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**Selective One-Pot-Three-Steps Cascade Reaction: from aromatic aldehydes to 2,2-diphenylethanol derivatives**

Muriel Billamboz, Claire Imbs, Estelle Banaszak-Léonard, and Christophe Len

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4 **diphenylethanol derivatives**  
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8 Muriel Billamboz,<sup>a,b</sup> Claire Imbs,<sup>c</sup> Estelle Banaszak-Léonard,<sup>a</sup> and Christophe LEN<sup>\*,c</sup>  
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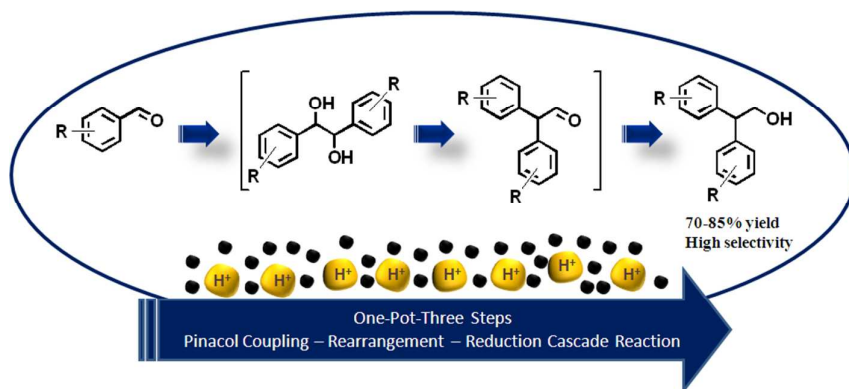
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## Table of Contents graphic



1  
2  
3 **ABSTRACT:** We report herein a green and scalable one-pot-three-steps pinacol-coupling-  
4 rearrangement-reduction cascade reaction useful for the formation of 2,2-diphenylethanol  
5 derivatives. The reaction is carried out in water in presence of a commercially available and  
6 regenerable supported acid under moderate pressure. A dozen of aromatic aldehydes have  
7 been successfully submitted to the standard protocol giving the target 2,2-diarylethanol  
8 derivatives in good yield (70-85%).  
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17 **Key words:** Pinacol coupling / Rearrangement / Cascade reaction / Green chemistry /  
18 microwave / Scale-up  
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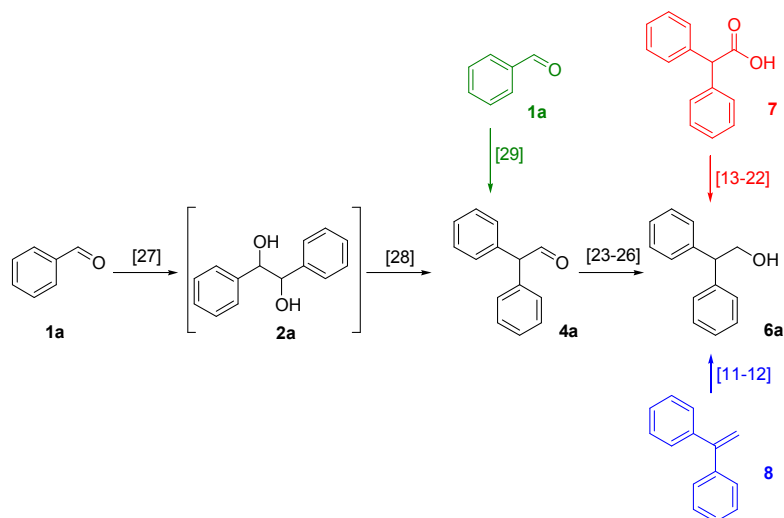
## 22 INTRODUCTION

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25 2,2-Diphenylethanol derivatives are often used for the formation of new biologically active  
26 compounds<sup>1-6</sup> or formulated in a wide range of applications.<sup>7-10</sup> As a consequence,  
27 methodologies to selectively obtain such compounds are of great interest.  
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32 From literature data, 2,2-diphenylethanol (**6a**) is mainly obtained by three synthetic routes,  
33 coming from (i) the reduction of 2,2-diphenylethanal (**4a**); (ii) the direct reduction of the  
34 corresponding carboxylic acid **7** into alcohol or (iii) the hydroboration/oxidation process of  
35 1,1-diphenylethylene (**8**) (Scheme 1).  
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44 **Scheme 1. Literature data for the formation of 2,2-diphenylethanol (6a)**  
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Only two recent works described the conversion of 1,1-diphenylethylene (**8**) to 2,2-diphenylethanol (**6a**): the first has been reported by Horvath et al. using an immobilized rhodium catalyst<sup>11</sup> and the second reported a flow method for hydroboration/oxidation of olefins.<sup>12</sup> The direct reduction of carboxylic acid to alcohol is much more studied and several efficient reducing systems have been developed: H<sub>2</sub> gas/transition metal,<sup>13</sup> NaBH<sub>4</sub>-additive protocol,<sup>14</sup> borane reducing reagents such as (BH<sub>3</sub>)<sub>2</sub>,<sup>15</sup> BH<sub>3</sub>-SMe<sub>2</sub>,<sup>16</sup> 9-borabicyclo[3.3.1]nonane (9-BBN),<sup>17</sup> strong aluminum hydrides such as AlH<sub>3</sub>,<sup>18</sup> LiAlH<sub>4</sub>,<sup>19</sup> DIBAL-H,<sup>20</sup> EtMe<sub>2</sub>SiH/ruthenium-based catalyst,<sup>21</sup> 1,1,3,3-tetramethyldisiloxane (TMDS)/Cu(OTf)<sub>2</sub>.<sup>22</sup> In most of these cases, reactions are carried out under harsh conditions, or generate stoichiometric amounts of inorganic salts. Successful protocols based on metal-induced reactions<sup>24</sup> such as solvent-less iron-catalyzed hydrosilylation<sup>24a</sup> or iron-tetraphos complex hydrogenation<sup>24b</sup> have been reported for the reduction of 2,2-diphenylethanal (**4a**) to 2,2-diphenylethanol (**6a**).<sup>23</sup> Typically, metal hydrides as well as other stoichiometric reagents are used for this transformation on a laboratory scale. Boron derivatives such as *N*-heterocyclic carbene boranes are often described for this transformation.<sup>25</sup> An innovative

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3 protocol also proposed the catalytic frustrated Lewis pair hydrogenation of 2,2-  
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5 diphenylethanal (**4a**) in moderate yield.<sup>26</sup>  
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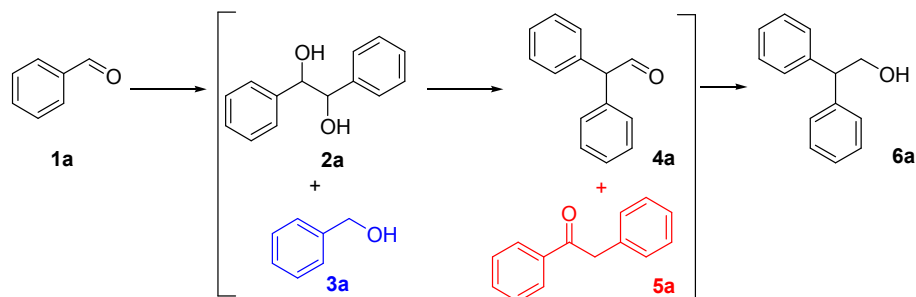
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8 Collecting all these data, it appears than reported methodologies for the formation of 2,2-  
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10 diphenylethanol (**6a**) included at least one of the following statement: (i) the use of complex  
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12 metal-catalyzed reactions; (ii) the use of sensitive reactant such as carbene borane,  
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14 borohydride or hydrogen; (iii) the use of organic solvents. As a consequence, simple protocol  
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16 to obtain 2,2-diphenylethanol (**6a**) in a green and recyclable medium is of particular interest.  
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18 Moreover, methodologies able to furnish 2,2-diphenylethanol derivatives from the  
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20 corresponding benzaldehyde derivatives in large scale is desirable.  
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24 Following our continuous interest for the development of sustainable pinacol coupling  
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26 reactions,<sup>27</sup> direct formation of 2,2-diphenylethanal (**4a**) from benzaldehyde (**1a**) has been  
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28 examined. 2,2-Diphenylethanal (**4a**) can be obtained by pinacolic rearrangement of pinacol **2a**  
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30 under acidic conditions (Lewis acid supported on silica gel,<sup>28a</sup> H<sub>2</sub>SO<sub>4</sub> in AcOH<sup>28b</sup>, ionic-  
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32 liquid-mediated rearrangement<sup>28c</sup>...<sup>28</sup> Moreover, two protocols using the combination of a  
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34 noble-metal catalyst and a promoter have been reported for the one-pot-two-steps formation  
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36 of 2,2-diphenylethanal (**4a**) from benzaldehyde (**1a**).<sup>29</sup> The first one consisted in a  
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38 combination of a platinumium complex and a polyoxometalate<sup>29a</sup> and led to 2-2-  
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40 diphenylacetaldehyde **4a** in 72% yield with 86% global selectivity. The second protocol was  
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42 mediated by indium in THF in presence of trimethylsilylchloride in excess and gave the  
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44 targeted product **4a** in 88% yield.<sup>29b</sup>  
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48 In order to improve the cost and sustainability of the process, a focus on the acid and metal  
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50 catalyzed one-pot-three steps pinacol coupling-rearrangement-reduction of aromatic  
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52 aldehydes to 2,2-diphenylethanol derivatives has been examined (Scheme 2). In the frame of  
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54 green chemistry principles, water was selected as solvent and particular attention was paid to  
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56 the selectivity, scalability and recyclability of the system. In fact, several side-products such  
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as the reduction product **3a** (benzyl alcohol) and deoxybenzoin **5a** are expected to be observed (Scheme 2).

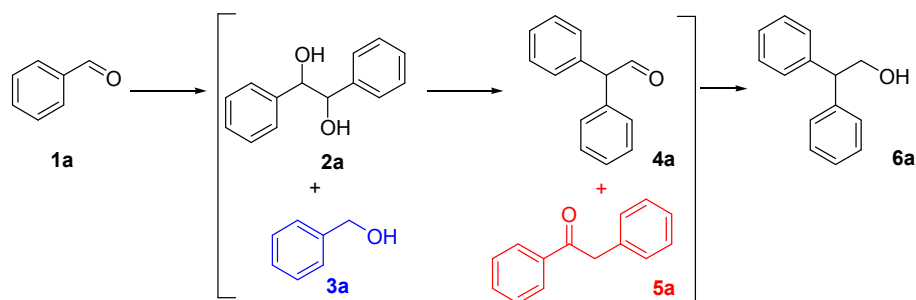
**Scheme 2. Envisaged cascade reaction with all potential intermediates and side-products**



## RESULTS AND DISCUSSION

At first, the cascade reaction was realized in sole water under microwave irradiation. Combining literature data, the protocol was divided into two parts: (i) heating at 70°C during 1 hour to achieve the pinacol coupling reaction, then (ii) heating at 150°C during 1 additional hour to realize the pinacol rearrangement of the preformed pinacol derivative and the subsequent reduction of 2,2-diphenylacetaldehyde **4a** to 2,2-diphenylethanol (**6a**). From literature data, zinc was selected as electron supplier and Amberlyst®H15 was chosen as supported acid (Table 1, entry 1). Starting aldehyde **1a** was completely converted. Target 2,2-diphenylethanol (**6a**) was obtained in an encouraging 55% yield. The selectivity for the pinacolic rearrangement was high and very few deoxybenzoin **5a** was recovered at the end of the cascade reaction. However, a high amount of benzylic alcohol **3a**, coming from the direct reduction of benzaldehyde (**1a**) before pinacol coupling was observed (28% yield, Table 1, entry 1). A small amount of pinacol derivative **2a** was also obtained (5%) proving that the pinacolic rearrangement was not complete.

**Table 1. One-Pot-3-Steps cascade reaction from benzaldehyde (1a) to 2,2-diphenylethanol (6a)<sup>a</sup>**



Entry	equiv	equiv	Conversion (%)	2a (%)	3a (%)	4a (%)	5a (%)	6a (%)	SEL PC/R <sup>b</sup>	SEL R/D <sup>c</sup>
	Amberlyst® H15	Metal								
1	3	4 (Zn)	100	5	28	-	2	55	69:31	96:4
2	3	4 (Mg)	80	10	70	-	-	-	12:88	-
3	3	4 (Al)	0	-	-	-	-	-	-	-
4	3	4 (Mn)	0	-	-	-	-	-	-	-
5	3	2	95	3	24	-	2	42	66:34	95:5
6	1	4	89	28	28	-	1	11	59:41	92:8

<sup>a</sup> Typical procedure: a 30 mL pyrex vessel adapted to microwave irradiation was charged with benzaldehyde (1a, 1.5 mmol), Amberlyst® H15 and zinc. 5 mL of water were then added. The mixture was stirred and heated at 70°C during 1 hour then at 150°C during 1 additional hour.

<sup>b</sup> SEL PC/R defined the selectivity between pinacol coupling reaction and direct reduction.

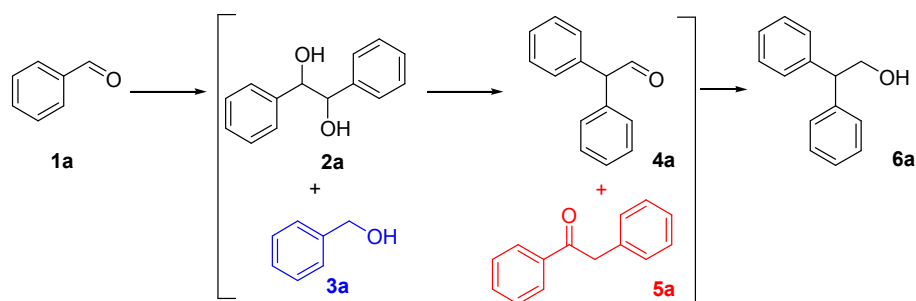
<sup>c</sup> SEL R/D referred to the selectivity between pinacolic rearrangement and dehydration of pinacol 2a.

Based on these results, several experiments were carried out to limit the amount of reduced compound 3a. As expected, changing the metal source did not allowed better selectivity nor yield in 6a (Table 1, entries 2-4). Decreasing the amount of zinc to 2 equivalents allowed to limit the amount of benzylic alcohol 3a to 24% yield but with a partial conversion (Table 1, entry 5). With 1 equivalent of supported acid, the conversion decreased and the rate of



pinacolic rearrangement was low (Table 1, entry 6). From these first partial results, we concluded that the amount of Amberlyst®H15 or zinc did not have a high impact on the amount of benzyl alcohol **3a** but played a key role in selectivities and rates of the cascade reaction. As a consequence, different sources of acid were screened to master the reduction side reaction (Table 2).

**Table 2. Screening of acid sources<sup>a</sup>**



Entry	acid source	Conversion (%)	<b>2a</b> (%)	<b>3a</b> (%)	<b>4a</b> (%)	<b>5a</b> (%)	<b>6a</b> (%)	SEL PC/R <sup>b</sup>	SEL R/D <sup>c</sup>
1	Amberlyst®H15 (3 equiv)	100	5	28	-	2	55	69:31	96:4
2	NH <sub>4</sub> Cl sat. (-)	86	5	50	-	-	-	10:90	-
3	AcOH (3 equiv)	100	15	73	-	-	-	17:83	-
4	CH <sub>3</sub> SO <sub>3</sub> H (3 equiv)	100	24	40	-	1	28	57:43	96:4
5	Al(CF <sub>3</sub> SO <sub>3</sub> ) <sub>3</sub> (1 equiv)	100	37	56	-	-	-	40:60	-
6	VCl <sub>3</sub> (1 equiv)	100	38	32	-	-	-	54:46	-
7	Dowex <sup>®</sup> 50WX8 (3 equiv)	100	13	23	-	2	39	70:30	95:5
8	Nafion <sup>®</sup> NR50 (3 equiv)	92	2	11	-	1	15	62:38	94:6
9	Amberlite <sup>®</sup> IR120 (3 equiv)	100	26	21	-	2	35	75:25	95:5

<sup>a</sup> Reaction conditions: benzaldehyde (1,5 mmol), zinc (4 eq.) and acid source in water (5 mL) are stirred at 1200 rpm under microwave irradiation at 70°C during 1 hour then at 150°C during 1 additional hour.

<sup>b</sup> SEL PC/R defined the selectivity between pinacol coupling reaction and direct reduction.

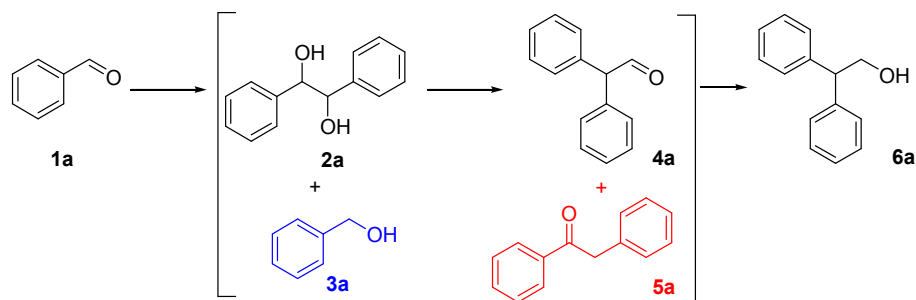
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3 ° SEL R/D referred to the selectivity between pinacolic rearrangement and dehydration of  
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5 pinacol **2a**.  
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11 Running the reaction in saturated ammonium chloride as acid source did not allow any  
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13 pinacolic rearrangement nor dehydration *but* a large amount of benzyl alcohol **3a** was  
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15 observed at the end of the reaction (Table 2, entry 2). Acetic acid was reported as promoter  
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17 for the pinacol coupling reaction at room temperature.<sup>27a</sup> However, at 70°C, acetic acid  
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19 favored the direct reduction of the aldehyde **1a** to the corresponding alcohol **3a** in 73% yield.  
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21 Methanesulfonic acid, a strong homogeneous acid, allowed the cascade reaction but with a  
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23 low selectivity towards pinacol coupling (Table 2, entry 4). Lewis acids were also reported to  
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25 promote the pinacol coupling reaction.<sup>28a,30</sup> Trifluoromethanesulfonic aluminium (III) at  
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27 stoichiometric amount was evaluated for the cascade reaction conducting to a total  
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29 conversion in favor of benzyl alcohol **3a** (Table 2, entry 5). Vanadium chloride, previously  
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31 described<sup>31</sup> as promoter for the pinacol coupling reaction gave pinacol product **2a** at 38%  
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33 yield accompanied by 32% of undesired alcohol **3a** and some minor undetermined side  
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35 products (Table 2, entry 6). As Lewis acids and homogeneous acids (NH<sub>4</sub>Cl, AcOH or  
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37 CH<sub>3</sub>SO<sub>3</sub>H) were not able to limit benzyl alcohol formation supported Brønsted acids were  
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39 investigated.  
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45 Dowex<sup>®</sup> 50WX8 hydrogen form is a strongly acidic cation exchange resin which allowed  
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47 the pinacol coupling reaction and the pinacolic rearrangement. Indeed, 39% of target 2,2-  
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49 diphenylethanol (**6a**) was obtained starting from the aldehyde **1a** accompanied by some  
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51 residual pinacol **3a** (Table 2, entry 6). It is notable that a lower amount of undesired benzylic  
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53 alcohol **3a** was formed compared with the use of Amberlyst<sup>®</sup> H15 (Table 2, entries 1 and 6).  
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55 Moreover, the selectivity for pinacolic rearrangement compared with dehydration is very  
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high. Nafion<sup>®</sup>NR50, a hydroscopic super acidic ion exchange resin catalyst, promoted the conversion of benzaldehyde (**1a**) but low target product **6a** was observed at the end of the reaction (15% yield). Moreover, the pellets swelled and it was difficult to recover all products for analysis (Table 2, entry 7). As a consequence Nafion<sup>®</sup>NR50 was not selected for further optimization. Amberlite<sup>®</sup>IR120, a strongly acidic gel-type resin with sulfonic acid functionality, allowed the total conversion of aldehyde **1a** and gave 35% of target product **6a** with an excellent selectivity (Table 2, entry 8). Comparing these four supported acidic media led to the conclusion that Amberlite<sup>®</sup>IR120 displayed the higher potential in terms of selectivities and Amberlyst<sup>®</sup>H15 in terms of reaction rate. Consequently, these two supported acids were selected for further optimization.

**Table 3. Optimization with Amberlyst<sup>®</sup>H15**



Entry	equiv acid	equiv Zn	Solvent (mL)	$T_1$ (°C)	$t_1$ (min)	$T_2$ (°C)	$t_2$ (min)	rpm	Conversion (%)	<b>2a</b> (%)	<b>3a</b> (%)	<b>5a</b> (%)	<b>6a</b> (%)
1 <sup>a</sup>	3	4	H <sub>2</sub> O (5)	70	60	150	60	1200	100	5	28	2	55
2 <sup>a</sup>	1	4	H <sub>2</sub> O (5)	70	60	150	60	1200	89	44	28	<1	11
3 <sup>a</sup>	3	2	H <sub>2</sub> O (5)	70	60	150	60	1200	95	2	24	2	42
4 <sup>a</sup>	3	4	H <sub>2</sub> O (5)	70	60	180	60	1200	100	1	29	4	55
5 <sup>a</sup>	3	4	H <sub>2</sub> O (3)	70	60	180	60	1200	99	-	22	4	49
6 <sup>a</sup>	3	4	H <sub>2</sub> O (8)	70	60	180	60	1200	92	-	28	4	47
7 <sup>a</sup>	3	4	EtOH (5)	70	60	150	60	1200	78	-	3	4	24
8 <sup>a</sup>	3	4	EtOH (5)	70	60	180	60	1200	75	-	2	5	37

9 <sup>a</sup>	3	4	96%EtO H (5)	70	60	150	60	1200	60	10	9	5	12
10 <sup>a</sup>	3	4	EtOH (4) H <sub>2</sub> O (1)	70	60	150	60	1200	75	31	18	4	20
11 <sup>a</sup>	3	4	EtOH (2,5) H <sub>2</sub> O (2,5)	70	60	150	60	1200	100	28	19	5	11
12 <sup>b</sup>	3	4	H <sub>2</sub> O (5)	70	30+30	180	60	600	100	-	27	4	64
13 <sup>b</sup>	3	4	H <sub>2</sub> O (5)	50	10+50	180	60	600	100	6	27	4	55
14 <sup>b</sup>	3	4	H <sub>2</sub> O (5)	70	30+30			600	68	20	21	3	6
15 <sup>b</sup>	3	4	H <sub>2</sub> O (5)	50	10+50			600	50	15	17	0	0
16 <sup>b</sup>	3	4	H <sub>2</sub> O (5)			150	60	600	95	8	23	3	50
17 <sup>c</sup>	3	4	H <sub>2</sub> O (5)			180	60	600	100	-	27	3	64

<sup>a</sup> Reaction conditions: benzaldehyde (1.5 mmol), zinc and acid source in solvent (H<sub>2</sub>O/EtOH)

are stirred under microwave irradiation at 70°C during 1 hour then at T<sub>2</sub> during 1 additional hour.

<sup>b</sup> Reaction conditions: benzaldehyde (1.5 mmol), zinc and acid source in water (5 mL) are stirred under microwave irradiation. T<sub>1</sub> [(x + y) min] is reached in x minutes then the reaction medium is stirred at T<sub>1</sub> during y minutes. After that, if needed, the mixture is heated as fast as possible to T<sub>2</sub> and stirred at T<sub>2</sub> during 1 additional hour.

<sup>c</sup> Reaction conditions: benzaldehyde (1.5 mmol), zinc and acid source in water (5 mL) are heated and stirred at 180°C during 1 hour.

Using 1 equivalent of Amberlyst®H15 decreased the global conversion (89% vs 100%) and hindered the pinacolic rearrangement step (Table 3, entries 1 and 2). Decreasing the amount of zinc to 2 equivalents allowed to reach a very good conversion of aldehyde **1a** (95%) and 42% of target compound **6a** was obtained. However, 24% of alcohol **3a** still remained in the medium (Table 3, entry 3).

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3 Increasing the temperature of the second step to 180°C or concentrated the reaction  
4 medium did not help (Table 3, entries 1-5). Diluting the medium decreased the rate of reaction  
5 and did not allow to limit the side reactions or increase the selectivity for pinacol coupling or  
6 pinacolic rearrangement (Table 4, entry 6). As a consequence, the initial concentration at  
7 0.3M was kept for further experiments.  
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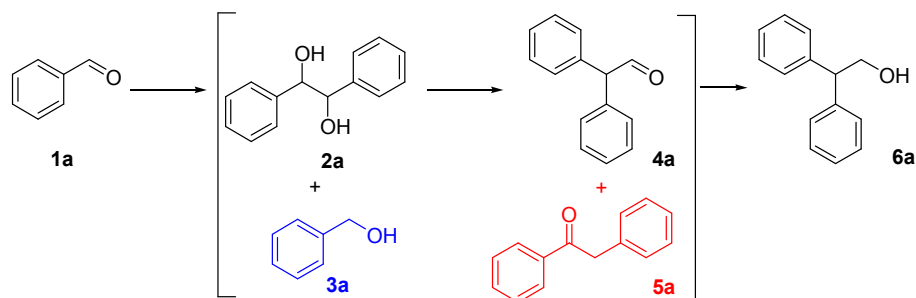
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15 Ethanol, reported as able to limit the reduction side reaction, was evaluated (Table 3,  
16 entries 7-11). In absolute ethanol, even if lower amounts of benzyl alcohol were observed,  
17 conversions decreased and lot of unpreviously observed side products were obtained (Table 3,  
18 entries 7 and 8). As a consequence, some experiments in a mixture of ethanol and water were  
19 attempted (Table 3, entries 9-11) but with limited success. The more water was added in the  
20 medium, the more benzyl alcohol was obtained (Table 3, entries 8-11). As a consequence, the  
21 replacement of water by bio-sourced ethanol, even if it slowed the reduction side reaction,  
22 was abandoned.  
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34 In order to limit the amount of benzyl alcohol **3a** some experiments were carried out with  
35 a monitored heating to the target temperature  $T_1$ . It is noteworthy that decreasing the speed of  
36 stirring to 600 rpm led to the production of **6a** in 64% yield with total conversion of  
37 benzaldehyde (**1a**) and pinacol **2a**. However, 27% of benzyl alcohol **3a** is still observed,  
38 accompanied by a small amount of deoxybenzoin **5a** (4%) (Table 3, entry 12). Conducting the  
39 reaction at 50°C led to a total conversion but without improvement of the selectivity (Table 3,  
40 entry 13). Comparing these two experiments, it was decided to stop the reaction after heating  
41 at  $T_1$  (Table 3, entries 14 and 15). From these results, it seems that the majority of the reaction  
42 is carried out at the higher temperature  $T_2$ . As a consequence, the reaction was realized in a  
43 sole step at the higher temperature and confirmed our hypothesis: 50% of target compound **6a**  
44 is obtained, with good conversions in benzaldehyde (**1a**) and pinacol **2a**. 23% of benzyl  
45 alcohol **1a** is produced and a high selectivity for pinacolic rearrangement is observed (Table  
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3, entry 16). Conducting the reaction at 180°C and 600 rpm led to total conversions with 64% yield in **6a** (Table 3, entry 12).

All these experiments in hand, Amberlite®IR120 was optimized as a potential supported acid which would limit the reduction side reaction at 0.3M as defined for Amberlyst®H15. A slow heating at 70°C and a second step at 180°C were then attempted (Table 4, entry 2). This protocol did not allow the total conversion of aldehyde **1a** but the profile of the reaction remained the same. From literature, metal(III) chloride as additive could help the pinacol coupling reaction and decreased the amount of benzyl alcohol **3a**.<sup>32</sup> In our conditions, the addition of iron (III) chloride boosted the formation of the reduced product **3a** and inhibited the pinacolic rearrangement step (Table 4, entry 3).

**Table 4. Optimization with Amberlite®IR120**



Entry	equiv acid	equiv Zn	T <sub>1</sub> (°C)	t <sub>1</sub> (min)	T <sub>2</sub> (°C)	t <sub>2</sub> (min)	rpm	Conversion (%)	<b>2a</b> (%)	<b>3a</b> (%)	<b>4a</b> (%)	<b>5a</b> (%)	<b>6a</b> (%)
1 <sup>a</sup>	3	4	70	60	150	60	1200	100	26	21	-	2	35
2 <sup>b</sup>	3	4	70	30+30	180	60	1200	79	16	18	-	2	39
3 <sup>b,c</sup>	3	4	70	30+30	180	60	1200	89	35	33	-	1	1
4 <sup>d</sup>	3	4			160	120	600	88	15	16	-	2	53
5 <sup>d</sup>	3	4			180	120	900	82	5	15	-	2	46
6 <sup>d</sup>	2	2			180	120	900	60	10	8	8	2	25
7 <sup>d</sup>	3	3			180	120	900	81	8	16	4	2	48

8 <sup>d</sup>	4	3			180	120	900	83	-	12	4	2	53
9 <sup>e</sup>	4	3	90	60	160	10+50	600	100	19		8	-	72
10 <sup>e</sup>	4	3	90	60	180	10+50	600	94	19		10	-	62
11 <sup>e</sup>	5	3	90	60	160	10+50	600	100	16		-	-	80
12 <sup>e</sup>	5	2	90	60	160	10+50	600	85	18		18		47

<sup>a</sup> Reaction conditions: benzaldehyde (1.5 mmol), zinc and Amberlite® IR120 in water (5 mL) are stirred at 1200 rpm under microwave irradiation at 70°C during 1 hour then at 150°C during 1 additional hour.

<sup>b</sup> Reaction conditions: benzaldehyde (1,5 mmol), zinc and Amberlite® IR120 in water (5 mL) are stirred at 1200 rpm and gradually heated in 30 minutes to 70°C under microwave irradiation. The mixture is maintained at 70°C during 30 additional minutes then at 180°C during 1 additional hour.

<sup>c</sup> Reaction realized in presence of FeCl<sub>3</sub> (1 eq).

<sup>d</sup> Reaction conditions: benzaldehyde (1.5 mmol), zinc and Amberlite® IR120 in water (5 mL) are heated at T<sub>2</sub> during 2 hours under microwave irradiation.

<sup>e</sup> Reaction conditions: benzaldehyde (1.5 mmol), zinc and Amberlite® IR120 in water (5 mL) are heated at 90°C during 1 hour under microwave irradiation then gradually heated in 10 minutes to T<sub>2</sub>. The mixture is maintained at T<sub>2</sub> during 50 additional minutes.

From the optimized protocol for Amberlyst® H15, fast heating at the higher temperature T<sub>2</sub> was carried out (Table 4, entries 4-8). A first attempt at 160°C during 2 hours at 600 rpm led to the target compound **6a** in 53% yield with an excellent selectivity. Moreover, only 16% of alcohol **3a** was obtained, which was twice less than with Amberlyst® H15 in equivalent conditions (Table 4, entry 4). Increasing the temperature and stirring speed slowed down the reaction (Table 4, entry 5). As a consequence, the proportions between acid and zinc were

1  
2  
3 screened to determine the best ratio (Table 4, entries 6-8). Decreasing the quantity of metallic  
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5 reductor impacted on the reduction of diphenylethanal **4a** to diphenylethanol **6a** as **4a** was  
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7 observed in 4 to 8% yield at the end of the process (Table 4, entry 6). Increasing the quantity  
8  
9 of supported acid accelerated the pinacolic rearrangement (Table 4, entries 7 and 8).  
10  
11 However, for all experiments, independently of the reductor/acid ratio, aldehyde **1a** was not  
12  
13 totally converted in two hours. As a consequence, a reaction step at 90°C was introduced to  
14  
15 allow the total conversion of benzaldehyde **1a** (Table 4, entry 9). The reaction mixture was  
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17 heated under moderate stirring as fast as possible at 90°C and maintained at this temperature  
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19 during one hour. During that stirring, no over-pressure was monitored and reactants were on  
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21 the liquid phase. After one hour, the mixture was slowly heated for 10 minutes to 160°C and  
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23 maintained at that temperature for 50 minutes. As expected, this 2-hour process led to a total  
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25 conversion of aldehyde **1a** and 72% of target product **6a** was obtained (Table 4, entry 9). 19%  
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27 of benzyl alcohol and only 1% of deoxybenzoin **5a** were produced. Moreover 8% of residual  
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29 pinacol **2a** could be converted to **6a** to optimize the target yield. A second attempt was  
30  
31 realized using the same protocol and zinc/acid ratio but with 180°C as higher temperature.  
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33 This small difference had a dramatic impact on conversion and yield of **6a** (Table 4, entry 10).  
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35 As a consequence, 160°C was kept for the last experiments and the amount of resin was  
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37 increased to 5 equivalents in order to reach 80% yield of **6a** with an excellent selectivity. With  
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39 this amount of acid, 16% of benzyl alcohol **2a** were observed and less than 1% of  
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41 deoxybenzoin **5a**, resulting from a dehydration side-reaction was monitored (Table 4, entry  
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43 11). Our last attempt was to decrease the amount of zinc to 2 equivalents but this led to lower  
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45 conversions and yields (Table 4, entry 12).  
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51  
52 To summarize, two optimized methodologies for the one-pot-three-steps cascade reaction  
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54 from aldehyde **1a** to 2,2-diphenylethanol (**6a**) were realized in sole water under microwave  
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56 irradiation using commercially available supported acids (Table 5).  
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**Table 5. Optimized methodologies for the cascade reaction**

Entry	acid source	equiv	$T_1$	$t_1$	$T_2$	$t_2$	Conversion	<b>3a</b>	<b>5a</b>	<b>6a</b>
		Zn	(°C)	(min)	(°C)	(min)	(%)	(%)	(%)	(%)
1 <sup>a</sup>	Amberlite®IR120 (5 equiv)	3	90	60	160	10+50	100	16	1	80
2 <sup>b</sup>	Amberlyst®H15 (3 equiv)	4			180	60	100	27	64	3
3 <sup>a</sup>	Amberlyst®H15 (5 equiv)	3	90	60	160	10+50	100	35	5	55
4 <sup>b</sup>	Amberlite®IR120 (3 equiv)	4			180	60	62	15	3	36

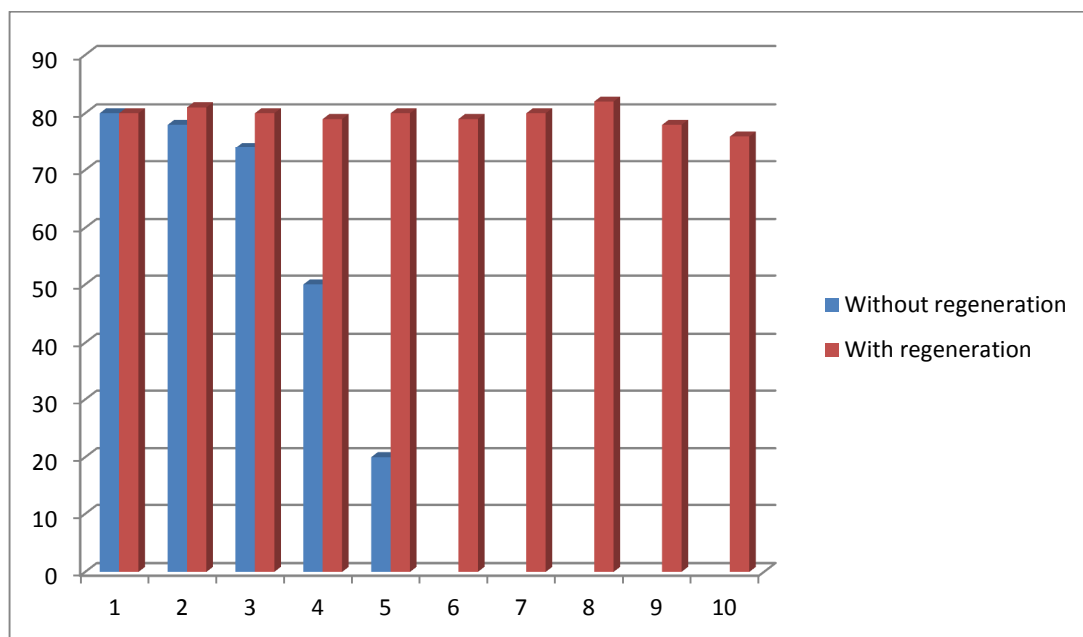
<sup>a</sup> Reaction conditions: benzaldehyde (1.5 mmol), zinc and acid in water (5 mL) are stirred at 600 rpm under microwave irradiation at 90°C during 1 hour then at 160°C during 1 additional hour.

<sup>b</sup> Reaction conditions: benzaldehyde (1.5 mmol), zinc and acid in water (5 mL) are stirred at 600 rpm under microwave irradiation at 180°C during 1 hour.

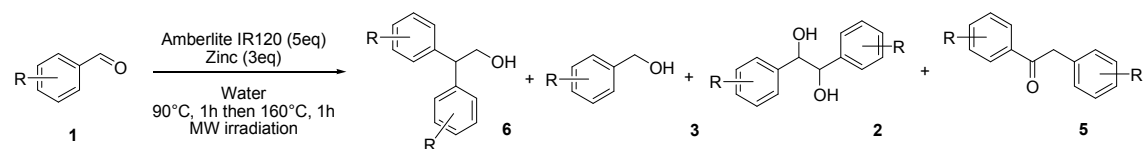
The more selective was based on the reactivity of Amberlite®IR120 at 90°C then 160°C during 2 hours (Table 5, entry 1). The protocol using Amberlyst®H15 was fast, with good selectivity and total conversion after 1 hour at 180°C (Table 5, entry 2). Using Amberlyst®H15 under the optimized conditions for Amberlite®IR120 led to bad results in terms of selectivity with a high amount of alcohol **3a** (Table 5, entry 3). As previously observed, using Amberlite®IR120 at 180°C during 1 hour led to moderate conversion (Table 5, entry 4). As a consequence, Amberlite®IR120 was kept for further investigations on the recycling of the system and the scope of the reaction.

One of the advantage of using supported media deals with the possibility of recycling the support by simple filtration to separate the filtrate, zinc and Amberlite®IR120. In our case, Amberlite®IR120 can be recycled twice before a dramatic decrease in activity, obviously related to the loss of protons on the surface of Amberlite®IR120 (Figure 1). In our conditions, the support showed no physical damages. A good activity was maintained for 10 runs without

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3 significant losses on selectivity after regeneration of the resin by an acidic washing (Figure 1).  
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5 Several aromatic aldehydes were then subjected to the optimized recyclable green reaction  
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7 conditions for the one-pot-three steps cascade reaction (Table 6).  
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36 **Figure 1.** Recycling of Amberlite®IR120 with or without regeneration between each run.  
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**Table 6. Scope of the cascade reaction**

Entry	Compound	R	conversion	6 (%)	2 (%)	3 (%)	5 (%)	SEL PC/R <sup>a</sup>	SEL R/D <sup>b</sup>
	<b>1</b>								<sup>b</sup>
1	<b>a</b>	H	100	80	-	16	1	84/16	98/2
2	<b>b</b>	4-CH <sub>3</sub>	100	85	-	11	2	89/11	98/2
3	<b>c</b>	4-F	90	75	-	13	2	86/14	97/3
4	<b>d</b>	4-Cl	100	78	-	19	2	81/19	97/3
5	<b>e</b>	4-Br	100	83	-	15	1	84/16	98/2
6	<b>f</b>	4-OMe	25	0	20	5	-	80/20	ND
7	<b>g</b>	3-CH <sub>3</sub>	100	82	-	15	3	85/15	97/3
8	<b>h</b>	2-CH <sub>3</sub>	100	83	-	15	2	85/15	97/3
9	<b>i</b>	3-Cl	100	78	-	17	3	83/17	96/4
10	<b>j</b>	2-Cl	100	70	-	25	3	74/26	96/4
11	<b>k</b>	3-Br	100	79	-	16	3	83/17	96/4

<sup>a</sup> SEL PC/R defined the selectivity between pinacol coupling reaction and direct reduction.

<sup>b</sup> SEL R/D referred to the selectivity between pinacolic rearrangement and dehydration of pinacol **2a**.

It is notable than few differences were observed when derivatives of aldehyde **1a** were used as substrate except for 4-methoxybenzaldehyde (**1f**). In our conditions, the formation of the ketyl radical seems to be the limiting step. As a consequence, the efficiency of the reaction was directly correlated with the electrophily of the carbon atom of the carbonyl group. Compared with benzaldehyde (**1a**), derivatives with a mesomeric donating group at *para* or *ortho* position are expected to react slowly than those in *meta* position. As a consequence, 4-methoxybenzaldehyde (**1f**), as expected, reacted very slowly to give only 25% conversion and

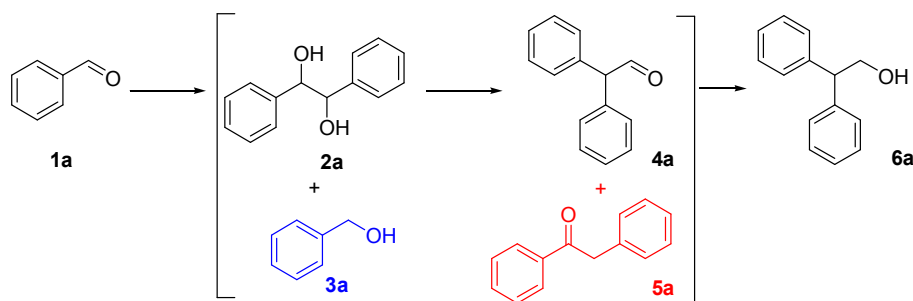
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3 20% of the corresponding pinacol **2f** (Table 6, entry 6). Moreover, this donating-group seems  
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5 to hinder the pinacolic/pinacolone rearrangement. Derivatives with moderate donating groups  
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7 either by mesomeric or inductive effects gave total conversions and good yields (Table 6,  
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9 entries 3-5 and entries 9-11). Derivatives with methyl groups exhibit the same reactivity,  
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11 independently of the substituent position on the aromatic ring (Table 6, entries 2, 7 and 8),  
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13 with total conversions and high yields and selectivities for 2,2-diphenylethanol derivatives **6b**,  
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15 **6g** and **6h**. It is notable than the chloro-derivatives gave higher amounts of chlorobenzyl  
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17 alcohols **3d**, **3i** and **3j** than the others halogenated substrates. This tendency for direct  
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19 reduction was previously reported by our group.<sup>27</sup> In a general manner, the selectivity for the  
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21 pinacol coupling reaction *versus* direct reduction to alcohol is good and the selectivity for  
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23 pinacolic rearrangement to 2,2-diphenylethanol **6** is excellent (SEL R/D >96%).  
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28 As our main goal is to produce 2,2-diphenylethanol (**6a**) in large scale, efforts have then  
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30 been focused on the evaluation of the reaction in a larger scale. Considering that flow  
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32 microwave devices are less industrially used than autoclaves, some experiments in sealed  
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34 vessels have been carried out using the optimized protocol with Amberlite®IR120 (Table 7  
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36 and Figure 2).  
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53 **Figure 2.** Devices used for scale-up study  
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Table 7. Scale-up study using sealed devices under conventional heating



Entry	Device	Volume (mL)	Masse 1a (g)	conversion	6a (%)	2a (%)	3a (%)	4a (%)	5a (%)	SEL PC/R <sup>a</sup>	SEL R/D <sup>b</sup>
1	MW glass vessel	30	0.159	100	80	-	16	-	1	84/16	98/2
2	Glass vessel	30	0.159	95	79	trace	10	6	Trace	89/11	99/1
3	Teflon reactor	60	0.318	100	80	trace	16	<1	4	84/16	95/5
4 <sup>c</sup>	Teflon reactor	300	5	100	77	8	11	trace	4	89/11	95/5
5 <sup>c</sup>	Steel reactor	750	12	100	79	5	13	trace	3	87/13	96/4

<sup>a</sup> SEL PC/R defined the selectivity between pinacol coupling reaction and direct reduction.

<sup>b</sup> SEL R/D referred to the selectivity between pinacolic rearrangement and dehydration of pinacol 2a. <sup>c</sup> Concentration was put at 100g.L<sup>-1</sup>

As expected, the reactivity in the 30 mL sealed pyrex vessel under conventional heating is similar to those under microwave heating (Table 7, entries 1-2). No effect of microvaves has been observed for the cascade reaction. Scaling-up in 60 mL then 300 mL Teflon reactors allowed to obtain 2,2-diphenylethanol (6a) gave similar yields and selectivity (Table7, entries 3-4). Working on a 5 gram-scale did not significantly change the selectivity. In fact, 8% of pinacol 2a was observed at the end of heating. As a consequence, increasing the time of heating could help to totally convert pinacol 2a (Table 7, entry 4). Conducting the cascade reaction on a 12 gram-scale in a steel reactor gave the expected results (Table 7, entry 5). A good 79% yield in targeted 2,2-diphenylethanol (6a) is obtained, accompanied by small

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3 amounts of side products. The conversion of pinacol **2a** is not complete and could led to an  
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5 increase in yield by a longer heating at 160°C.  
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## 8 **CONCLUSION**

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10 A simple, green and reusable medium has been optimized for the one-pot-three-step pinacol-  
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12 coupling-rearrangement-reduction cascade reaction to give 2,2-diphenylethanol derivatives in  
13  
14 70-85% yields from aromatic aldehydes in water. The originality of this medium is the use of  
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16 Amberlite®IR120 as heterogeneous regenerable proton supplier and zinc as cheap electron  
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18 supplier. This supported acid proved to enhance the selectivities of the reaction. Due to its  
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20 high stability, regenerated Amberlite®IR120 can be reuse 10 times without degradation or  
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22 loss in activity, allowing limiting waste production. Moreover, scale-up of the process can be  
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24 made using autoclaves without significant loss in reactivity nor selectivity.  
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## 32 **EXPERIMENTAL SECTION**

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35 **General.** All commercially available products and solvents were used without further  
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37 purification. Reactions were monitored by TLC (Kieselgel 60F254 aluminum sheet) using a  
38  
39 cyclohexane/AcOEt eluent with detection by UV light or potassium permanganate acidic  
40  
41 solution. Column chromatography was performed on silica gel 40–60 μm. Flash column  
42  
43 chromatography was performed on an automatic apparatus, using silica gel cartridges. <sup>1</sup>H and  
44  
45 <sup>13</sup>C NMR spectra were recorded on a 400 MHz/54 mm ultralong hold. Chemical shifts (δ) are  
46  
47 quoted in parts per million (ppm) and are referenced to TMS as an internal standard. Coupling  
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49 constants (J) are quoted in hertz. Comparisons with known or reported compounds have been  
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51 used to confirm the NMR peak assignments.  
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3       **General procedure.** A 30 mL pyrex vessel adapted to microwave irradiation was charged  
4 with the aldehyde (**1**) (1.5 mmol), Amberlite IR120 (1.75 g, 5.0 eq), zinc (294 mg, 3.0 eq) and  
5 water (5 mL). The mixture was irradiated under stirring (rpm 600) at 90°C for 1 hour then  
6 gradually heated to 160°C in 10 minutes. The resulting mixture was kept at 160°C during 50  
7 additional minutes under stirring. At the end of the reaction, zinc and Amberlite IR120 are  
8 filtered and the final product is extracted from the filtrate with EtOAc (3 × 10 mL). The  
9 organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude  
10 product was purified over a column of silica gel and eluted with a gradient of cyclohexane /  
11 ethyl acetate.  
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23       **Procedure for the 12g scale process.** A 750 mL steel reactor was charged with  
24 benzaldehyde (12 g, 120 mmol), Amberlite IR120 (140 g, 5 eq), zinc (23.5 g, 3 eq) and water  
25 (400 mL). The mixture was heated at 90°C for 1 hour then gradually heated to 160°C in 10  
26 minutes. The resulting mixture was kept at 160°C during 50 additional minutes under stirring.  
27 At the end of the reaction, zinc and Amberlite IR120 are filtered and the final product is  
28 extracted from the filtrate with EtOAc (3 × 300 mL). The organic phase was washed twice by  
29 sole water (2\*250 mL), dried over anhydrous sodium sulfate and concentrated in vacuo. The  
30 crude product was then recrystallized from ethanol to give 2,2-diphenylethanol **6a** in 79%  
31 yield.  
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43       **2,2-Bis(4-fluorophenyl)ethanol (6c).** A 30 mL pyrex vessel adapted to microwave  
44 irradiation was charged with 4-fluorobenzaldehyde (**1c**) (186 mg, 1.5 mmol), Amberlite  
45 IR120 (1.75 g, 5.0 eq), zinc (294 mg, 3.0 eq) and water (5 mL). The mixture was irradiated  
46 under stirring (rpm 600) at 90°C for 1 hour then gradually heated to 160°C in 10 minutes. The  
47 resulting mixture was kept at 160°C during 50 additional minutes under stirring. At the end of  
48 the reaction, zinc and Amberlite IR120 are filtered and the final product is extracted from the  
49 filtrate with EtOAc (3 × 10 mL). The organic phase was dried over anhydrous sodium sulfate  
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3 and concentrated in vacuo. The crude product was purified over a column of silica gel and  
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5 eluted with a gradient of cyclohexane / ethyl acetate to give the product **6c** (131 mg, 75%  
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7 yield) was isolated as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.47 (bs, 1H, OH),  
8  
9 4.20-4.11 (m, 3H,  $\text{CH}-\text{CH}_2-\text{OH}$ ), 7.04-6.99 ( $t_{\text{app}}$ ,  $\text{H}_{1/1'}$ ,  $^3J_{\text{H-H}}=^3J_{\text{H-F}} = 8.7$  Hz, 4H), 7.20 (dd,  
10  
11  $\text{H}_{2/2'}$ ,  $^3J_{\text{H-H}} = 8.5$  Hz,  $^4J_{\text{H-F}} = 5.4$  Hz, 4H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 52.0 ( $\text{CH}_2$ ), 66.1  
12  
13 (CH), 115.6 (d, 2  $\text{C}_{1/1'}$ ,  $^2J_{\text{C-F}} = 21.2$  Hz, 2 CHAr), 129.7 (d, 2  $\text{C}_{2/2'}$ ,  $^3J_{\text{C-F}} = 7.9$  Hz, 2 CHAr),  
14  
15 137.0 (d,  $^4J_{\text{C-F}} = 3.0$  Hz, 2  $\text{C}_{\text{IV}}$ , 2  $\text{C}_{3/3'}$ ), 162.8 (d,  $^1J_{\text{C-F}} = 245$  Hz, 2  $\text{C}_{\text{IV}}$ , 2  $\text{C}_{4/4'}$ ). HRMS:  
16  
17 235.0911 (100%), calculated 235.0934  $[\text{M} + \text{H}]^+$ ; 257.0724 calculated 257.0754  $[\text{M} + \text{Na}]^+$ .  
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24 **2,2-Di-*meta*-toluylethanol (6g).** A 30 mL pyrex vessel adapted to microwave irradiation  
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26 was charged with 3-methylbenzaldehyde (**1g**) (180 mg, 1.5 mmol), Amberlite IR120 (1.75 g,  
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28 5.0 eq), zinc (294 mg, 3.0 eq) and water (5 mL). The mixture was irradiated under stirring  
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30 (rpm 600) at 90°C for 1 hour then gradually heated to 160°C in 10 minutes. The resulting  
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32 mixture was kept at 160°C during 50 additional minutes under stirring. At the end of the  
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34 reaction, zinc and Amberlite IR120 are filtered and the final product is extracted from the  
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36 filtrate with EtOAc (3 × 10 mL). The organic phase was dried over anhydrous sodium sulfate  
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38 and concentrated in vacuo. The crude product was purified over a column of silica gel and  
39  
40 eluted with a gradient of cyclohexane / ethyl acetate to give the product **6g** (139 mg, 82%  
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42 yield) was isolated as a colorless oil.  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 1.66 (bs, 1H, OH),  
43  
44 2.31 (bs, 6H, 2  $\text{CH}_3$ ), 4.10 (bs, 3H,  $\text{CH}-\text{CH}_2-\text{OH}$ ), 7.06-7.01 (m, 6H, CHAr), 7.19 (t,  $J = 8.0$   
45  
46 Hz, 2H, HAr).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.6 (2  $\text{CH}_3$ ), 53.7 ( $\text{CH}_2$ ), 66.2 (CH), 125.3  
47  
48 (2 CHAr), 127.6 (2 CHAr), 128.6 (2 CHAr), 129.2 (2 CHAr), 138.3 (2  $\text{C}_{\text{IV}}$ ), 141.5 (2  $\text{C}_{\text{IV}}$ ).  
49  
50 HRMS: 227.1514 (100%), calculated 227.1436  $[\text{M} + \text{H}]^+$ ; 249.1278 calculated 248.1255  $[\text{M}$   
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52 +  $\text{Na}]^+$ .  
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**2,2-Di-ortho-toluylethanol (6h).** A 30 mL pyrex vessel adapted to microwave irradiation was charged with 2-methylbenzaldehyde (**1h**) (180 mg, 1.5 mmol), Amberlite IR120 (1.75 g, 5.0 eq), zinc (294 mg, 3.0 eq) and water (5 mL). The mixture was irradiated under stirring (rpm 600) at 90°C for 1 hour then gradually heated to 160°C in 10 minutes. The resulting mixture was kept at 160°C during 50 additional minutes under stirring. At the end of the reaction, zinc and Amberlite IR120 are filtered and the final product is extracted from the filtrate with EtOAc (3 × 10 mL). The organic phase was dried over anhydrous sodium sulfate and concentrated in vacuo. The crude product was purified over a column of silica gel and eluted with a gradient of cyclohexane / ethyl acetate to give the product **6h** (141 mg, 83% yield) was isolated as a colorless oil. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.30 (bs, 6H, 2 CH<sub>3</sub>), 4.08 (d, *J* = 7.0 Hz, 2H, CH<sub>2</sub>-OH), 4.54 (t, *J* = 7.0 Hz, 1H, CH), 7.17-7.15 (m, 8H, CHAr). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 19.5 (2 CH<sub>3</sub>), 45.7 (CH<sub>2</sub>), 64.9 (CH), 126.2 (2 CHAr), 126.6 (2 CHAr), 127.26 (2 CHAr), 130.8 (2 CHAr), 136.9 (2 C<sub>IV</sub>), 139.0 (2 C<sub>IV</sub>). HRMS: 227.1488 (100%), calculated 227.1436 [M + H]<sup>+</sup>; 249.1185 calculated 248.1255 [M + Na]<sup>+</sup>.

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### Notes

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## 8 SUPPORTING INFORMATION

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11 Experimental part for known products. <sup>1</sup>H and <sup>13</sup>C NMR spectra for all compounds are  
12 provided as supporting information.  
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