-alcohols when using the ADH-A and the Ras-ADH (92->99% *ee*), while the evo-1.1.200 led in all five cases to the enantiopure antipodes (*S*)-**6b**-**f**. Interestingly, a dramatic change in the selectivity was found for the Lb-ADH depending on the starting ketone (entries 4, 8, 12, 16 and 20).

All this opened the possibility to explore the semi-preparative bioreductions of the ketones **8a**-**f** under optimized conditions (20-30 mg of substrate), leading to excellent isolated yields of enantiopure (*R*)- or (*S*)-alcohols depending on the enzyme of choice, Ras-ADH or evo-1.1.200 respectively, after a simple liquid-liquid extraction protocol (Table 4).

Table 4. Semi-preparative bioreductions of ketones **8a**-**f** (200 mM) at 30 ºC and 250 rpm.

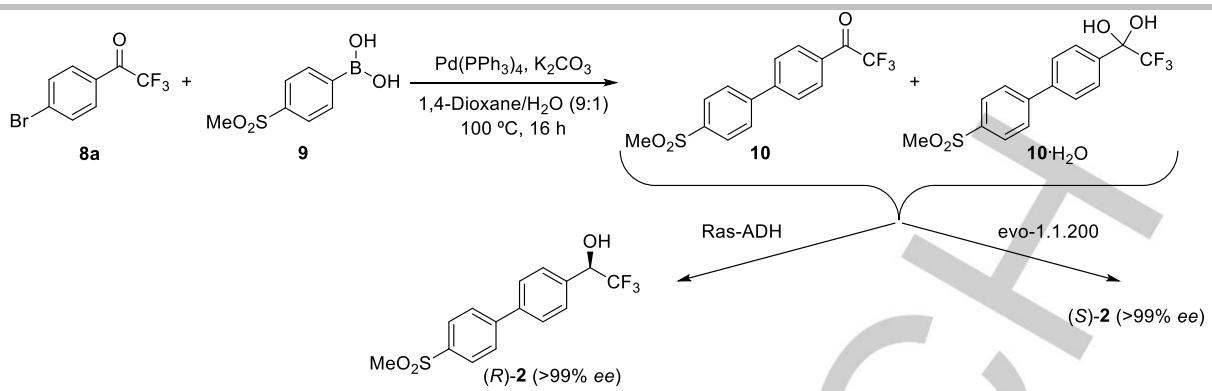
Entry	Ketone	ADH	t (h)	c (%)[a]	Yield (%)[b]	*ee* (%)[a,c]
1	 **8a**	Ras-ADH (1:1.5)[d]	0.3	>99	99	>99 (*R*)
2		evo-1.1.200 (0.1 mg)[e]	4	>99	99	>99 (*S*)
3	 **8b**	Ras-ADH (1:2)[d]	5	>99	99	99 (*R*)
4		evo-1.1.200 (0.1 mg)[e]	20	>99	99	>99 (*S*)
5	 **8c**	Ras-ADH (1:2)[d]	5	>99	99	>99 (*R*)
6[f]		evo-1.1.200 (0.2 mg)[e]	15	>99	98	>99 (*S*)
7	 **8d**	Ras-ADH (1:2)[d]	5	>99	95	>99 (*R*)
8		evo-1.1.200 (0.5 mg)[e]	96	86	n.d.	>99 (*S*)
9[g]		evo-1.1.200 (0.5 mg)[e]	50	99	98	>99 (*S*)
10	 **8e**	Ras-ADH (1:2)[d]	5	>99	99	99 (*R*)
11		evo-1.1.200 (0.1 mg)[e]	20	>99	99	>99 (*S*)
12	 **8f**	Ras-ADH (1:1.5)[d]	5	>99	99	92 (*R*)
13		ADH-A (1:2)[h]	20	>99	99	98 (*R*)
14		evo-1.1.200 (0.2 mg)[e]	20	>99	99	>99 (*S*)

[a] Conversion and enantiomeric excess values measured by GC and/or HPLC (see Supporting Information for additional information). [b] Yields of alcohol after liquid-liquid extraction with EtOAc (3 x 5 mL). n.d.: Not determined. [c] Absolute configuration of the alcohol appears in brackets. [d] Reaction conditions: **8a-f** (0.12 mmol, 200 mM), Ras-ADH (ratio ADH:ketone in weight), $NADP^+$ (1 mM), glucose (600 mM, 65 mg), GDH (25 U, 0.5 mg) in 1,4-dioxane (60 µL, 10% v/v) and Tris·HCl buffer (50 mM, pH 7.5, 540 µL) at 30 ºC and 250 rpm. [e] Reaction conditions: **8a-f** (0.12 mmol, 200 mM), evo-1.1.200 (0.1-0.5 mg), NAD^+ (1 mM), $MgCl_2$ (2 mM), isopropanol (60 µL, 10% v/v) in Tris·HCl buffer (50 mM, pH 7.5, 540 µL) at 30 ºC and 250 rpm. [f] A mixture of 1,4-dioxane (60 µL, 10% v/v) and isopropanol (30 µL, 5% v/v) was employed. [g] The reaction was carried out at 100 mM substrate concentration. [h] NAD^+ was used as cofactor, 2.5% v/v of isopropanol for cofactor recycling purposes and 7.5% v/v of 1,4-dioxane as cosolvent.

Monitoring the biotransformations over time, and after optimization of the conditions in terms of enzyme loading, the reduction of 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**, entries 1 and 2), 1-phenyl-2,2,2-trifluoroethanone (**8b**, entries 3 and 4) and 1-(3-bromophenyl)-2,2,2-trifluoroethanone (**8c**, entries 5 and 6) were successfully achieved between 20 min and 20 h. A slow kinetic was observed with the ortho-substituted 1-(2-bromophenyl)-2,2,2-trifluoroethanone (**8d**, entries 7 and 8) requiring for the evo-1.1.200 a lower substrate concentration of 100 mM to reach 99% conversion after prolonged reaction times (50 h, entry 9). Interestingly, 2,2,2-trifluoro-1-(naphtalen-1-yl)ethanone (**8e**) and 2,2,2-trifluoro-1-(naphtalen-2-yl)ethanone (**8f**) were completely reduced and with total selectivity after 5 h for the Ras-ADH (entries 10 and 12) and 20 h for the evo-1.1.200 (entries 11 and 14), finding with the latest substrate **8f** a better selectivity with the ADH-A for the production of the (*R*)-**6f** (entry 13).

Synthesis of an Odanacatib precursor through a palladium-catalyzed cross-coupling and bioreduction sequence

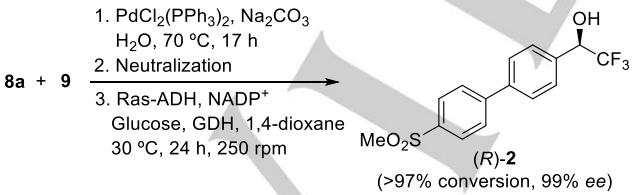
At this time, the Odanacatib diaryl precursor **10** was synthesized by a cross-coupling reaction between 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**) and 3 equivalents of boronic acid **9** catalyzed by $Pd(PPh_3)_4$ (5 mol%) in a mixture of 1,4-dioxane and water (9:1 v/v) at 100 ºC (Scheme 3). The analysis of the reaction crude by ^{1}H-NMR showed that the product appears mostly in its hydrated form (**10**·H_2O), as a geminal diol, thanks to the greater stability conferred by the combined electronic effects of the trifluoromethyl group and the sulfonyl group.[25] However, this did not prove to be a drawback for the Ras-ADH and the evo-1.1.200, finding that it was possible to independently obtain the two enantiomers of alcohol **2** (Scheme 3). Due to the low solubility of the substrate, the reactions were carried out at a 20 mM concentration, studying the behavior of different cosolvents such as dimethylsulfoxide, 1,4-dioxane, tetrahydrofuran and toluene. The best results were obtained using a 10% v/v ratio of 1,4-dioxane, reaching a complete conversion towards the synthesis of enantiopure (*R*)-**2** and (*S*)-**2** using Ras-ADH or evo-1.1.200, respectively.



Scheme 3. Synthesis of the Odanacatib diaryl precursor **10** obtained as a mixture with its hydrated form **10**·H_2O, and subsequent stereoselective bioreduction using complmentary stereoselective enzymes Ras-ADH and evo-1.1200.

Once RasADH was identified as a suitable biocatalyst for the asymmetric reduction of **10** towards the pursued alcohol enantiomer, the next step was to explore the possibility of carrying out the palladium catalyzed coupling reaction in a compatible medium with the reductase. For this purpose, the procedure described by Gröger and co-workers was followed,[12a] where 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**) and boronic acid **9** were used in stoichiometric amounts at 33 mM concentration, employing in this case $PdCl_2(PPh_3)_2$ as catalyst (2 mol%) and water as solvent in the presence of 10 equivalents of sodium carbonate. Satisfactorily, ketone **10** was obtained in 95% yield, precipitating in the reaction medium as a white solid with excellent purity after isolation through a simple filtration.

Exploring the two-step sequential process of palladium-catalyzed Suzuki-Miyaura cross coupling followed by a Ras-ADH-catalyzed bioreduction, the reaction was carried out in stochiometric amounts of **8a** and **9** in water (Scheme 4), neutralizing the pH of the resulting cross-coupling reaction medium with an aqueous HCl 1 M solution that enables a proper enzymatic activity. The addition of Ras-ADH (2:1 w/w enzyme *vs* **10**), $NADP^+$ (1 mM), glucose (100 mM), GDH (15 U) and 1,4-dioxane (100 µL) as cosolvent to solubilize the ketone intermediate led to the formation of the alcohol (*R*)-**2**, that was isolated in enantiopure form and complete conversion.



Scheme 4. Sequential palladium-catalyzed Suzuki-Miyaura cross coupling/ Ras-ADH bioreduction for the synthesis of Odanacatib alcohol precursor (*R*)-**2**.

Optimization of the sequential process towards alcohol (*R*)-2

At this point, the avoidance of the intermediate neutralization step was attempted by employing different tris(hydroxymethyl)aminomethane (Tris) or phosphate (KPi) buffers at pH 7.5 in the cross-coupling reaction (Table 5). The Tris salt was found to inactivate the palladium catalyst reaching a 50% conversion when a 50 mM buffer was used (entry 1), while total inactivation was observed when increasing it up to 1.0 M (entry 2). On the contrary, the use of a KPi buffer led to higher conversions (entires 3-5), achieving the complete transformation of the substrate in a 1 M buffer. This is due to the need to maintain a slightly basic pH for the reaction to proceed, so KPi solutions of 50 and 100 mM do not have sufficient regulatory capacity to neutralize the acid formed, obtaining in these cases a final pH of the solution between 5 and 6. Unfortunately, the use of 1,4-dioxane as cosolvent, used to improve the solubilization of the ketone intermediate **10**, resulted incompatible with the cross-coupling reaction.

Table 5. Suzuki-Miyaura cross-coupling reactions of **8a** and **9** in stoichiometric amounts using $PdCl_2(PPh_3)_2$ (2 mol%) in buffer pH 7.5 after 24 h.[a]

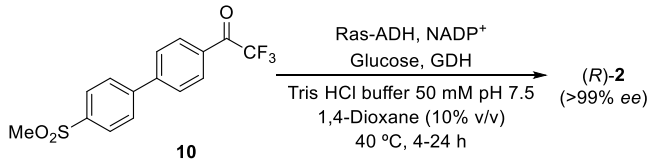
Entry	Buffer (mM)	T (ºC)	*c* (%)[a]
1	Tris (50)	70	50
2	Tris (1000)	70	<1
3	KPi (50)	30	78
4	KPi (100)	30	86
5	KPi (1000)	30	>99

[a] Conversion values measured by GC analyses of the reaction crudes (see Supporting Information for additional information).

After optimization of the reaction conditions it was possible to perform both steps in a sequential manner at the same temperature (40 ºC) by using a KPi buffer 1 M pH 7.5. In this manner, the Pd-catalyzed cross-coupling went to completion after 20 h, and then the Ras-ADH (1:2.5 enzyme *vs* **10**) among with the cofactor, its regeneration system and the cosolvent were added, isolating the enantiopure alcohol (*R*)-**2** after additional 4 h in a 97% global yield. Unfortunately, a concurrent approach remained unfeasible since remarkable inactivation of both the palladium catalyst, by the enzymatic crude, and of the ADH, due to the presence of the boronic acid **9**, were observed.

The next step was trying to improve the productivity of the catalytic system by working under high substrate concentrations, firstly studying the bioreduction process. Thus, moving from ketone concentrations in the ADH-catalyzed reactions between 33 mM to up to 800 mM, high to excellent conversions were observed (Table 6), attaining complete conversion even at 400 mM of **10** (entry 3). A 15% of starting material was recovered after a liquid-liquid extraction in the 800 mM reaction (entry 4) due to ketone solubility issues in the reaction medium. Interestingly, similar results were obtained at 30 ºC, while a decrease in the enzyme activity was observed at 60 ºC (data not shown).

Table 6. Bioreduction of **10** at different ketone concentrations.[a]



Entry	[**10**] (mM)	Ras-ADH[a]	t (h)	*c* (%)[b]
1	100	1:2	4	>97
2	200	1:3	24	>97
3	400	1:6	24	>97
4	800	1:6	24	85

[a] Reaction conditions: Ketone **10** (100-800 mM) ADH (19.7-120 mg, ratio enzyme *vs* substrate in weight), $NADP^+$ (1 mM), glucose (1.5 eq) and GDH (10-40 U) in Tris·HCl buffer (50 mM, pH 7.5) and 1,4-dioxane (10% v/v) at 40 ºC under magnetic stirring. [b] Conversion values measured by ^{1}H-NMR of the reaction crude, while enantiomeric excess values were measured by HPLC (see Supporting Information for additional information).

The design of cross-coupling reactions at higher substrate concentrations (0.1-1.0 M) was then investigated, although low conversions were reached using the buffer pH 7.5. This was attributed to the resulting medium pH, that must be kept alkaline to activate the boronic acid, but turned slightly acidic as the reaction advanced. Thus, using a 1.0 M KPi solution at pH 9, despite not acting as a buffer up to pH 8, the cross coupling proceeds towards complete conversion while the pH of the medium decreases to optimal values for the enzymatic step (7.5-8). Hence, the sequential process was operated in a straightforward manner selecting a situation of compromise such as 500 mM ketone concentration. First, the reaction was carried for a total volume of 0.55 mL, leading to 70 mg of enantiopure (*R*)-**2** (85% yield) after 20 h of cross-coupling reaction at 60 ºC and additional 4 h for the bioreduction at 40 ºC, which gave a remarkable 128 g L^{-1} d^{-1} productivity. Then, the process was scaled-up by using 402 mg of ketone **8a** in the reaction, achieving an 82% overall yield after 48 h. Interestingly, in both cases it was not necessary to adjust the pH in the intermediate stage, and the product was recovered after liquid-liquid extractions with ethyl acetate.

Conclusions

In the search for a stereoselective route towards Odanacatib, different ADHs with complementary enantiopreference have been identified to carry out the asymmetric reduction of a series of 1-aryl-2,2,2-trifluoroethanones **8a**-**f**. Ras-ADH and evo-1.1.200 were found to be suitable enzymes for the bioreduction accessing the corresponding chiral alcohols with excellent conversions and optical purity. Subsequently, the development of a chemoenzymatic sequential strategy combining a palladium-catalyzed cross coupling processes between 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**) and 4-(methylsulfonyl)phenylboronic acid (**9**) followed by the bioreduction of the corresponding ketone intermediate **10** has been extensively studied, leading to the desired (*R*)-2,2,2-trifluoro-1-(4′-(methylsulfonyl)-[1,1′-biphenyl]-4-yl)ethanol (**2**) in enantiomerically pure form and 85% isolated yield with a 128 g L^{-1} d^{-1} productivity.

Experimental Section

Materials and methods. Commercially available lyophilized evo-1.1.200 (6.7 U/mg where 1 U is defined as the amount of ADH that converts 1 µmol of the model substrate, ethyl acetoacetate, in one minute) was purchased from Evoxx Technologies GmbH. Glucose dehydrogenase (GDH-105, 44 U/mg) was obtained from Codexis Inc. The activity of Ras-ADH is approximately 0.3 U/mg for the bioreduction of its model substrate (propiophenone). Nicotinamide cofactors NAD^+ and $NADP^+$ were acquired from Sigma Aldrich. ADHs from *Rhodococcus* species (ADH-A),[17] *Thermoanaerobacter* species (ADH-T),[18] *Thermoanaerobacter ethanolicus* (TeS-ADH),[19] *Ralstonia* species (Ras-ADH),[20] *Lactobacillus brevis* (Lb-ADH)[21] and *Sphingobium yanoikuyae* (Sy-ADH)[22] were overexpressed in *E. coli* cells and used as freeze-dried whole cells after a lyophilization process of the growth medium.

General procedure for the bioreduction experiments with ADHs overexpressed in *E. coli* without addition of external nicotinamide cofactor. In an Eppendorf tube, the *E. coli* cells containing the corresponding ADH (3-15 mg) were suspended in Tris·HCl buffer 50 mM, pH 7.5 (600 µL). Then, isopropanol (25 µL) as a cofactor regeneration system and the corresponding ketone **8a**-**f** or **10** (0.012 mmol) were added and the mixture incubated in an orbital shaker at 250 rpm and 30 °C. The reaction was stopped and extracted with EtOAc (3 x 500 µL), and the combined organic phases washed with water (500 µL), dried over Na_2SO_4 and analyzed by GC, HPLC and/or ^{1}H-NMR (see Table 3 and Supporting Information for further details).

General procedure for the bioreduction experiments with ADH evo-1.1.200. In an Eppendorf tube, the corresponding ketone **8a**-**f** or **10** (0.012 mmol) was mixed with isopropanol (25 µL), NAD^+ (1 mM), $MgCl_2$ (1.25 mM), the enzyme evo-1.1.200 (20 µL of a stock prepared by dissolving 1 mg of enzyme in 1 mL of Tris·HCl buffer 50 mM pH 7.5) and the Tris·HCl buffer 50 mM pH 7.5 (600 µL total volume) and incubated in an orbital shaker at 250 rpm and 30 °C. The reaction was stopped and extracted with EtOAc (3 x 500 µL), and the combined organic phases washed with water (500 µL), dried over Na_2SO_4 and analyzed by GC, HPLC and/or ^{1}H-NMR.

General procedure for the bioreduction experiments using *E. coli*/Ras-ADH with addition of external nicotinamide cofactor. On a solution of alcohol **8a**-**f** (0.12 mmol) in dioxane (60 µL, 10% v/v), $NADP^+$ (1 mM), glucose (600 mM) and GDH (0.5 mg, 25 U) and Tris·HCl buffer 50 mM, pH 7.5 (540 µL). *E. coli*/Ras-ADH (1:1.5 to 1: 2 enzyme-substrate w/w) were added and stirred at 250 rpm and 30 °C for the indicated time (see Table 4). Once the reaction was complete, the product was extracted using EtOAc (3 x 5 mL), and the combined organic phases washed with water (500 µL), dried over Na_2SO_4 and filtered. After solvent evaporation, the final product was isolated without further purification.

1-(4-Bromophenyl)-2,2,2-trifluoroethanol (6a). R_f (20% EtOAc/hexane): 0.58. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 3.20 (brs, 1H), 4.96 (q, $^3J_{HF}$ = 6.6 Hz, 1H), 7.33 (d, $^3J_{HH}$ = 8.2, 2H), 7.51-7.57 (m, 2H) ppm. ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 72.3 (q, $^2J_{CF}$ = 32.4 Hz, CH), 123.9 (C), 124.1 (q, $^1J_{CF}$ = 282.2 Hz, C), 129.2 (2CH), 131.9 (2CH), 132.9 (C) ppm. ^{19}F-NMR ($CDCl_3$, 282.35 MHz): δ –78.50 (d, $^3J_{HF}$ = 6.7 Hz) ppm. $[\alpha]_D^{20}$ = –32.0 (*c* 1, CH_2Cl_2, >99% *ee* (*R*)-**6a**); lit. $[\alpha]_D^{20}$ = –27.5 (*c* 1.06, EtOH, 92% *ee*).[26]

1-Phenyl-2,2,2-trifluoroethanol (6b). R_f (30% EtOAc/hexane): 0.80. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 3.06 (brs, 1H), 5.00 (q, $^3J_{HF}$ = 6.8 Hz, 1H), 7.38-7.51 (m, 5H) ppm. ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 72.9 (q, $^2J_{CF}$ = 32.6 Hz, CH), 124.4 (q, $^1J_{CF}$ = 282.1 Hz, C), 127.6 (2CH), 128.7 (2CH), 129.7 (CH), 134.1 (C) ppm. ^{19}F-NMR ($CDCl_3$, 282.35 MHz): δ –78.38 (d, $^3J_{HF}$ = 6.8 Hz) ppm. $[\alpha]_D^{20}$ = –29.8 (*c* 1, CH_2Cl_2, >99% *ee* (*R*)-**6b**); lit. $[\alpha]_D^{20}$ = –12.5 (*c* 0.4, CH_2Cl_2, 56% *ee*).[27]

1-(3-Bromophenyl)-2,2,2-trifluoroethanol (6c). ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.88 (brs, 1H), 5.02 (q, $^3J_{HF}$ = 6.7 Hz, 1H), 7.03 (t, $^3J_{HH}$ = 7.8 Hz, 1H), 7.43 (d, $^3J_{HH}$ = 7.7 Hz, 1H), 7.57 (d, $^3J_{HH}$ = 7.8 Hz, 1H), 7.73 (s, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 72.2 (q, $^2J_{CF}$ = 32.3 Hz, CH), 122.8 (C), 124.1 (q, $^1J_{CF}$ = 282.3 Hz, C), 126.3 (q, $^4J_{CF}$= 1.4 Hz, CH), 130.3 (CH), 130.6 (q, $^4J_{CF}$ = 1.2 Hz, CH), 132.8 (CH), 136.1 (q, $^3J_{CF}$ = 1.2 Hz, C) ppm. ^{19}F-NMR ($CDCl_3$, 282.35 MHz): δ –78.35 (d, $^3J_{HF}$ = 6.7 Hz) ppm. HRMS (ESI$^-$, *m/z*) $(C_8H_5BrF_3O)^-$ (M-H)$^-$: calculated 252.9481, found 252.9468. $[\alpha]_D^{20}$ = –23.5 (*c* 1, CH_2Cl_2, >99% *ee* (*R*)-**6c**); lit. $[\alpha]_D^{20}$ = –7.3 (*c* 0.11, CH_2Cl_2, 51% *ee*).[28]

1-(2-Bromophenyl)-2,2,2-trifluoroethanol (6d). ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.95 (brs, 1H), 5.67 (q, $^3J_{HF}$ = 6.3 Hz, 1H), 7.31 (td, $^3J_{HH}$ = 7.8, $^4J_{HH}$ = 1.7 Hz, 1H), 7.45 (td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.0 Hz, 1H), 7.65 (dd, $^3J_{HH}$ = 8.0, $^4J_{HH}$ = 1.2 Hz, 1H), 7.73 (d, $^3J_{HH}$ = 7.7 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 71.3 (q, $^2J_{CF}$ = 32.5 Hz, CH), 124.0 (C), 124.4 (q, $^1J_{CF}$ = 282.9 Hz, C), 128.0 (CH), 129.4 (q, $^4J_{CF}$ = 1.5 Hz, CH), 131.1 (CH), 133.1 (CH), 133.8 (q, $^3J_{CF}$ = 1.2 Hz, C) ppm. ^{19}F-NMR ($CDCl_3$, 282.35 MHz): δ –77.62 (d, $^3J_{HF}$ = 6.3 Hz) ppm. HRMS (ESI$^-$, *m/z*): $(C_8H_5BrF_3O)^-$ (M-H)$^-$: calculated 252.9481, found 252.9491. $[\alpha]_D^{20}$ –15.4 (*c* 0.5, CH_2Cl_2, >99% *ee* (*R*)-**6d**).

2,2,2-Trifluoro-1-(naphthalene-1-yl)etanol (6e). ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.90 (brs, 1H), 5.89 (q, $^3J_{HF}$ = 6.5 Hz, 1H), 7.50-7.61 (m, 3H), 7.84 (d, $^3J_{HH}$ = 7.3 Hz, 1H), 7.89-7.95 (m, 2H), 8.05 (d, $^3J_{HH}$ = 8.2 Hz, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 69.0 (q, $^2J_{CF}$ = 32.3 Hz, CH), 122.9 (CH), 124.8 (q, $^1J_{CF}$ = 283.0 Hz, C), 125.3 (CH), 125.9 (q, $^4J_{CF}$ = 1.4 Hz, CH), 126.1 (CH), 127.0 (CH), 129.1 (CH), 130.1 (q, $^3J_{CF}$ = 1.0 Hz, C), 130.3 (CH), 131.2 (C), 133.8 (C) ppm. ^{19}F-NMR ($CDCl_3$, 282.35 MHz): δ –76.85 (d, $^3J_{HF}$ = 6.4 Hz) ppm. $[\alpha]_D^{20}$: –17.8 (*c* 1, CH_2Cl_2, 99% *ee* (*R*)-**6e**); lit. $[\alpha]_D^{20}$ = –14.6 (*c* 0.47, CH_2Cl_2, 60% *ee*).[28]

2,2,2-Trifluoro-1-(naphthalen-2-yl)etanol (6f). White solid. Mp= 96-98 ºC. ^{1}H-NMR ($CDCl_3$, 300.13 MHz): δ 2.93 (brs, 1H), 5.19 (q, $^3J_{HF}$ = 6.7 Hz, 1H), 7.50-7.61 (m, 3H), 7.84-7.91 (m, 3H), 7.95 (s, 1H) ppm . ^{13}C-NMR ($CDCl_3$, 75.5 MHz): δ 73.1 (q, $^2J_{CF}$ = 32.1 Hz, CH), 124.4 (CH), 124.5 (q, $^1J_{CF}$= 282.3 Hz, C), 126.7 (CH), 127.0 (CH), 127.5 (CH), 127.9 (CH), 128.4 (CH), 128.6 (CH), 131.4 (C), 133.0 (C), 133.9 (C) ppm. ^{19}F-NMR ($CDCl_3$, 282.35 MHz): δ –76.05 (d, $^3J_{HF}$ = 6.8 Hz) ppm. $[\alpha]_D^{20}$ = –35.8 (*c* 1, CH_2Cl_2, 98% *ee* (*R*)-**6f**); –23.7 (*c* 0.16, CH_2Cl_2, 71% *ee*).[27]

General procedure for the sequential transformation towards (*R*)-2,2,2-trifluoro-1-[4'-methylsulfonyl-(1,1'-biphenyl)-4-yl]ethanol (2) at 100 mM of reactants. In a tube, 4-(methylsulfonyl) phenylboronic acid (**9**, 13 mg, 0.065 mmol), 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**, 0.06 mmol, 15 mg) and $PdCl_2(PPh_3)_2$ (0.0012 mmol, 0.8 mg) were dissolved in a KPi solution 1.0 M, pH 9.0 (600 µL) and stirred at 40 °C for 24 h. Once the first step was finished, a pH measurement of 8 was obtained in the reaction medium so 1,4-dioxane (60 µL, 10% v/v), $NADP^+$ (0.4 mg, 1 mM), GDH (0.4 mg, 18 U), glucose (16 mg, 100 mM) and *E. coli*/ Ras-ADH (6.5 mg, 1:3 ratio enzyme:**10** w/w) and stirred for another 4 h keeping the temperature at 40 °C. The product was recovered after extracting with EtOAc (3 x 3 mL) and the combined organic phases washed with water (5 mL), dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure, obtaining the alcohol (*R*)-**2** as a yellow solid (19 mg, 97% overall yield). R_f (50% EtOAc/hexane): 0.35. Mp: 153.8-154.9 ºC. ^{1}H-NMR (THF-d_8, 300.13 MHz): δ 3.05 (s, 3H), 5.06-5.16 (m, 1H), 5.96 (d, $^3J_{HH}$ = 5.1 Hz, 1H), 7.60-7.66 (m, 2H), 7.70-7.73 (m, 2H), 7.84-7.89 (m, 2H), 7.98-8.03 (m, 2H) ppm. ^{13}C-NMR (THF-d_8, 75.5 MHz): δ 44.4 (CH_3), 72.5 (q, $^2J_{CF}$ = 30.7 Hz, CH), 126.1 (q, $^1J_{CF}$ = 282.9 Hz, C), 128.1 (2CH), 128.6 (2CH), 128.9 (2CH), 129.3 (2CH), 137.4 (C), 140.7 (C), 141.5 (C), 146.3 (C) ppm. ^{19}F-NMR (THF-d_8, 282.35 MHz): δ –80.83 (d, $^3J_{HF}$ = 7.1 Hz) ppm. $[\alpha]_D^{20}$ = –27.2 (*c* 1.5, THF, >99% *ee* for (*R*)-**2**).

General procedure for the sequential transformation towards (*R*)-2,2,2-trifluoro-1-[4'-methylsulfonyl-(1,1'-biphenyl)-4-yl]ethanol (2) at 500 mM of reactants. Na_2CO_3 (228 mg, 2.15 mmol) was dissolved in a KPi buffer 1.0 M, pH 8 (3.2 mL) and 4-(methylsulfonyl) phenylboronic acid (**9**, 318 mg, 1.59 mmol), 1-(4-bromophenyl)-2,2,2-trifluoroethanone (**8a**, 402 mg, 1.59 mmol,) and $PdCl_2(PPh_3)_2$ (22 mg, 0.032 mmol) were added. The mixture was stirred for 24 h at 60 ° C obtaining a pH of 8 at the end of the first reaction step. Next, 1,4-dioxane (300 µL), $NADP^+$ (2.5 mg, 1 mM), GDH (5 mg, 220 U), glucose (347 mg, 550 mM) and the lyophilized enzyme crude of Ras-ADH (150 mg, ratio 1:3.5 enzyme:**11** w/w) and stirred at 40 °C for 24 h. The product was extracted in a Falcon centrifuge tube using EtOAc (4 x 20 mL), the combined organic phases were washed with water (2 x 20 mL) and filtered through a silica gel path. The mixture was dried over Na_2SO_4, filtered and the solvent evaporated under reduced pressure, obtaining alcohol (*R*)-**2** (430 mg, 82% overall yield).

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Keywords: Alcohol dehydrogenase• Asymmetric synthesis • Bioreduction • Cascade reactions • Odanacatib

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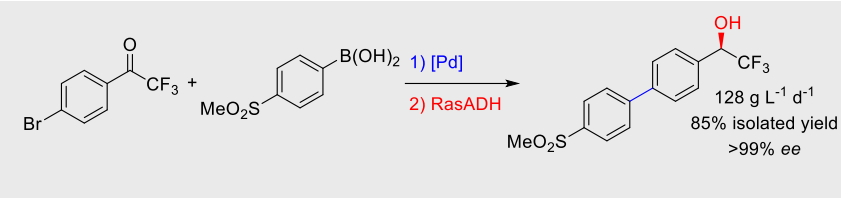

A good compatibility between palladium and alcohol dehydrogenase from *Ralstonia* species has been found for the successful development of a sequential chemoenzymatic transformation towards the formation of a valuable enantiopure Odanacatib precursor.

*Daniel González-Martínez, Vicente Gotor, Vicente Gotor-Fernández**

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