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Candida parapsilosis ATCC 7330 mediated oxidation of aromatic (activated) primary alcohols to aldehydes

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A green, simple and high yielding [up to 86% yield] procedure is developed for the oxidation of aromatic (activated) primary alcohols to aldehydes using whole cells of *Candida parapsilosis* ATCC 7330. The biotransformation is carried out under mild conditions at 25 °C, in hexane: water (48: 2) (v/v).

Introduction

Aldehydes are useful precursors in the synthesis of a variety of pharmaceuticals e.g. anti-malarial drugs,[1] anti-cancer drugs,[2] antioxidants and anti-bacterials,[3] anti-amoebics,[4] drugs for the treatment of iron overload and iron deficiency[5] and antipsychotic drugs[6] among others. Several chemical reagents are reported so far for the oxidation of primary alcohols to aldehydes.[7] The limitations that are associated with the chemical reagents, (e.g. removal of metallic by-products, formation of side products, difficulty in handling of hygroscopic reagents, requirements of low[8] or high temperature[9] which is an additional setup to maintain the temperature) make it important to develop alternate green methods for this oxidation. In the search of green catalytic methods using chemical catalysts, different non-metal based oxidizing agents[10] and ligands that can be used in catalytic amounts[11] were developed. But this involves the synthesis of ligands or reagents. In this context, biocatalysts offer attractive possibilities as oxidizing agents because most living systems which require oxygen to survive have the machinery for 'oxidation' and these biocatalysts are easy to handle at room temperature in addition to the fact that they are also selective.[12]

Biocatalysed alcohol oxidation is not as well explored as asymmetric reduction.[13] Biocatalytic oxidation of substituted benzyl alcohols, aliphatic, allylic, and acetylinic alcohols to the corresponding aldehydes is reported using whole cells of *Janibacter terrae* DSM 13953.[14,12] Bio-oxidation of benzyl alcohol to benzaldehyde using immobilized whole cells of *Pichia pastoris* is known.[15] Oxidation of aliphatic and aromatic alcohols to the corresponding aldehydes using whole cells of *Gluconobacter oxydans* DSM 2343 is reported.[16] Benzyl alcohol oxidation to benzaldehyde using different commercial oxidases and alcohol dehydrogenases,[12] and laccases with mediators is also known.[17,18] The laccase cross-linked enzyme aggregates are reported for the aerobic oxidation of linear C_5–C_{10} aliphatic alcohols, to the corresponding aldehydes.[18] Alditols to D-aldoses using alditol oxidase [19] and oxidation of primary alcohols hexan-1-ol, hexen-1-ols, epoxyhexan-1-ols and 3-phenylglycidol to their corresponding aldehydes catalysed by chloroperoxidase is reported.[20, 21]

For oxidation of primary alcohols mainly two types of reaction media are reported. They are, water or buffer at different pH[12, 14, 16, 17, 19, 21-28] and biphasic systems *i.e* use of water or buffer with an immiscible organic solvent (*e.g*. hexane, xylene, isooctane, ethyl acetate, toluene, octanol, octane, hexadecane).[15, 20, 29, 30] In the case of biphasic systems, aqueous phase provides a natural enzyme environment whereas the organic phase acts as a substrate reservoir and a product sink to avoid substrate or product inhibition.[31, 32] This can also overcome the problem of low productivity in aqueous media due to poor substrate solubility.[33] Moreover the use of biphasic systems in the case of primary alcohol oxidation helps in the extraction of hydrophobic aldehydes *in situ* avoiding over oxidation to acids [34] or reduction to alcohols that happens in aqueous media.

It is well known that yeasts are rich in oxido-reductases which are responsible for the oxidation of alcohols.[13, 35] *C. parapsilosis* ATCC 7330, a yeast, is known to catalyse deracemization of several secondary alcohols[36-39] and asymmetric reduction of ketones.[39-41] Deracemization using *C. parapsilosis* ATCC 7330 proceeds through stereoinversion.[38] Based on this observation, *C. parapsilosis* ATCC 7330 mediated enantioselective oxidation of secondary alcohols,[42] regio- and enantioselective oxidation of diols were optimised.[43] In the current study the same yeast is used for the oxidation of primary alcohols.

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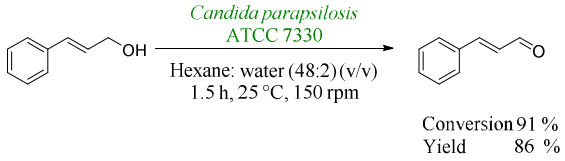
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Results and Discussions

Cinnamyl alcohol **1** [Scheme 1, Table 2] was the model substrate for the oxidation of primary alcohols using whole cells of *C. parapsilosis* ATCC 7330. The reaction was monitored by HPLC using reverse phase C_{18} column. Several parameters like reaction medium, reaction time, substrate concentration and proportion of solvents for reaction were optimized in order to get maximum conversion.



Scheme 1 Oxidation of cinnamyl alcohol by *C. parapsilosis* ATCC 7330

Optimization of reaction conditions

The 14 h culture of *C. parapsilosis* ATCC 7330 as reported for the enantioselective oxidation of secondary alcohols, was used for the oxidation of primary alcohols.[42]

Reaction medium

Initially, oxidation of cinnamyl alcohol **1** (0.06 mmol) was carried out in water (5 ml) using acetone (4%, 200 µl) as co-solvent for 2.6 g wet cells (dry cell mass 696 mg) at 25 °C, 150 rpm. Maximum conversion (21%) was observed at 15 min. In order to increase the conversion, a buffer at different values of pH, ranging from 6-8 was used. Decrease in conversion was observed. Water was therefore used for further studies. Different cosolvents *viz*. 1, 4- dioxane (conversion 17%), acetonitrile (conversion 18%) and dimethylsulfoxide (conversion 15%) were screened for maximum conversion instead of acetone. Cosolvents can affect the rate of enzymatic reactions by altering the free energy gap between ground and transition states and also the conformational motility of the enzyme.[44] A biphasic system of hexane: water (48: 2) (v/v) was tried based on an earlier report for the hexanol oxidation where the yield was 96%. [29]

Reaction time

Using hexane: water (48: 2) (v/v) as reaction medium, the reaction time was optimized. Maximum conversion of 75% was observed at 1.5 h. Cinnamyl alcohol **1** was added to the reaction medium using hexane.

Hexane volume

In order to optimise the volume of hexane required, the water volume was kept constant and the following biphasic systems were tried: Hexane: water (3:2) (v/v), (8:2) (v/v), (28:2) (v/v) and (68:2) (v/v) and the conversions were 17%, 26%, 45%, 75% and 62% respectively. The hexane: water ratio of 48:2 (v/v) was used for further studies as it gave the best conversion (75%).

Substrate concentration

Under the above optimized conditions, substrate concentration was optimized to 0.05 mmol (6 mg) to give a conversion of 82% for 2.6 g wet cell mass.

Biomass

For this biocatalysed reaction, which uses whole cells, biomass concentration has significant effects on a biotransformation,[45] therefore in order to maximise the conversion, biomass concentration (dry cell weight) was also optimized. Maximum conversion 91% was observed at 2 g of wet biomass. Finally at optimum reaction conditions as discussed above oxidation of cinnamyl alcohol **1** to cinnamaldehyde showed 91% conversion with yield 86% (51 mg). The same reaction conditions were used for the oxidation of the other primary alcohols with change in the reaction times.

Cosolvent optimization

For solid substrates, cosolvent screening was done using 4-methyl benzyl alcohol **4** [Table 3] as model substrate. Different cosolvents acetone, acetonitrile, dimethyl sulfoxide, dimethylformamide, ethanol, 1,4-dioxane and diisopropyl ether were screened. Among the cosolvents screened, acetonitrile (0.4% of the total volume 50 ml) showed maximum conversion 60% at 22 h with a yield of 54% (29 mg). Biocatalytic oxidation of **4** [Table 3] *i.e*. with *p*-Me substituent resulted in average conversion of 60% with an isolated yield of 54%, which was also reported using lyophilized cells of *Janibacter terrae* [conversion 16%] in 24 h.[12] For other solid substrates acetonitrile was used as cosolvent.

Table 1: Optimum conditions for the oxidation of primary alcohols by *Candida parapsilosis* ATCC 7330 (Cinnamyl alcohol as model substrate)

Reaction parameters	Optimum	Conversion (%)
Medium	Hexane:water(1.5 h)	75
Hexane: water ratio	(48:2)(v/v)	75
Substrate concentration	0.05 mmol	82
Biomass	2 g wet cells	91
Cosolvent* (for solids)	Acetonitrile [200 µL, (0.4% of the total volume 50 mL)]	60

*Cosolvent optimization was done for *p*-Me benzyl alcohol **4** [Table 3]

Substrate scope [Table 2]

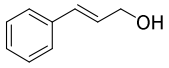
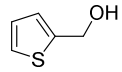
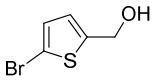
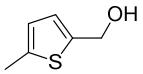
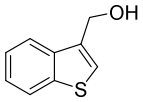
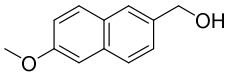
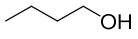
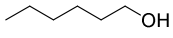
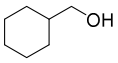
To increase the substrate spectrum, different primary alcohols were subjected to oxidation. Under the above optimized conditions thiophen-2-ylmethanol **2** [Table 2] showed a conversion of 81% in 16.5 h with a yield 73% (37 mg). Substitution to 5-Br in the case of (5-bromothiophen-2-yl)methanol **3** [Table 2] with an increased reaction time of 24 h, gave a conversion of 86%, yield 77% (66 mg) to the corresponding 5-bromothiophene-2-carbaldehyde.

Substitution to a Me group at 5th position instead of 5-Br, *i.e*. of (5-methylthiophen-2-yl) methanol **4** [Table 2] gave a reduced conversion of 76% with a of yield 67% (38 mg) to 5-methylthiophene-2-carbaldehyde. Attachment of benzene ring in benzo[b]thiophen-3-ylmethanol **5** [Table 2] did not show conversion after 24 h. Similar observation, *i.e*. increase in size of the alcohol with a decrease in catalytic efficiency was reported for *Saccharomyces cerevisiae* ADH1.[46, 47] Starting from cinnamyl alcohol **1** considering the other alcohols **2**-**4**, [Table 2] the reaction time increased and a decrease in conversion was observed which may be due to steric hindrance at the alcoholic carbon for hydride ion transfer.[46] In the case of cinnamyl alcohol **1**, the –OH group is 3 carbons away from the aromatic ring, while for the rest of the alcohols the aromatic ring is attached to the same carbon as the –OH group. Biotransformation of (6-methoxynaphthalen-2-yl) methanol **6** [Table 2] did not show any oxidized product even after 24 h.

Oxidation of **1** [Table 2]was reported by lyophilized cells of *Janibacter terrae* with conversion 36% in 24 h at 30 ˚C.[14] Oxidation of **1** was also reported by $Pd(OAc)_2$ as catalyst and tertiary *n*-butyl phosphine oxide [O=P(*n*-Bu)$_3$] as ligand in 24 h at 80 ˚C with a yield of 98% and additionally, [O=P(*n*-Bu)$_3$] needs to be synthesized.[48] Oxidation of thiophen-2-ylmethanol **2** was also reported by *tert*-butyl nitrite (*t*-BuONO) as an oxidant in 13 h at 100 ˚C with a yield of 82% (calculated by GC) and 2-thiophenecarboxylic acid was also formed in 17% yield (calculated by GC).[49] Another report for thiophen-2-ylmethanol **2** is using Ru/C at 50 ˚C in 24 h, giving yield of 87 %.[50] Hence the present method is more efficient: faster for the oxidation of **1** *i.e*. in less reaction time and for **2** it is neat *i.e* without side products. Oxidation of **3** and **4** to their corresponding aldehydes is not reported so far either by chemical or biological methods.

Under these experimental conditions aliphatic alcohols *n*-butyl alcohol **7** [Table 2], hexan-1-ol **8** [Table 2] and cyclohexyl methanol **9** [Table 2] did not show any oxidation products. The fact that deracemization of aliphatic β- hydroxy esters occurs using the same biocatalyst and deracemization proceeds *via* stereo inversion, there is a good possibility that this biocatalyst can be used for the oxidation of aliphatic substrates, but conditions need to be optimized.[51, 52]

Table 2 Oxidation of primary alcohols to aldehydes by *C. parapsilosis* ATCC 7330

	Substrate	Reaction time (h)	Conversion to aldehyde (%)	Yield of aldehyde[a] (%)
1		1.5	91±3	86±3
2		16.5	81±4	73±4
3		24	86±2	77±1
4		24	76±3	67±2
5		24	-	-
6		24	-	-
7		24	-	-
8		24	-	-
9		24	-	-

[a]Yield experiments were done for 0.45 mmol substrate.

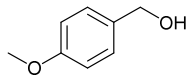
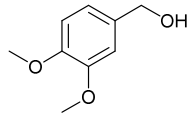
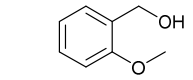
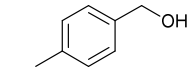
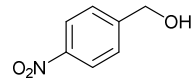
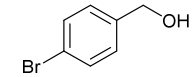
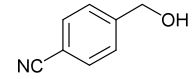
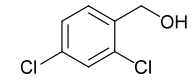
(-) no conversion

Effect of substitution [Scheme 2 Table 3]

In order to check the effect of substitution on the aromatic ring in the case of benzyl alcohols different substituents were tried under the above optimized conditions (Scheme 2, Table 3).

Oxidation of *p*-OMe benzyl alcohol **1** [Table 3] to *p*-OMe benzaldehyde showed 68% conversion with the yield of 59%

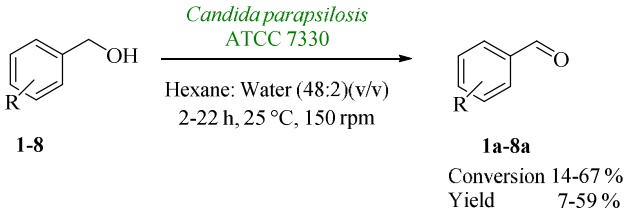
Table 3 Oxidation of substituted benzyl alcohols to aldehydes by *C. parapsilosis* ATCC 7330

	Substrate	Reaction time (h)	Conversion to aldehyde (%) 1a-8a	Yield of aldehyde[a] 1a-8a (%)
1		2	68±2	59±3
2		5	43±2	35±1
3		16	26±1	19±1
4		22	60±1	54±1
5		22	-	-
6		22	14	7±2
7		22	24±2	16±2
8		22	-	-

[a] Yield experiments were done for 0.45 mmol substrate.

(-) no conversion

(36 mg). Biocatalytic oxidation of *p*-OMe benzyl alcohol to *p*-OMe benzaldehyde was reported by laccase-with the aid of AZADO (2-azaadamantane N-oxyl) as mediator in 4 h with a yield of 98%,[53] and by lyophilized cells of *Janibacter terrae* [conversion 46% in 24 h, at 30˚C][14]. Oxidation of **1** [Table 3] was also reported by vanadium catalyst with yield of 35% at 90 ˚C in 22 h, but here, the corresponding acid was also formed in 26% yield.[54] Hence the present developed method is better for the preparation of *p*-OMe benzaldehyde with respect to time and without the formation of the acid.



Scheme 2 Oxidation of substituted benzyl alcohols [Table 3] by *C. parapsilosis* ATCC 7330

For 3, 4-diOMe benzyl alcohol **2**, [Table 3] the reaction time was increased to 5 h and the conversion reduced to 43% with yield of 35% (26 mg). Very low conversion was reported for the oxidation of **2** [Table 3] mediated by *Gluconobacter oxydans* DSM 2343 in 24 h with conversion <5% at 28 ˚C due to steric hindrance.[16] For *o*-OMe **3**, [Table 3] when the reaction time was increased to 16 h, the conversion was reduced to 26%, giving a yield of 19% (12 mg).

An electron withdrawing *p*-NO_2 group **5** [Table 3] did not show any oxidized product even after 24 h. The *p*-Br subtituted benzyl alcohol **6** [Table 3] gave a considerably low conversion (14%) and yield (7%; 6mg) at 22 h. The electron withdrawing substituent *p*-CN in **7** [Table 3] showed low conversion 24%, with a yield of 16% (9. mg). The 2,4- dichloro substituent in **8** [Table 3] did not show the oxidation product in 24 h. Poor yields were reported for the electron withdrawing substituent *p*-NO_2 **5** (4.9%) using [Cu(3,3′-disulfanediyl-bis(N-((1H-benzo[d]imidazol-2-yl)ethyl)propan amide))(NO_3)]·NO_3[55] and for the *p*-CN **7** (15%), using a (nitrosyl)Ru(salen) complex as catalyst.[56] Similarly, for **6** with a *p*- Br substituent, reduced yield 40% was reported using 2-butanone catalyzed by iridium complex.[57]

Over all, the electron withdrawing groups *p*-NO_2 and *p*-CN did not show any conversion or less conversion respectively. Electron donating substituents *p*-OMe **1**, 3, 4-diOMe **2** and *p*-Me **4** showed better conversion. Similarly *p*-Br **6** showed poor conversion and 2, 4-dichloro **8** did not show any conversion (chlorine is more electronegative than bromine). Similar types of observations were reported for *p*-OMe (conversion 46%), *p*-Cl (conversion 11%), *p*-Br (conversion 6%) and *p*-NO_2 (conversion 8%) benzyl alcohols using *Janibacter terrae* whole cells.[14]

Cell viability [Table 4]

A reaction time of 24 h warrants a check on cell viability. Viability of *C. parapsilosis* ATCC 7330 cells in the hexane: water (48:2)(v/v) reaction medium was checked up to 24 h using the agar plate method.[58]

Table 4 Cell viability of *Candida parapsilosis* ATCC 7330 cells in hexane: water (48:2)(v/v) reaction medium

Reaction time (h)	Cell viability (%)
14	48
24	4

[a] Experiments were performed in triplicate and average values are given.

Experimental

C. parapsilosis ATCC 7330 was bought from ATCC Manassas, A 201018, USA and maintained at 4 °C in yeast malt agar (Himedia). All yeast malt broth media components (Glucose, soyapeptone, yeast extract and malt extract) were purchased from Himedia. All substituted benzaldehydes were purchased from Spectrochem, hexan-1-ol from S.D.Fine Chemicals *n*-butyl alcohol from Rankem, butyraldehyde and cyclohexane carboxaldehyde from Sigma Aldrich, hexanal and cyclohexyl methanol from Lancaster, sodium borohydride from Merck were purchased. *p*-OMe benzyl alcohol, 1-butanol, 1-hexanol and cyclohexylmethanol were analyzed by GC using DB Wax column. GC conditions are as follows: injector temperature: 240 °C, oven temperature: 250 °C, split: 1:10, carrier gas: Helium, flow: 3 mL/min. GC programmed: 90 °C hold for 1 min, at the rate 3 °C/min to 200 °C, hold for 15 min. Remaining alcohols were analyzed by HPLC (Jasco PU-1580 liquid chromatography with a PDA detector) using (100 RP 18e (Hibar® RT), 250 x 4.6 mm, 5 µm from Merck) C18 column, acetonitrile: water (85:15) (v/v) as mobile phase. Products were characterized by ^{1}H and ^{13}C NMR, spectra were recorded in $CDCl_3$ on Bruker AVANCE III 500 MHz spectrometer operating at 500 and 125 MHz respectively.

Cultivation of *C. parapsilosis* ATCC 7330

C. parapsilosis ATCC 7330 was grown and harvested according to the earlier report[45] and used for biotransformation.

General procedure for biocatalytic oxidation

Hexane: water (48:1) (v/v) was sonicated for 5 min using Ultra sonicator (pulse 5 sec on, 5 sec off, amplitude 38) prior to the reaction, to make the reaction medium homogeneous. Wet cells 2 g (dry cell weight 535 mg) of *C. parapsilosis* ATCC 7330 were suspended in hexane: water (48:1)(v/v) with 1 ml water, now total reaction volume is 50 ml. Cinnamyl alcohol **1** 0.05 mmol (6 mg) was added to the cell suspension, incubated at 25 °C, 150 rpm for 1.5 h. For yield experiment reaction was performed in 10 different flasks (*i.e* 6 mg X 10 flasks, *i.e.* 0.45 mmol). After 1.5 h reaction mixture from all flasks was combined and product was extracted with ethyl acetate 3X50 ml, dried over anhydrous sodium sulphate and concentrated using rotary evaporator. Conversion was checked using HPLC on C18 column (Table 2). Isolated yield for the products was determined after column chromatography using hexane: ethyl acetate (98:2) (v/v) as an eluent.

The same procedure was followed for the other primary alcohols **2**-**9** in [Table 2] and **1**-**8** in [Table 3] using *C. parapsilosis* ATCC 7330. Reaction time was optimized for every substrate. For the substrates HPLC was used to check the conversion by acetonitrile: water (85:15) (v/v) was the mobile phase. The reactions were repeated in triplicate for consistent results and control experiments were done in parallel without the whole cells and also using heat killed cells under identical conditions.

Spectral data of products

Spectral data for the compounds **1a**,[48] **2a**,[59] **3a**,[60] **4a**[61] from Table 2 and **1a**,[48] **2a**,[62] **3a**,[11] **4a**,[48] **6a**,[11] **7a**[62] from Table 3 were in coincidence with the earlier reported values.

Conclusion

Oxidation of primary alcohols to aldehydes is reported for the first time using whole cells of *C. parapsilosis* ATCC 7330. Cinnamyl alcohol showed good conversion [91%] with a yield of 86%. Thiophen-2-ylmethanol and its substituents showed good conversions [76-86%] with yields of [67-77%]. Benzo[b]thiophen-3-ylmethanol, (6-methoxynaphthalen-2-yl) methanol, *n*-butyl alcohol, 1-hexanol and cyclohexyl methanol did not show oxidized products after 24 h. *p*-OMe Benzyl alcohol showed highest conversion 68% with a yield of 59% among differently substituted benzyl alcohols. 3, 4-Dimethoxy and *p*-Me benzyl alcohols showed average conversion while *o*-OMe, *p*-Br and *p*-CN benzyl alcohols showed very less conversion. *p*-NO_2 and 2,4-dichloro benzyl alcohols did not show any oxidized product even after 24 h. Addition of cosolvent (ACN) in the case of solids, increased the reaction time to 22 h compared to the liquid substrates. Over all substituted thiophenyl alcohols showed good conversion [76 to 86%] compared to the substituted benzyl alcohols [14 to 68 %] thus emphasising the usefulness of the developed biocatalyst mediated 'green' method.

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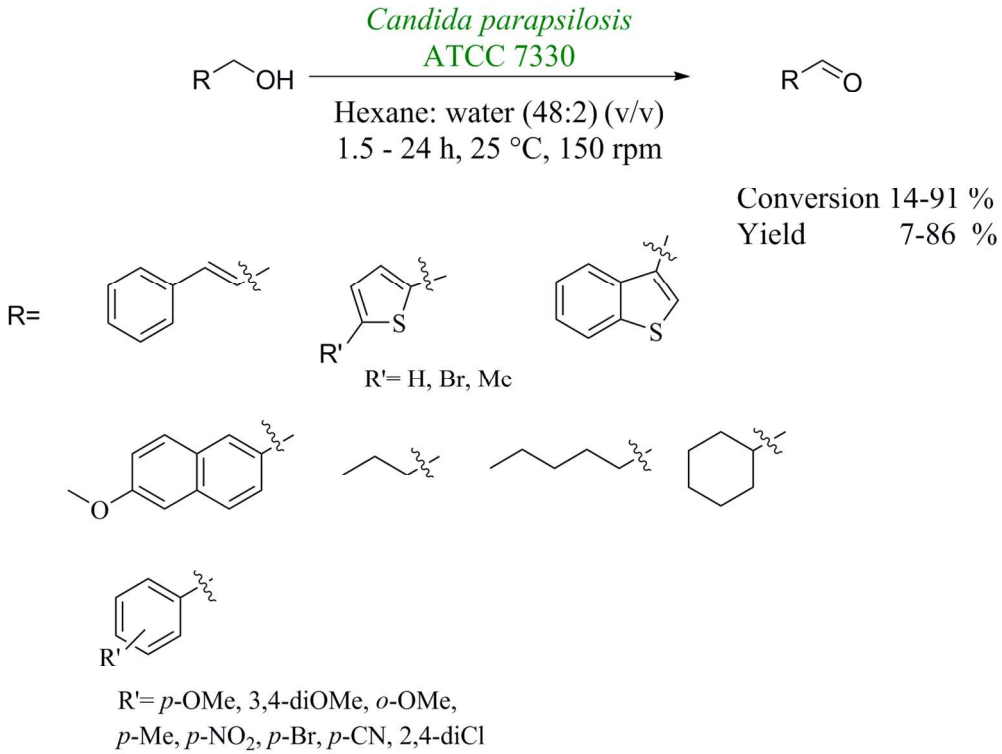

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