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First Pinacol Coupling in Emulsified Water: Key Role of Surfactant and Impact of Alternative Activation Technologies

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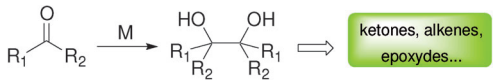
For the first time, the influence of surfactants on the radical pinacol coupling reaction is investigated. The rate and selectivity of this reductive C-C coupling are compared under three different activation technologies: thermal activation, microwave irradiation, and sonication. The use of IgepalCO520, a neutral surfactant, led to the successful conversion of aromatic or α,β-unsaturated aliphatic carbonyl compounds in moderate to excellent yield (55-90%). An insight on the potential mechanism involved in the reaction is also proposed, based on microscopic observations and particle size measurement.

Introduction

The reductive dimerization of carbonyl compounds, the so-called pinacol coupling, is a useful synthetic method for constructing vicinally functionalized carbon–carbon bonds. One-electron transfer from a metal to a carbonyl function generates the corresponding ketyl radical, which can dimerize to give either *dl* and/or *meso* isomers of 1,2-diols. These vicinal diols can serve as structural motif in total synthesis, chiral auxiliaries or chiral ligands, crosslinker agents in polymer synthesis, pesticides, and substrates useful in structural biology.[1] These diols can even be converted into a number of high value compounds such as aminoalcohols, epoxides, ketones, and so on. (Scheme 1).



Scheme 1. Pinacol coupling: a versatile reaction.

A variety of methods have been used to perform this reaction. Among them, the most reliable protocols use low-valent metals or metal complexes in stoichiometric or catalytic amounts. In each pinacol coupling reaction, the selectivity between pinacol formation and side reactions (reduction of the carbonyl group, McMurry reaction, pinacolic rearrangement, or dehydration)[2] has to be taken into account to design an efficient reaction medium. Pinacol-type couplings were developed by using a Zn–Cu couple,[3] Mg,[4] Mn,[5] Zn,[6] In,[7] Sm,[8] Al,[9] Ga,[10] and other metals.[11] Some also reported the use of metallocene compounds to promote the reaction such as Ti-, V-, or Zr- derivatives.[12]

Recently, organic reaction in water or aqueous media has attracted great interest in organic synthesis from the vantage points of cost, safety, and environmental concerns. Therefore, the development of an efficient synthetic methodology to form carbon–carbon bonds in water or aqueous media appears to be very important. In the case of radical reactions, it was also demonstrated that solvent plays a crucial role and water allows control of radical reactions.[13] On the basis of these observations, pinacol coupling has already been carried out in aqueous media.[14]

However, few methods have been reported for pinacol coupling in pure water, and each suffers from drawbacks: use of an excess of low-valent metal, long time of reaction (from 8 h to 3 days), limited selectivity, and so on. Moreover, the potential scope of aqueous pinacol coupling is drastically reduced when highly hydrophobic substrates are involved in the chemical transformations.[15] To overcome this problem, some works deal with the use of additives to enhance the reactivity in pure water.[16a–d] Among them, micellar catalysis has been intensively developed during the last two decades.[16] However no successful method using surfactant has been already reported for the pinacol coupling.

We herein describe the pinacol coupling reaction in emulsified water via three different activation methods: thermal activation, microwave irradiation, and sonication. Comparison of commercially available surfactants with phase-transfer agents, kinetics, selectivity, and limitations of the reaction will be discussed for each activation technology. Moreover, some micro-

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scopic observations and particle size measurements have been carried out, leading to a mechanistic proposal.

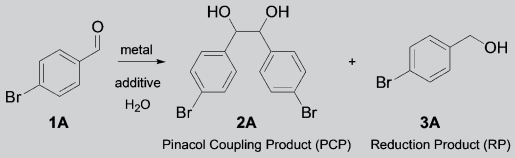
Results and Discussion

Objectives and methodological study under conventional heating

In order to design adapted protocol for coupling of highly hydrophobic and insoluble substrates in water, 4-bromobenzaldehyde (**1 A**) was selected as a model (Table 1). Firstly, 4-bromobenzaldehyde (**1 A**) was subjected to previously reported methods for pinacol coupling in water.[4a,6a,9a] Using a large excess of Mg in the presence of 0.1 M NH_4Cl did not allow complete conversion after 15 h but gave a very good selectivity (Table 1, entry 1).[4a] Decreasing the quantity of metal led to lower conversion but still very good selectivity, showing the potential of NH_4Cl as acid source to control the selectivity but also the limited ability of Mg to activate the reaction (Table 1, entries 4 and 5). In our study, performed according to the Hazarika and Dutta protocol,[6a] zinc combined with $AlCl_3$ as Lewis acid at room temperature led to low conversion and selectivity after 15 h of reaction (Table 1, entry 2).

However, Zn seems more active than Mg at low quantity. When reaction was carried out according to Yuan et al the combination of Al/oxalic acid did not allow good conversion nor selectivity (Table 1, entry 3).[9a] Based on these results, zinc (2 equiv) as cheaper low valent metal and ammonium chloride solution as solvent were selected for further studies.

Table 1. Initial study in water with 4-bromobenzaldehyde **1 A** as model substrate.



Entry	Metal [equiv]	Acid ([C])	T [°C]	t [h]	Conversion [%]	**2 A** [%]	**2 A**/**3 A** [%]
1[4a]	Mg (21 equiv)	NH_4Cl (0.1 M)	rt	15	55	45	90/10
2[6a]	Zn (1.5 equiv)	$AlCl_3$ (0.1 M)	rt	15	33	17	67/23
3[9a]	Al (2 equiv)	oxalic acid (0.04 M)	45	18	30	10	25/75
4	Mg (10 equiv)	NH_4Cl (0.1 M)	rt	15	35	31	89/11
5	Mg (2 equiv)	NH_4Cl (0.1 M)	rt	15	< 5	traces	ND[a]
6		NH_4Cl (0.1 M)	rt	15	30	28	90/10
7		NH_4Cl (0.5 M)	rt	15	45	39	89/11
8		NH_4Cl (1 M)	rt	15	60	52	87/13
9		NH_4Cl saturated	rt	15	70	53	76/24
10		NH_4Cl (1 M)	45	0.5	39	27	82/18
11	Zn (2 equiv)	NH_4Cl (1 M)	45	1	57	43	82/18
12		NH_4Cl (1 M)	45	2	77	55	83/17
13		NH_4Cl (1 M)	45	14	97	57	82/18
14		NH_4Cl (1 M)	80	1	56	46	82/18
15		NH_4Cl (1 M)	80	2	70	55	80/20
16		NH_4Cl (1 M)	80	6	85	70	82/18
17	Zn (1 equiv)	NH_4Cl (1 M)	45	2	58	45	78/22

[a] ND = not determined

The concentration of ammonium chloride and the temperature of reaction were then screened for a maximal time of 15 h. At room temperature, the kinetics of reaction improved with increasing ammonium chloride concentration but was accompanied by a decrease in selectivity (Table 1, entries 6–9). The use of NH_4Cl (1 M) afforded the same yield and a better selectivity for compound **2 A** compared with that obtained with saturated NH_4Cl (Table 1, entries 8 and 9). To avoid the incomplete conversion of starting material **1 A**, higher temperatures were investigated. At 45 °C, complete conversion was achieved only after 14 h (Table 1, entry 13) but only 1–2 h were sufficient to obtain the same results as after 15 h at room temperature (Table 1, entries 8, 11 and 12). For few hours of reaction (1–2 h), similar results were observed at 45 °C and 80 °C (Table 1, entries 11, 12, 14, and 15). For each temperature, conversion of 4-bromobenzaldehyde (**1 A**) increased with time without affecting the yield of target compound **2 A** after 2 h at 45 °C (Table 1, entry 12) and 6 h at 80 °C (Table 1, entry 16). These results mean that side reactions are preferentially conducted when time of reaction was too long. The main difference appeared after 6 h of reaction at 80 °C, when 70% yield was observed (Table 1, entry 16). Decreasing the zinc amount to 1 equivalent led to poorer yield and selectivity after 2 h (Table 1, entry 17).

From these results, in order to achieve short reaction times and find a compromise between rate and selectivity, the reaction was carried out at 45 °C with 1 M ammonium chloride as aqueous medium and 2 equivalents of zinc as metallic reductor for one hour (Table 1, entry 11). Using these optimized conditions, phase transfer agents or surfactants were added in order to study their potential effect.

Effects of additives on yields and selectivity

In a first screening, the amount of commercial additives was set at 1 wt.% and different families of phase transfer agents [18-crown-6, tetra-n-butylammonium bromide (TBAB)] and surfactants [cetyltrimethylammonium bromide (CTAB), SDS, Brij, Tween, Triton, IgepalCO] were studied (Table 2). From this screening it was clear that additives played an essential role during the pinacol coupling reaction in water. In fact, 70% yield was achieved using BrijL4 as additive compared with 43% under the same conditions without any promoter (Table 2, entries 1 and 6). The use of neutral and cationic phase

Table 2. Effects of commercial additives (1 wt.%) when pinacol coupling starting from compound **1 A** is carried out 1 hour at 45 °C.

Entry	Additive	Charge	Conversion	**2 A** [%]	**3 A** [%]	Other [%]	Global sel. [%][a]	**2 A**/**3 A** [%]
1	none	–	57	43	9	11	75	82/18
2	18-crown-6	neutral	54	39	4	10	72	91/9
3	TBAB	cationic	83	43	13	27	52	77/23
4	CTAB	cationic	78	44	12	22	56	78/22
5	SDS	anionic	40	31	4	5	77	88/12
6	BrijL4	neutral	94	70	11	13	75	86/14
7	Tween 20	neutral	92	66	11	15	72	86/14
8	IgepalCO630	neutral	82	66	8	8	81	89/11
9	Triton X100	neutral	85	63	8	14	74	89/11
10	Brij98	neutral	87	60	10	17	69	86/14
11	BrijC10	neutral	86	55	10	21	64	85/15
12	Monomuls90 L12	neutral	74	50	8	16	68	86/14
13	Sympatens AC100	neutral	76	50	8	18	66	86/14
14	Tween 80	neutral	75	51	7	17	68	88/12

[a] Global selectivity is defined as PCP/conversion. PCP = pinacol coupling product.

transfer agents did not allow any improvement in yield (Table 2, entries 2 and 3). Cationic phase transfer agent like TBAB and cationic surfactant CTAB seem to boost the kinetics of reaction. Indeed, cationic additives allowed to achieve high conversions but limited yields of compound **2 A**, which dramatically decreases the global selectivity of the reaction. In fact, numerous side products were observed with such cationic promoters. It could be hypothesized that cationic species such as quaternary ammonium N^+ replace Zn^{2+} in some intermediate species of reaction. As Zn^{2+} is essential for the ketyl radicals to meet, its replacement by a non-chelating species results in many undesired products. Moreover, using a cationic promoter increases the salinity of the media and acts on kinetics, for example by increasing the concentration of NH_4Cl (Table 2, entries 3 and 4). Using SDS as promoter led to a decrease in kinetics even if global and relative good selectivities were maintained (Table 2, entry 5). This could be explained by electrostatic repulsions between the charged intermediates of reaction (complexes of Zn^{2+} and ketyl radicals) and the anionic polar head of SDS.

Different neutral surfactants were tested (Table 2, entries 6–14). In our study, all neutral surfactants led to yields above 50% (compared with 43% without any promoter) and global and relative selectivities are similar (Table 2, entries 6–14). Particularly, BrijL4, Tween 20, IgepalCO630, and Triton X-100 all allowed a great improvement in kinetics and good yield (Table 2, entries 6–9). BrijL4 and IgepalCO630 share lot of structural similarities. In fact, they both consist of a hydrophobic tail and a linear hydrophilic PEG chain. The major difference between the two surfactants is the presence of an aromatic ring spacer in IgepalCO630. From these data, IgepalCO630 proved to be less active on kinetics than BrijL4 but the quality of the reaction seems better as less side-products are obtained. In this regards, the IgepalCO family was further studied to determine the optimal structure of the hydrophilic part (Table 3).

It seems that a shorter hydrophilic head is better for an improved yield in pinacol coupling product **2 A**. In fact, for the IgepalCO derivatives, the best candidate is the one with the shorter polar head (Table 3, entry 1). As a consequence, IgepalCO520, exhibiting an HLB around 10, was selected for further optimization.

Table 3. Influence of the PEG length on yield for the IgepalCO family.

Entry	Surfactant	Number of PEG units [*n*][a]	**2 A** [%]
1	IgepalCO520	5	68
2	IgepalCO630	10	66
3	IgepalCO720	12	57

[a] *n* = number of PEG units of the hydrophilic head.

Green aspects

Some adjustments were made to respect as far as possible the green chemistry concepts. In these regards the energy saving, the catalyst loading and the recycling of the medium were studied with variation of reaction time and surfactant concentration. For IgepalCO520, after 1 hour of reaction, the best concentration was confirmed at 1 wt.% (Figure 1). In our hands, higher conversion of aldehyde **1 A** and selectivity were observed after 2 h in the presence of IgepalCO520 (1 wt.%) (Table 4, entry 2). Decreasing the quantity of reductant led to a drop in yield from 80% to 54% (Table 4, entry 3). As a consequence, the scope of reaction was investigated with zinc (2 equiv), IgepalCO520 (1wt.%) in NH_4Cl (1 M) as medium at 45 °C over 2 h.

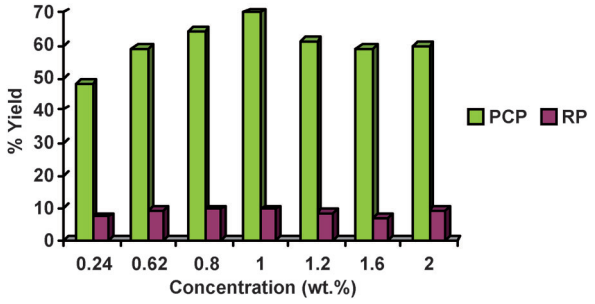


Figure 1. Yield of **2 A** versus concentration (wt.%) of IgepalCO520. PCP = pinacol coupling product, RP = reduction product.

In these conditions, recycling of the medium was realized. The aqueous medium, containing IgepalCO520 and NH_4Cl can be successfully recycled 4 times without significant loss of activity or selectivity, although zinc is oxidized and cannot be reused easily. At the end of the reaction, zinc and zinc salts are filtered off and the aqueous medium is extracted by ethyl ace-

Table 4. Study of time of pinacol coupling reaction for IgepalCO520 (1 wt.%)

Entry	Metal	*t* [h]	**2A** [%]	**3A** [%]	Global sel. [%][a]	**2A**/**3A** [%]
1	Zn (2 equiv)	1	68	6	85	92/8
2	Zn (2 equiv)	2	80	18	84	82/18
3	Zn (1 equiv)	2	54	10	84	84/16

[a] Global selectivity is defined as PCP/conversion.

tate to recover the products. The organic phase is discarded and the aqueous phase can be reengaged in reaction with the addition of zinc (2 equiv) (Figure 2). The slow decrease in reactivity can be attributed to a loss of surfactant during the extraction step by ethyl acetate.

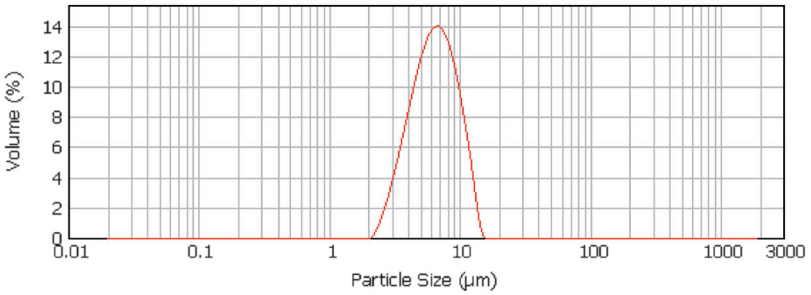


Figure 3. Dynamic light scattering: particle distribution in reaction medium.

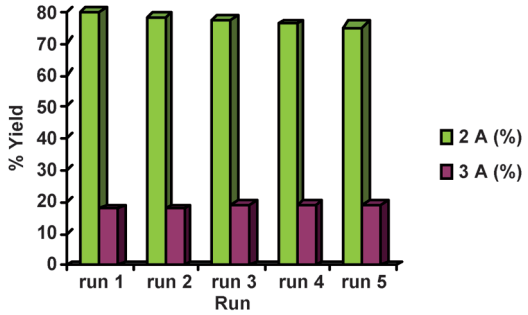


Figure 2. Recycling of the aqueous medium for 2 h of reaction.

Mechanistic proposal

Knowing that size and charge of the surfactant involved in the reaction is of importance in reactivity and selectivity, some physical observations and measurements were carried out to better understand the mechanism of pinacol coupling reaction in emulsified water under classical activation.

Aggregation behavior was investigated in reaction conditions. Bromobenzaldehyde (**1A**), NH_4Cl, and zinc were suspended in aqueous IgepalCO520 (1% *w*/*w*). The mixture was stirred at room temperature for 10 min and then aqueous medium was filtered off. The aqueous phase was analyzed by dynamic light scattering and by direct ocular microscopy with and without addition of a lipophilic colorant.

First of all, dynamic light scattering studies (Figure 3) reveal that compounds spontaneously self-assemble in aqueous solution and that bromobenzaldehyde (**1A**) interacts with the obtained micro-structures. The size of the structures observed is between 3 and 10 micrometers, largely above the classical size for micelles.

Moreover, direct observation by ocular microscopy proved that the reaction medium is composed of droplets of "oil" dispersed in water (Figure 4). The term "oil" refers to the mixture of bromobenzaldehyde (**1A**) and surfactant. To prove the formation of droplets, some lipophilic colorant was added in the pre-formed medium. It is obvious that the lipophilic additive dissolved gradually in the oil phase (Figure 5).

When combining all results, it could be hypothesized that the pinacol coupling reaction takes place on the surface of the droplets formed by the association of the surfactant and aldehydes. The droplet could act as a reservoir for bromobenzaldehyde (**1A**). During the course of reaction, apparent orientation of the different intermediates occurred at the oil–water interface. Indeed, the aromatic ring and the chelate between metal and oxygen atoms have high affinities with oil and water, respectively. Consequently, a mechanistic proposal for pinacol coupling reaction could be realized as detailed in Scheme 2.

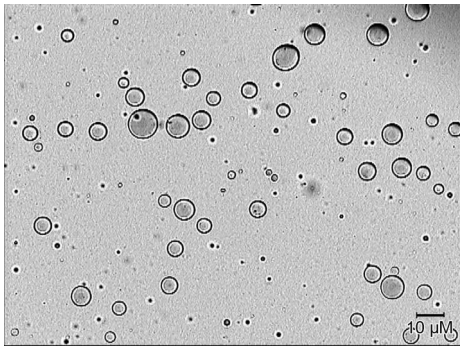


Figure 4. DLS: evolution of the medium when the aqueous medium is sonicated. (A) under 10 min of classical stirring; (B) the same solution after 5 min of sonication at 100 Hz.

Scope of the reaction

Various carbonyl compounds were submitted to the pinacol coupling reaction under these optimized conditions. Several structurally different aromatic or aliphatic aldehydes underwent reductive coupling to the corresponding 1,2-diols in good to high yields (Table 5). The reaction rates were faster than those described in many existing methods. The selectivities of the pinacol coupling reaction are above 50% for all

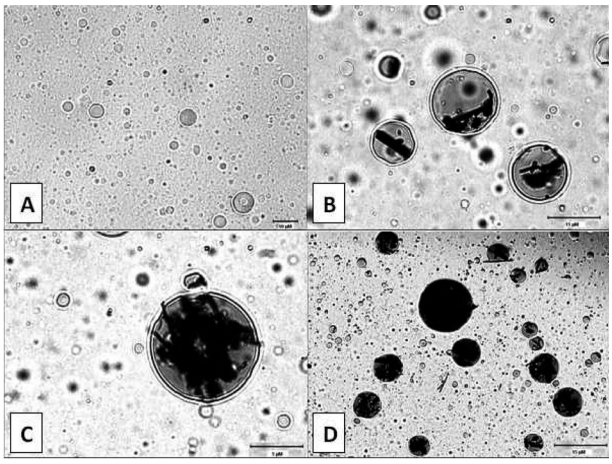
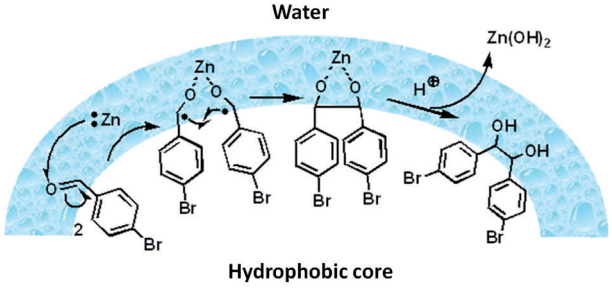


Figure 5. Direct observation of the dissolution of the lipophilic colorant (organoblue) in the droplets. (A) medium whithout colorant; (B) beginning of the absorption of colorant in the "oil" phase; (C) progressive dissolution of the lipophilic additive in the droplet; (D) quasi-totale coloration of the lipophilic phase. The length of the scale bars are: (A) 10 μm, (B) 15 μm, (C) 5 μm, (D) 15 μm.



Scheme 2. Mechanistic proposal for the pinacol coupling assisted by surfactants.

compounds, even if some of them react slowly (Table 5, entries 9, 11, 13, 19, 21 and 22).

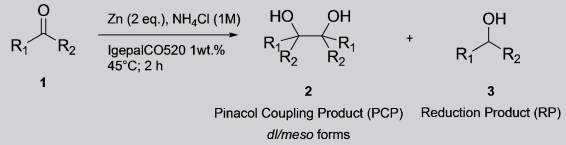
First, we were interested in the pinacol coupling of aliphatic α,β-unsaturated compounds (Table 5, entries 1–7). Indeed, even if numerous natural α,β-unsaturated carbonyl compounds exist such as citral A (**1G**), their transformation is rarely described in the literature. Upon checking the few reported methods in water, we found that no studies have dealt with the coupling of such compounds. Moreover, under traditional conditions (with co-solvents for instance), the yields in pinacol coupling products are low. For example, pinacol coupling of trans-2-hexenal was performed using TiI_4 in EtCN with a 16% yield.[17] Geranial was coupled by electrochemical reduction in EtOH-Ph5 buffer in around 35% yield.[18] Our methodology enables the coupling of aliphatic α,β-unsaturated compounds in good-to-excellent yields, even for hindered or long chain substrates (Table 5, entries 1–7). Trans-2-hexenal (**1B**) proved to be a perfect substrate for pinacol coupling leading **2B** in an excellent 90% yield with high selectivity (Table 5, entry 1). Long chain compounds such as 2-trans-decenal (**1C**) and 2,4-decadienal (**1D**) (Table 5, entries 2 and 3) gave moderate yields. This could be explained by their interaction with the hydrophobic tail of the surfactant, which gave high stability of the products in the aggregates and prevented pinacol coupling. Comparing 2-trans-decenal (**1C**) with 2,4-decadienal (**1D**) having the same skeleton, the global selectivity decreased for **1D** due to a higher stability of ketyl radical but the *meso* isomer was obtained quantitatively (Table 6, entries 2 and 3). Due to the absence of chiral inductor, this result was of particular interest. Some much hindered aliphatic α,β-unsaturated compounds were then tested, such as trans-2-methylbutenal (**1E**), trans-2-methylpentenal (**1F**), and citral A (**1G**) (Table 5, entries 4–6). It is notable that an increase in the steric hindrance around the carbonyl group affected distribution of the ratio of *meso* and *dl* isomers. In fact, as proved by products **2E** and **2F**, if the position 2 is substituted by a methyl group, the *meso* isomer is obtained selectively (Table 5, entries 4 and 5). It is noteworthy than citral A (**1G**), a long chain hindered natural aliphatic α,β-unsaturated aldehyde, reacted well under these conditions to result in a mixture of *meso* and *dl* isomers (Table 5, entry 6). To our knowledge, it is the first time that citral A (**1G**) proved to be a good substrate for pinacol coupling in water. Cinnamaldehyde (**1H**) (Table 5, entry 7) gave moderate conversion and yield. It could be attributed to the particular stabilization of the ketyl radical.

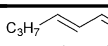
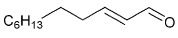
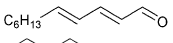
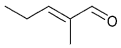
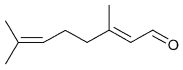
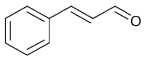
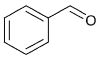
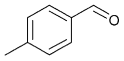
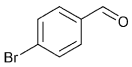
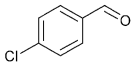
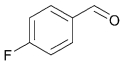
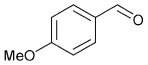
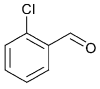
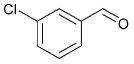
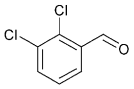
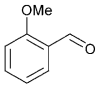
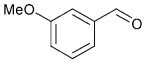
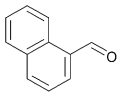
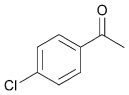
In a second part, some aromatic aldehydes **1** having various electrostatic effect on the aromatic ring and steric hindrance near the carbonyl group were subjected to our pinacol coupling system. Products **2** were always obtained with an excess of the *meso*-type isomer (Table 5). Compounds **1J**, **1K**, and **1S** reacted slowly under these conditions (Table 5, entries 9, 11, and 19) probably due to the observed aggregation around the magnetic stirrer at the end of the reaction. Moreover, 1-naphtaldehyde (**1S**) is highly hindered, which could decrease its own reactivity. To avoid aggregation, much vigorous stirring was attempted without real success. Aromatic aldehydes substituted by electron-withdrawing group gave higher yields than by electron-donating group at the same position. For example, 4-bromo- and 4-fluorobenzaldehydes **1A** and **1I** gave higher yields than 4-methoxybenzaldehyde (**1M**) (Table 5, entries 10, 12 and 13). In the same manner, compounds **1N** and **1O** having a chlorine atom in position 2 and 3 on the aromatic ring gave better results than compounds **1Q** and **1R** having a methoxy group in the same position (Table 5, entries 14, 15, 17 and 18). The 2,3-dichlorobenzaldehyde (**1P**) gave quantitative conversion and similar yields to those obtained for the chloro analogues **1N** and **1O** (Table 5, entry 17).

Heteroatomic aromatic aldehyde such as furfural **1T** reacted quickly under these conditions giving **2T** in a moderate 51% yield. Numerous side products were observed, which is not surprising due to the known instability of furfural (Table 5, entry 20).

Concerning acetophenone derivatives **1U** and **1V** (Table 6, entries 21 and 22), their very slow reactivities could be attributed to the difficulty in generating and stabilizing the ketyl radical on this aromatic ketone compared with aromatic aldehydes as previously described.[19] It is noteworthy that total selectivities and excess in *dl* isomer were obtained with acetophenone derivatives.

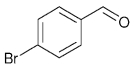
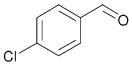
Table 5. Scope of the pinacol coupling reaction.



Entry	Substrate (**1**)		Conversion	**2** [%]		**3** [%]		*dl*/*meso*[a]	Global sel. [%][b]	**2**/**3** [%]
1		**1B**	100	90	**2B**	5	**3B**	40/60	90	95/5
2		**1C**	65	58	**2C**	4	**3C**	38/62	89	93/7
3		**1D**	90	65	**2D**	ND	**3D**	0/100	72	ND
4		**1E**	100	90	**2E**	9	**3E**	0/100	90	91/9
5		**1F**	100	83	**2F**	7	**3F**	0/100	83	92/8
6		**1G**	90	62	**2G**	ND	**3G**	39/61	69	ND
7		**1H**	70	55	**2H**	5	**3H**	46/54	79	92/8
8		**1I**	100	78	**2I**	20	**3I**	42/58	78	80/20
9		**1J**	40	26	**2J**	12	**3J**	48/52	65	68/32
10		**1A**	95	80	**2A**	18	**3A**	27/73	84	82/18
11		**1K**	40	28	**2K**	8	**3K**	26/74	70	78/22
12		**1I**	89	71	**2I**	18	**3I**	34/66	80	80/20
13		**1M**	17	12	**2M**	4	**3M**	48/52	71	75/25
14		**1N**	100	69	**2N**	31	**3N**	11/89	69	69/31
15		**1O**	100	77	**2O**	22	**3O**	19/81	77	77/23
16		**1P**	100	78	**2P**	20	**3P**	16/84	78	80/20
17		**1Q**	90	60	**2Q**	29	**3Q**	30/70	67	67/33
18		**1R**	91	73	**2R**	7	**3R**	24/76	80	91/9
19		**1S**	10	9	**2S**	1	**3S**	12/88	90	90/10
20		**1T**	100	51	**2T**	29	**3T**	32/68	51	64/36
21		**1U**	5	5	**2U**	0	**3U**	54/46	100	100
22		**1V**	6	6	**2V**	0	**3V**	59/41	100	100

[a] The *dl*/*meso* ratio was determined by ^{1}H NMR of the crude product. [b] Global selectivity is defined as PCP/conversion.

Table 6. Comparison of activation technologies.

Entry	Substrate	(1)	Activation method	*t* [h]	*T* [°C]	2 [%]
1		**1 A**	silent	2	45	80
2			)))[b]	1.5	rt to 80	81
3			MW[a]	2	45	25
4			MW[a]	1.5	80	72
5		**1 K**	silent	2	45	28
6			)))[b]	1.5	rt to 80	72
7			MW[a]	2	45	8
8			MW[a]	1.5	80	33

[a] for the reaction under microwave, the temperature was controlled by an external probe. [b] for sonication, the temperature was followed by an internal probe.

In order to improve the reactivity of slow reactive substrates or acetophenone derivatives and avoid aggregation issues, some alternative activation technologies were studied.

Impact of alternative activation technologies

Among all alternative activation technologies, microwave and ultrasound are the most popular, due to their high ability to increase rate and selectivity of reaction.

On the one hand, with its high dielectric constant, water is potentially a very useful solvent for microwave-mediated synthesis.[20] Indeed, microwave heating has been widely recognized as an efficient tool, and its benefits have been well-documented.[21] Since many reactions are known to result in higher yield and/or shorter reaction times, this alternative technology was developed in our group for Suzuki–Miyaura cross-coupling of uridine analogues or micellar Tsuji–Trost reaction in pure water.[22]

Nevertheless, to the best of our knowledge, there is no protocol for pinacol coupling in pure water under microwave heating. Only two protocols are described using Al/NaOH in MeOH[23] and $SmBr_2$, SmI_2, or YbI_2 in THF.[24] On the other hand, ultrasound has increasingly been used in organic synthesis. The main advantages of sonication are to increase reaction rate in the presence of metallic multiphasic medium or generate radicals.[25] In this regard, Li et al reported two protocols for pinacol coupling in acidic water with Mg/NH_4Br 0,1 M and Zn/H_3PO_4 3 N.[26]

In order to compare microwave irradiation and sonication, reaction was attempted on 4-bromobenzaldehyde (**1 A**) and 4-chlorobenzaldehyde (**1 K**) (Table 6). At 45 °C, under microwave irradiation, both aldehydes **1 A** and **1 K** reacted slowly giving lower yield than under thermal activation (Table 6, entries 3 and 7). Increasing temperature to 80 °C with a 1.5-hour reaction time, compound **1 A** proved to react smoothly and **1 K** was always poorly reactive. Concerning ultrasound activation, aldehyde **1 A** afforded the target compound **2 A** with yields similar to those obtained by classical activation (Table 6, entries 1–2). However, the slow reactive substrate **1 K** furnished the corresponding pinacol **2 K** in a good 72% yield (Table 6, entries 5 and 6).

During sonication, an ice bath was used to maintain a moderate temperature in the reaction medium. The maximal temperature reached was 80 °C within the medium. It is clear that sonication was attempted to help less reactive compounds (Table 7). Sonication greatly improved the reactivity of aldehydic substrates **1 H**, **1 J**, **1 K**, **1 M**, **1 S**, and **1 U** allowing total conversions for most of them (Table 7, entries 2, 4, 6 and 10). As expected, sonication prevents aggregation of the substrate and enhances its reactivity. For 4-methoxybenzaldehyde (**1 M**), the impact of sonication is less impressive but the conversion and yield are tripled with very good selectivities (Table 7, entry 8). Acetophenone (**1 U**), even under sonication, proved to react slowly, but with a total selectivity towards the pinacol coupling product **2 U** (Table 7, entry 12). For all compounds except **2 K**, the *dl*/*meso* ratio is similar under conventional heating and sonication.

The enhancement of reactivity under sonication can be related to the size of droplets involved in the reaction. In fact, it is obvious than smaller droplets are obtained when the aqueous medium is sonicated (Figure 6). Dynamic light scattering studies also proved that a new family of smaller droplets is created during sonication (Figure 7). As the reaction takes place at the interface between the oil phase and water, it can be hypothesized that the kinetics of reaction are better if droplets are smaller. In fact, the interface is larger and the reactivity of aldehydes (**1**) increased.

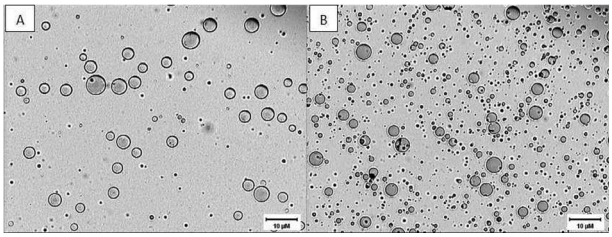
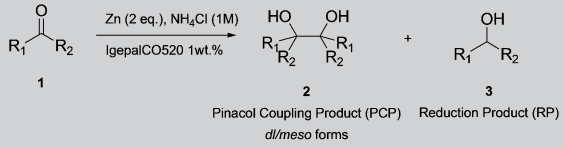


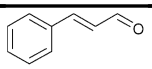
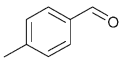
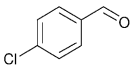
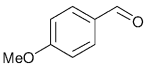
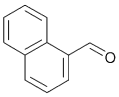
Figure 6. Evolution of the microemulsion when the aqueous medium is sonicated. (A) under 10 min of classical stirring; (B) the same solution after 10 min of sonication at 100 Hz.

Conclusion and perspectives

A novel, fast, and efficient protocol for the pinacol coupling of aromatic and α,β unsaturated aliphatic aldehydes has been realized thanks the use of IgepalCO520, a commercial neutral surfactant in water. Three activation technologies have been screened, and show different abilities. For this radical reaction, microwave irradiation has minimal effect but sonication proved to highly activate the reaction, avoiding aggregation issues. A mechanistic proposal has been suggested for the pinacol coupling under thermal activation, explaining all practi-

Table 7. Scope of the pinacol coupling assisted by IgepalCO520 under sonication and comparison with thermal activation.



Entry	Substrate	(1)	Activation method[a]	Conversion [%]	2 [%]		3 [%]		dl/meso[b]	Global sel. [%][c]	2/3 [%]
1			silent	70	55		5		46/54	79	91/9
2		1H	)))	100	88	2H	8	3H	45/55	88	83/17
3			silent	40	26		12		48/52	65	68/32
4		1J	)))	100	55	2J	45	3J	45/55	55	61/39
5			silent	40	28		8		26/74	70	78/22
6		1K	)))	100	72	2K	18	3K	45/55	72	80/20
7			silent	17	12		4		48/52	71	75/25
8		1M	)))	40	37	2M	3	3M	46/54	92	92/8
9			silent	10	9		1		12/88	90	90/10
10		1S	)))	100	88	2S	8	3S	10/90	88	92/8
11			silent	5	5		0		54/46	100	100
12		1U	)))	11	11	2U	0	3U	55/45	100	100

[a] For silent method, the reaction is carried out at 45 °C during 2 h; for sonication, the reaction is carried out during 1 h 30 at 200 Hz with an ice bath [b] The *dl/meso* ratio was determined by ^{1}H NMR of the crude product. [c] Global selectivity is defined as PCP/conversion.

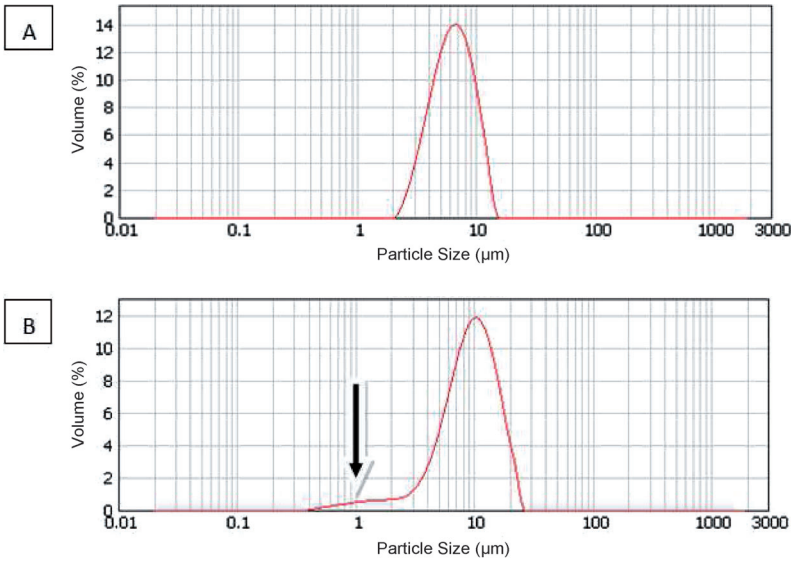


Figure 7. Direct observation of reaction medium.

cal observations. As far as we know, the pinacol coupling assisted by surfactant in water has never been described, especially for natural high value α,β-unsaturated aliphatic aldehydes such as citral A. This should be a method of choice to valorize other natural compounds such myrtenal, jasminaldehyde, and so on. As good-to-excellent diastereoselectivities were observed without chiral inductors, further investigation on the chiral intermediates should be carried out.

Experimental Section

Materials and methods

All commercially available products and solvents were used without further purification. Reactions were monitored by TLC (Kieselgel 60F254 aluminum sheet) with detection by UV light, or potassium permanganate acidic solution. Column chromatography was performed on silica gel 40–60 µm. Flash column chromatography was performed on an automatic apparatus, using silica gel cartridges. ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz/54 mm ultralong hold. Chemical shifts (δ) are quoted in parts per million (ppm) and are referenced to TMS as an internal standard. Coupling constants (J) are quoted in hertz. Microwave experiments were conducted in a commercial microwave reactor especially designed for synthetic chemistry. Monowave300

(Anton Paar, Austria) is a monomode cavity with a microwave power delivery system ranging from 0 to 850 W. The temperatures of the reactions were monitored via a contactless infrared pyrometer, which was calibrated in control experiments with a fiber-optic contact thermometer. Sealed vessels and a magnetic stir bar inside the vessel were used. Temperature and power profiles were monitored in both cases through the software provided by the manufacturer. For sonication, Reactions were performed with a 200 W ultrasonic probe (Bioblock Scientific, Vibra cell 75042) and monitored by HPLC assays. The *dl*/*meso* ratios were determined by means of ^{1}H NMR of the crude product for all compounds.

Light scattering measurements:

Dynamic light scattering measurements were carried out on a Mastersizer 2000 analyzer (Malvern Instruments Ltd, Worchestershire, UK). Increased sub-micrometer resolution was delivered via a dual-wavelength detection system. A short wavelength blue light source (0.3 mW LED, $\lambda = 470$ nm) was used in conjunction with forward and backscatter detection for enhanced sizing performance. This, combined with red-light measurements (4 mW He–Ne laser, $\lambda = 633$ nm), provided superior sensitivity across a wide size range. The Mastersizer 2000 was equipped with a Hydro2000SM wet sample dispersion unit.

Synthetic procedures

Conventional heating: A 10 mL flask was charged with the desired carbonyl compound (2,3 mmol), NH_4Cl (2 equiv, 248 mg), Zinc (2,1 equiv, 320 mg). The solution of the surfactant in water (1 wt.%, 5 mL) was then added. The mixture was heated at 45 °C for 2 h. At the end of the reaction, zinc is filtered and the final product is extracted with EtOAc (3×5 mL) before purification.
Microwave irradiation: A 30 mL vessel was charged with the desired carbonyl compound (2,3 mmol), NH_4Cl (2 equiv, 248 mg), Zinc (2,1 equiv, 320 mg). The solution of the surfactant in water (1 wt.%, 5 mL) was then added. The mixture was heated at the desired temperature (45 °C or 80 °C) for the optimized time (1.5 h or 2 h). At the end of the reaction, zinc is filtered and the final product is extracted with EtOAc (3×5 mL) before purification.
Sonication: In a 20 mL Beaker containing an IgepalCO520 aqueous solution (10 mg in 10 mL), zinc (451 mg, 6.9 mmol), NH_4Cl (500 mg, 4,6 mmol) and carbonyl compound (2.3 mmol) were introduced. The mixture was sonicated for 90 min in an ice bath (the ultrasonic probe was placed at 1 cm from the bottom of the beaker to ensure a homogenous dispersion). At the end of the reaction, zinc was filtered and the final product was extracted with EtOAc (3× 5 mL) before purification.

Compound 2A:[6a,7,27] 1,2-Bis(4-bromophenyl)-1,2-ethanediol (*dl* and *meso*)

Table 6 entry 10, white solid: ***dl*-2A**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 4.53 (s, 2H, C*H*-OH), 6.89 (d, $J = 8.4$ Hz, 4H, CH_{Ar}), 7.30 ppm (d, $J =$ 8.4 Hz, 4H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 78.5$ (CH), 122.2 (C_{IV}), 128.7 (2 CH_{Ar}), 131.4 (2 CH_{Ar}), 138.4 ppm (C_{IV}); ***meso*-2A**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.74$ (s, 2H, C*H*-OH), 6.98 (dd, $J = 8.4$, 1.6 Hz, 4H, CH_{Ar}), 7.34 ppm (d, $J = 8.4$, 1.6 Hz, 4H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 77.2$ (CH), 122.1 (C_{IV}), 128.7 (2 CH_{Ar}), 131.3 (2 CH_{Ar}), 138.3 ppm (C_{IV}), MS (ESI): 370.92 (51%) $[M+H]^+$, 372.92 (100%), 374.92 (49%); mp = 155–157 °C.

Compound 2B:[16,28] (4*E*,8*E*)-dodeca-4,8-diene-6,7-diol (*dl* and *meso*)

Table 6 entry 1, colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.84$–0.80 (m, 6H, 2 CH_3), 1.35–1.29 (m, 4H, 2 CH_2), 1.97–1.92 (m, 4H, 2 CH_2), 2.82 (brs, 2H, OH), 3.81 (d, $J = 8.4$ Hz, 2H, C*H*-OH *dl form*), 4.00 (d, $J = 8.4$ Hz, 2H, C*H*-OH *meso form*), 5.42–5.31 (m, 2H, C*H*=CH), 5.68–5.60 ppm (m, 2H, C*H*=CH); ***dl*-2B**: ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.6$ (CH_3), 22.2 (CH_2), 34.4 (CH_2), 76.1 (CH), 128.8 (CH=CH), 134.2 ppm (CH=CH); ***meso*-2B**: ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.6$ (CH_3), 22.2 (CH_2), 34.4 (CH_2), 75.7 (CH), 128.0 (CH=CH), 134.5 ppm (CH=CH); HRMS (ESI): found 221.1519; calculated 221.1517 for $C_{12}H_{22}O_2Na$.

Compound 2C: (8*E*,12*E*)-icosa-8,12-diene-10,11-diol (*dl* and *meso*)

Table 6 entry 2, white solid: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.82$–0.79 (m, 6H, 2 CH_3), 1.32–1.19 (m, 20H, 8 CH_2, 2OH, 1H from non-equivalent CH_2), 2.01–1.94 (m, 6H, 2CH_2, 1H from non-equivalent CH_2), 3.84 (dd, $J = 8.4$, 1.6 Hz, 2H, C*H*-OH *dl form*), 3.99 (dd, $J = 8.4$, 1.6 Hz, 2H, C*H*-OH *meso form*), 5.42–5.32 (m, 2H, C*H*=CH), 5.70–5.64 ppm (m, 2H, C*H*=CH); ***dl*-2B**: ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 13.1 (CH_3), 21.7 (CH_2), 28.1 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 31.4 (CH_2), 75.0 (CH), 127.4 (CH=CH), 133.8 ppm (CH=CH), ***meso*-2B**: ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.1$ (CH_3), 21.7 (CH_2), 28.1 (CH_2), 28.1 (CH_2), 28.2 (CH_2), 30.8 (CH_2), 74.6 (CH), 126.7 (CH=CH), 134.3 ppm (CH=CH), mp = 30–32 °C; HRMS (ESI): found 333.2756; calculated 333.2770 for $C_{20}H_{38}O_2Na$.

Compound 2D: (6*E*,8*E*,12*E*,14*E*)-icosa-6,8,12,14-tetraene-10,11-diol (*meso*)

Table 6 entry 3, colorless oil: ***meso*-2D**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.83$–0.79 (m, 10H, 2 CH_3, 1 CH_2, 2 OH), 1.23–1.18 (m, 12H, 6 CH_2), 2.00 (dd, 2H, 1 CH_2), 4.10 (d, $J = 8.4$ Hz, 2H, C*H*-OH), 5.49 (dd, $J = 15.6$, 6.0 Hz, 2H, C*H*=CH), 5.65 (td, $J = 14.4$, 6.82 Hz, 2H, C*H*=CH), 5.97 (dd, $J = 15.2$, 10.4 Hz, 2H, C*H*=CH), 6.20 ppm (dd, $J =$ 15.2, 10.4 Hz, 2H, C*H*=CH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.0$ (CH_3), 22.5 (CH_2), 28.8 (CH_2), 31.4 (CH_2), 32.6 (CH_2), 75.5 (CH), 127.8 (CH=CH), 129.2 (CH=CH), 133.8 (CH=CH), 136.5 ppm (CH=CH); HRMS (ESI): found 329.2468; calculated 329.2457 for $C_{20}H_{34}O_2Na$.

Compound 2E: (2*E*,6*E*)-3,6-dimethylocta-2,6-diene-4,5-diol (*meso*)

Table 6 entry 4, colorless oil: ***meso*-2E**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.54$–1.53 (m, 12H, 4 CH_3), 2.25–2.14 (bs, 2H, 2 OH), 3.93 (s, 2H, 2 C*H*-OH), 5.50–5.44 ppm (m, 2H, 2 C*H*=CH), ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.9$ (CH_3), 13.1 (CH_3), 78.4 (CH), 122.8 (*C*H=C), 134.5 ppm (CH=*C*), HRMS (ESI): found 193.1201; calculated 193.1204 for $C_{10}H_{18}O_2Na$.

Compound 2F: (3*E*,7*E*)-4,7-dimethyldeca-3,7-diene-5,6-diol (*meso*)

Table 6 entry 5, colorless oil: ***meso*-2F**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.86$ (t, 6H, 2 CH_3), 1.53 (s, 6H, 2 CH_3), 1.94 (quint, $J = 7.6$ Hz, 4H, 2 CH_2), 2.30 (bs, 2H, 2 OH), 3.91 (s, 2H, 2 C*H*-OH), 5.35 ppm (td, 2H, 2 C*H*=C); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 11.8$ (CH_3), 13.8 (CH_3), 20.8 (CH_2), 78.8 (CH), 130.7 (CH=C), 133.0 ppm (CH=*C*); HRMS (ESI): found 221.1521; calculated 221.1517 for $C_{12}H_{22}O_2Na$.

Compound 2G: (6*E*,10*E*)-2,6,11,15-tetramethylhexadeca-2,6,10,14-tetraene-8,9-diol (*dl* and *meso*)

Table 6 entry 6, yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.70–1.54$ (m, 18H, 6 CH_3), 2.06–2.10 (m, 8H, 4 CH_2), 4.13 (m, 1H, C*H*-OH *dl form*), 4.23 (m, 1H, C*H*-OH *meso form*), 5.19–4.99 ppm (m, 4H, 4 C*H*=C); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 16.9$ (CH_3), 17.1 (CH_3), 17.7 (CH_3), 17.7 (CH_3), 23.5 (2 CH_3), 23.6 (2 CH_3), 25.7 (2 CH_3), 25.7 (2 CH_3), 26.3 (CH_2), 26.4 (CH_2), 26.6 (CH_2), 26.7 (CH_2), 32.6 (CH_2), 32.7 (CH_2), 39.7 (CH_2), 39.8 (CH_2), 70.9 (CH), 71.3 (CH), 71.8 (CH), 72.1 (CH), 122.8 (*C*H=C), 123.1 (*C*H=C), 123.6 (*C*H=C), 123.8 (*C*H=C), 123.9 (*C*H=C), 123.9 (*C*H=C), 123.9 (*C*H=C), 124.0 (*C*H=C), 131.7 (CH=*C*), 131.9 (CH=*C*), 132.4 (CH=*C*), 132.5 (CH=*C*), 141.5 (CH=*C*), 141.6 (CH=*C*), 141.7 (CH=*C*), 142.1 ppm (CH=*C*), HRMS (ESI): found 329.2461; calculated 329.2457 for $C_{20}H_{34}O_2Na$.

Compound 2H:[29] (1*E*,5*E*)-1,6-diphenylhexa-1,5-diene-3,4-diol (*dl* and *meso*)

Table 6 entry 7, white solid: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.21$ (dd, $J = 11.4$, 5.4 Hz, 2H, C*H*-OH *dl form*), 4.36 (dd, $J = 9.4$, 3.8 Hz, 2H, C*H*-OH *meso form*), 6.25–6.17 (m, 2H, CH=CH), 6.68–6.61 (m, 2H, CH=CH), 7.33–7.22 ppm (m, 10H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 78.5$ (CH), 122.2 (C_{IV}), 128.7 (2 CH_{Ar}), 131.4 (2 CH_{Ar}), 138.4 ppm (C_{IV}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 75.8$ (CH *meso form*), 75.9 (CH *dl form*), 126.6 (CH), 126.7 (CH), 127.1 (CH), 127.8 (CH), 127.9 (CH), 128.0 (CH), 128.6 (2 CH), 132.7 (CH), 133.0 (CH), 136.4 (C_{IV}), 136.5 ppm (C_{IV}), MS (ESI): 267.13 $[M+H]^+$, 289.12 $[M+Na]^+$ mp = 110–112 °C [*litt.* 106–155 °C].

Compound 2I:[4a,b,5a,6a,9a,c,11a,12a,14a,28,29,30] 1,2-Diphenyl-*1,2*-ethanediol (*dl* and *meso*)

Table 6 entry 8, white solid: ***dl*-2I**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 2.25–2.10 (bs, 2H, OH), 4.61 (s, 2H, C*H*-OH), 7.23–7.02 ppm (m, 10H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 79.1$ (*C*H-OH), 127.0 (2 CH_{Ar}), 128.0 (CH_{Ar}), 128.1 (2 CH_{Ar}), 139.8 ppm (C_{IV}); ***meso*-2I**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.25–2.10$ (bs, 2H, OH), 4.74 (s, 2H, C*H*-OH), 7.23–7.02 ppm (m, 10H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 78.1$ (CH-OH), 127.1 (2CH_{Ar}), 128.1 (CH_{Ar}), 128.2 (2CH_{Ar}), 139.7 ppm (C_{IV}), MS (ESI): 215.1 $[M+H]^+$, 237.1 $[M+Na]^+$, mp = 120–124 °C [*litt.* 119–159 °C].

Compound 2J:[4a,5a,9a–c,14a,29a–c,27e,31] 1,2-Bis(4-methylphenyl)-1,2-ethanediol (*dl* and *meso*)

Table 6 entry 9, beige solid: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.22$ (s, 6H, 2 CH_3), 2.26 (s, 6H, 2 CH_3), 4.57 (s, 2H, C*H*-OH *dl form*), 4.65 (s, 2H, C*H*-OH *meso form*), 7.10–6.93 ppm (m, 8H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.2$ (4 CH_3), 78.1 (*C*H-OH *meso form*), 78.8 (*C*H-OH *dl form*), 126.9 (2CH_{Ar}), 127.1 (2CH_{Ar}), 128.8 (2CH_{Ar}), 129.0 (2CH_{Ar}), 137.0 (2C_{IV}), 137.5 (C_{IV}), 137.8 ppm (C_{IV}), MS (ESI): 243.13 $[M+H]^+$, 267.12 $[M+Na]^+$, mp = 161–163 °C [*litt* 161–180 °C].

Compound 2K:[4a,5a,9a–c,14a,27e,29a–c,31,32] 1,2-Bis(4-chlorophenyl)-1,2-ethanediol (*dl* and *meso*)

Table 6 entry 11, white solid: ***dl*-2K**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 4.55 (s, 2H, C*H*-OH), 6.95 (d, $J = 8.4$ Hz, 4H, 2CH_{Ar}), 7.14 ppm (d, $J =$ 8.4 Hz, 4H, 2CH_{Ar}); ***meso*-2K**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.77$ (s, 2H, C*H*-OH), 7.03 (dd, $J = 8.4$, 1.6 Hz, 4H, 2CH_{Ar}), 7.18 ppm (m, 4H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 77.2$ (CH *meso form*), 78.6 (CH *dl form*), 128.4 (CH_{Ar}), 128.4 (CH_{Ar}), 128.4 (CH_{Ar}), 128.9 (CH_{Ar}), 131.6 (C_{IV}), 133.9 (C_{IV}), 137.8 (C_{IV}), 137.9 ppm (C_{IV}), MS (ESI): 283.02 (100%), 285.02 (64%), 284.02 (15%) $[M+H]^+$ mp = 147–149 °C.

Compound 2I:[4a,9b,31,33] 1,2-Bis(4-fluorophenyl)-1,2-ethanediol (*dl* and *meso*)

Table 6 entry 13, white solid: ***dl*-2I**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 2.49 (bs, 2H, OH), 4.56 (s, 2H, C*H*-OH), 6.84 (t, $J = 8.4$ Hz, 4H, 2CH_{Ar}), 6.96 ppm (dd, $J = 8.4$, 5.6 Hz, 4H, 2 CH_{Ar}); ***meso*-2I:** ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.49$ (bs, 2H, OH), 4.76 (s, 2H, C*H*-OH), 6.89 (t, $J = 8.4$ Hz, 4H, 2 CH_{Ar}), 7.07 ppm (dd, $J = 8.4$, 5.6 Hz, 4H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 77.3$ (CH *meso form*), 78.8 (CH *dl form*), 115.0 (CH_{Ar}), 115.2 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 135.1 (C_{IV})„ 135.2 (C_{IV}), 161.3 (C_{IV}), 163.7 ppm (C_{IV}), MS (ESI): 251.08 $[M+H]^+$, 274.07 $[M+Na]^+$, mp = 151–153 °C [*litt.* 143–177 °C].

Compound 2M:[4a,5a,9a,c,14a,29a–c,31,32,34] 1,2-Bis(4-methoxyphenyl)-1,2-ethanediol (*dl* and *meso*)

Table 6 entry 14, white solid: ***dl*-2M**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 3.69 (s, 6H, CH_3), 4.56 (s, 2H, C*H*-OH), 6.68 (dd, $J = 6.8$, 4.2 Hz, 4H, 2CH_{Ar}), 6.96 ppm (dd, $J = 8.4$, 5.6 Hz, 4H, 2 CH_{Ar}); ***meso*-2M**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 3.73$ (s, 6H, CH_3), 4.66 (s, 2H, C*H*-OH), 6.78 (dd, $J = 8.4$, 2.0 Hz, 4H, 2CH_{Ar}), 7.14 ppm (dd, $J = 6.8$, 2.0 Hz, 4H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 55.2$ (OCH_3), 55.3 (OCH_3), 77.8 (CH *meso form*), 78.8 (CH *dl form*), 113.5 (CH_{Ar}), 113.7 (CH_{Ar}), 128.2 (CH_{Ar}), 128.3 (CH_{Ar}), 132.0 (C_{IV}), 132.1 (C_{IV}), 159.0 (C_{IV}), 159.2 ppm (C_{IV}), MS (ESI): 275.12 $[M+H]^+$, 298.11 $[M+Na]^+$, mp = 165–166 °C [*litt.* 164–168 °C].

Compound 2N:[4a,6a,9a,c,14a,29a,b,31,32,33b] 1,2-Bis(2-chlorophenyl)-1,2-ethanediol (*dl* and *meso*)

Table 6 entry 15, white solid: ***dl*-2N**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 2.87 (bs, 2H, OH), 5.24 (s, 2H, C*H*-OH), 7.18–7.01 (m, 6H, CH_{Ar}), 7.54 ppm (dd, $J = 7.6$, 1.6 Hz, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 73.1$ (CH), 126.9 (CH_{Ar}), 129.2 (CH_{Ar}), 129.2 (CH_{Ar}), 129.2 (CH_{Ar}), 129.5 (CH_{Ar}), 132.6 (C_{IV}), 137.2 ppm (C_{IV}); ***meso*-2N**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.87$ (bs, 2H, OH), 5.49 (s, 2H, C*H*-OH), 7.18–7.01 ppm (m, 8H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 72.1$ (CH), 126.5 (CH_{Ar}), 128.8 (CH_{Ar}), 128.8 (CH_{Ar}), 128.9 (CH_{Ar}), 133.4 (C_{IV})„ 136.4 ppm (C_{IV}), MS (ESI): 283.02 (100%), 285.02 (64%), 284.02 (15%) $[M+H]^+$ mp = 137–139 °C [*litt.* 132–146 °C].

Compound 2O:[4a,29a–c,31,32] 1,2-Bis(3-chlorophenyl)-1,2-ethanediol (*dl* and *meso*)

Table 6 entry 16, white solid: ***dl*-2O**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 4.50 (s, 2H, C*H*-OH), 6.79 (d, $J = 8.0$ Hz, 2H, CH_{Ar}), 7.18–7.05 ppm (m, 6H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 78.3$ (CH), 125.2 (CH_{Ar}), 127.0 (CH_{Ar}), 128.3 (CH_{Ar}), 129.4 (CH_{Ar}), 134.2 (C_{IV}), 141.6 ppm (C_{IV}); ***meso*-2O:** ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.68$ (s, 2H, C*H*-OH), 6.91 (dd, $J = 8.0$, 1.2, 2H, CH_{Ar}), 7.18–7.05 ppm (m, 6H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 77.1$ (CH), 125.3 (CH_{Ar}), 127.2 (CH_{Ar}), 128.3 (CH_{Ar}), 129.4 (CH_{Ar}), 134.2 (C_{IV}), 141.5 ppm (C_{IV}), MS (ESI): 283.02 (100%), 285.02 (64%), 284.02 (15%) $[M+H]^+$ mp = 140–142 °C.

Compound 2P:[5a] **1,2-Bis(2,3-dichlorophenyl)-1,2-ethanediol (*dl* and *meso*)**

Table 6 entry 17, white solid: ***dl*-2P**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (bs, 2H, OH), 5.31 (s, 2H, C*H*-OH), 7.20 (t, J = 8.0 Hz, 2H, CH_{Ar}), 7.36 (dd, J = 8.0, 1.6 Hz, 2H, CH_{Ar}), 7.55 ppm (dd, J = 8.0, 1.6 Hz, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 73.0 (CH), 129.8 (C_{IV}), 127.2 (CH_{Ar}), 127.3 (CH_{Ar}), 130.1 (CH_{Ar}), 131.5 (C_{IV}), 139.7 ppm (C_{IV}); ***meso*-2P**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (bs, 2H, OH), 5.57 (s, 2H, C*H*-OH), 7.03 (t, J = 8.0 Hz, 2H, CH_{Ar}), 7.11 (dd, J = 7.9, 1.7 Hz, 2H, CH_{Ar}), 7.55 ppm (dd, J = 8.0, 1.6 Hz, 2H, CH_{Ar}), ^{13}C NMR (100 MHz, $CDCl_3$): δ = 77.1 (CH), 126.9 (2 CH_{Ar}), 129.8 (CH_{Ar}), 129.8 (C_{IV}), 132.5 (C_{IV}), 138.5 ppm (C_{IV}), MS (ESI): 352.94 (100%), 350.94 (78%), 354.94 (48%) $[M+H]^+$ mp = 177–179 °C.

Compound 2Q:[9b,c,35] **1,2-Bis(2-methoxyphenyl)-1,2-ethanediol (*dl* and *meso*)**

Table 6 entry 18, white solid: ***dl*-2Q**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.92 (bs, 2H, OH), 3.56 (s, 6H, CH_3), 4.96 (s, 2H, C*H*-OH), 6.67 (d, J = 8.0 Hz, 2H, CH_{Ar}), 6.76 (td, J = 7.5, 1.2 Hz, 2H, CH_{Ar}), 7.10–7.07 ppm (m, 2H, 2 CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2 (OCH_3), 74.5 (CH), 110.2 (CH_{Ar}), 120.5 (CH_{Ar}), 128.3 (CH_{Ar}), 128.4 (C_{IV}), 128.6 (CH_{Ar}), 157.0 ppm (C_{IV}); ***meso*-2Q**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.92 (bs, 2H, OH), 3.60 (s, 6H, CH_3), 5.17 (s, 2H, C*H*-OH), 6.72 (dd, J = 8.2, 1.2 Hz, 2H, CH_{Ar}), 6.81 (td, J = 7.5, 1.2 Hz, 2H, CH_{Ar}), 7.07 (dd, J = 7.5, 1.2 Hz, H, CH_{Ar}), 7.12 ppm (td, J = 7.5, 1.2 Hz, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3 (OCH_3), 73.7 (CH), 110.2 (CH_{Ar}), 120.5 (CH_{Ar}), 128.3 (CH_{Ar}), 128.5 (CH_{Ar}), 128.5 (C_{IV}), 156.9 ppm (C_{IV}); MS (ESI): 275.12 $[M+H]^+$, 298.11 $[M+Na]^+$, mp = 156–158 °C.

Compound 2R:[4a,9b,14a,27b,32,35] **1,2-Bis(3-methoxyphenyl)-1,2-ethanediol (*dl* and *meso*)**

Table 6 entry 19, pale yellow solid: ***dl*-2R**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (bs, 2H, OH), 3.62 (s, 6H, CH_3), 4.56 (s, 2H, C*H*-OH), 6.77–6.61 (m, 6H, CH_{Ar}), 7.06 ppm (bt, J = 7.8 Hz, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2 (OCH_3), 78.9 (CH), 112.2 (CH_{Ar}), 113.7 (CH_{Ar}), 119.2 (CH_{Ar}), 129.2 (CH_{Ar}), 141.5 (C_{IV}), 159.4 ppm (C_{IV}); ***meso*-2R**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (bs, 2H, OH), 3.65 (s, 6H, CH_3), 4.69 (s, 2H, C*H*-OH), 6.77–6.61 (m, 6H, CH_{Ar}), 7.14 ppm (bt, J = 7.9 Hz, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.2 (OCH_3), 78.0 (CH), 112.3 (CH_{Ar}), 114.0 (CH_{Ar}), 119.5 (CH_{Ar}), 129.2 (CH_{Ar}), 141.5 (C_{IV}), 159.5 ppm (C_{IV}), MS (ESI): 275.12 $[M+H]^+$, 298.11 $[M+Na]^+$, mp = 161–163 °C.

Compound 2S:[4a,5a,27b,32,33c,36] **1,2-Bis(1-naphtyl)-1,2-ethanediol (*dl* and *meso*)**

Table 6 entry 20, white solid: ***dl*-2S:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25–2.00 (bs, 2H, OH), 5.78 (s, 2H, C*H*-OH), 7.27 (m, 2H, CH_{Ar}), 7.41–7.34 (m, 4H, CH_{Ar}), 7.75–7.67 (m, 6H, CH_{Ar}), 7.86 ppm (d, J = 8.4 Hz, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.4 (CH-OH), 123.0 (CH_{Ar}), 124.9 (CH_{Ar}), 125.1 (CH_{Ar}), 125.4 (CH_{Ar}), 125.8 (CH_{Ar}), 128.6 (CH_{Ar}), 128.7 (CH_{Ar}), 130.9 (C_{IV}), 133.7 (C_{IV}), 136.1 ppm (C_{IV}), MS (ESI): 315.13 $[M+H]^+$, 337.12 $[M+Na]^+$, mp = 178–180 °C; ***meso*-2S**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.25–2.00 (bs, 2H, OH), 5.95 (s, 2H, C*H*-OH), 7.39–7.33 (m, 4H, CH_{Ar}), 7.44 (td, J = 8.0, 1.4 Hz, 2H, CH_{Ar}), 7.57 (dd, J = 7.2, 1.2 Hz, 2H, CH_{Ar}), 7.76 (d, J = 8.2 Hz, 2H, CH_{Ar}), 7.83 (d, J = 8.0 Hz, 2H, CH_{Ar}), 7.93 ppm (d, J = 8.0 Hz, 2H, CH_{Ar}); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 74.2 (CH-OH), 123.1 (CH_{Ar}), 124.9 (CH_{Ar}), 125.2 (CH_{Ar}), 125.5 (CH_{Ar}), 126.0 (CH_{Ar}), 128.6 (CH_{Ar}), 128.8 (CH_{Ar}), 131.4 (C_{IV}), 133.5 (C_{IV}), 135.8 ppm (C_{IV}), MS (ESI): 315.13 $[M+H]^+$, 337.12 $[M+Na]^+$, mp = 179–181 °C.

Compound 2T:[4a,5a,9b,14a,31,32] **1,2-di(furan-2-yl)ethane-1,2-diol (*dl* and *meso*)**

Table 6 entry 21, yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.75 (bs, 2H, OH *dl and meso forms*), 4.98 (s, 2H, C*H*-OH *dl form*), 5.01 (s, 2H, C*H*-OH *meso form*), 6.33–6.23 (m, 4H, CH_{Ar} *dl and meso forms*), 7.38–7.34 ppm (m, 2H, CH_{Ar} *dl and meso forms*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 69.9 (CH-OH *dl form*), 70.1 (CH-OH *meso form*), 108.0 (CH_{Ar}), 108.2 (CH_{Ar}), 110.3 (CH_{Ar}), 110.4 (CH_{Ar}), 142.4 (CH_{Ar}), 142.4 (CH_{Ar}), 152.6 (C_{IV}), 152.8 ppm (C_{IV}), MS (ESI): 195.06 $[M+H]^+$, 218.06 $[M+Na]^+$.

Compound 2U:[4a,9a,c,14a,28a,c,31,32,35,37] **2,3-diphenylbutane-2,3-diol (*dl* and *meso*)**

Table 6 entry 22, white solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 6H, CH_3 *dl form*), 1.49 (s, 6H, CH_3 *meso form*), 2.39 (bs, 2H, OH *dl and meso forms*), 7.16–7.10 ppm (m, 10H, CH_{Ar} *dl and meso forms*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.0 (CH_3 *dl form*), 25.1 (CH_3 *meso form*), 78.7 (C_{IV} *meso form*), 78.9 (C_{IV} *dl form*), 126.9 (CH_{Ar}), 127.0 (2 CH_{Ar}), 127.1 (CH_{Ar}), 127.2 (2 CH_{Ar}), 127.3 (2 CH_{Ar}), 127.4 (2 CH_{Ar}), 143.4 (C_{IV}), 143.8 ppm (C_{IV}), MS (ESI): 243.13 $[M+H]^+$, 267.12 $[M+Na]^+$, mp = 127–130 °C.

Compound 2V:[9c,29c,31,38] **2,3-bis(4-chlorophenyl)butane-2,3-diol (*dl* and *meso*)**

Table 6 entry 23, white solid: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 6H, CH_3 *dl form*), 1.46 (s, 6H, CH_3 *meso form*), 2.22 (bs, 2H, OH *dl* and *meso forms*), 7.23–7.00 ppm (m, 10H, CH_{Ar} *dl* and *meso forms*); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.8 (CH_3 *dl form*), 25.1 (CH_3 *meso form*), 78.3 (C_{IV} *meso form*), 78.5 (C_{IV} *dl form*), 126.8 (CH_{Ar}), 127.3 (2 CH_{Ar}), 127.4 (CH_{Ar}), 128.5 (2 CH_{Ar}), 128.6 (2 CH_{Ar}), 128.8 (2 CH_{Ar}), 133.0 (C_{IV}), 133.2 (C_{IV}), 141.7 (C_{IV}), 142.2 ppm (C_{IV}), MS (ESI): 243.13 $[M+H]^+$, 267.12 $[M+Na]^+$, mp = 141–142 °C.

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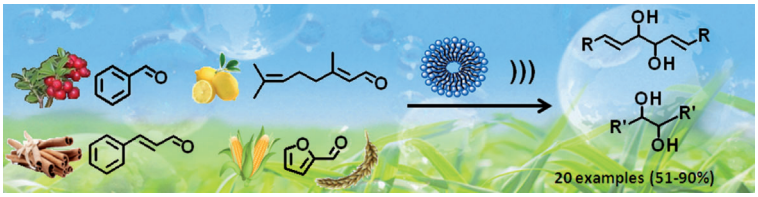

Emulsion as the solution: Combining surfactant effects with acoustic cavitation allowed the design of a novel, fast, and efficient protocol for pinacol coupling of aromatic and α,β-unsaturated aliphatic aldehydes in water. This protocol could be applied to natural high-value compounds such as citral A. The use of IgepalCO520, a neutral surfactant, led to the successful conversion of aromatic or α,β-unsaturated aliphatic carbonyl compounds in moderate-to-excellent yield.

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First Pinacol Coupling in Emulsified Water: Key Role of Surfactant and Impact of Alternative Activation Technologies