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CO_2-expanded liquids as solvents to enhance activity of *Pseudozyma antarctica* lipase B towards *ortho*-substituted 1-phenylethanols

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ABSTRACT

Pseudozyma (*Candida*) *antarctica* lipase B (CAL-B, Novozym 435®) is one of the most widely used and outstanding biocatalysts. However, CAL-B-catalyzed transesterification of *ortho*-substituted 1-phenylethanol analogs suffers low conversion. In this research, the reactions were accelerated by using CO_2-expanded liquids, liquids expanded by dissolving pressurized CO_2, such as CO_2-expanded hexane or CO_2-expanded MeTHF.

Introduction

Biocatalysts, especially lipases, have been studied extensively [1,2]. Among them, *Pseudozyma* (*Candida*) *antarctica* lipase B (CAL-B, Novozym 435®) is one of the most widely used and outstanding biocatalysts; CAL-B catalyzes transesterification of a wide range of secondary alcohols in organic solvents smoothly with excellent enantioselectivity [3–7]. However, CAL-B-catalyzed transesterification of *ortho*-substituted 1-phenylethanol analogs suffers much lower conversions than those of *meta* and *para*- substituted analogs (Supplementary information Section 2 and Table S1). Due to the limitation of the substrate scope of CAL-B, the dynamic kinetic resolution of *ortho*-substituted 1-phenylethanols also resulted in considerable retardations in the reactivity [7]. For example, reaction of 1-(2′-bromophenyl)ethanol took 7 days to complete whereas that of 1-phenylethanol took 3 h. The lipase-catalyzed resolution reaction became rate-limiting in the overall reactions. It was also reported that reactivities of *Burkholderia* (*Pseudomonas*) *cepacia* lipase for transesterification of *ortho*-substituted 1-phenylethanol analogs were extremely lower than those of *meta*- and *para*-substituted analogs [8].

The limitation of biocatalysts has been overcome by mutations and chemical modifications of enzymes and solvent engineering [1,9–17]. For solvent engineering, sustainable solvents should be should be chosen since they have been generating a massive amount of waste and burden both economically and environmentally [18,19]. Therefore, methods for minimizing the usage of solvents and replacing traditional organic solvents by environmentally friendly alternatives have been studied extensively [20–22]. As sustainable solvents, CO_2 related solvents such as supercritical CO_2 ($scCO_2$), liquid CO_2 and CO_2-expanded liquids have attracted great attentions [23–27]. Among them, CO_2-expanded liquids, liquids expanded by dissolving CO_2, have an advantage over $scCO_2$ and liquid CO_2; CO_2-expanded liquids can be used under lower pressures with wider temperature ranges than $scCO_2$ and liquid CO_2 [23]. As a liquid to be expanded by CO_2, it is desirable to use bio-based solvents such as 2-methyltetrahydrofuran (MeTHF), which can be derived from lignocellulosic biomass and has recently gained increasing interests as a promising solvent for various synthesis applications [28–30], including biocatalysis [31].

Previously, we have reported the utilization of CO_2-expanded bio-based liquids as effective reaction media for transesterification of alcohols catalyzed by CAL-B [27,32,33]. As shown in Fig. 1, the reaction is accelerated especially for 1-(2′-bromophenyl)ethanol using CO_2-expanded MeTHF. However, *ortho*-substituted 1-phenylethanol analogs, except 1-(2′-bromophenyl)ethanol, have not been used as substrates although these compounds are important as chiral intermediates for pharmaceuticals [34–38]. To assess the effectiveness of CO_2-expanded liquids for biocatalysis further, in this study, we investigated CAL-B-catalyzed transesterification of

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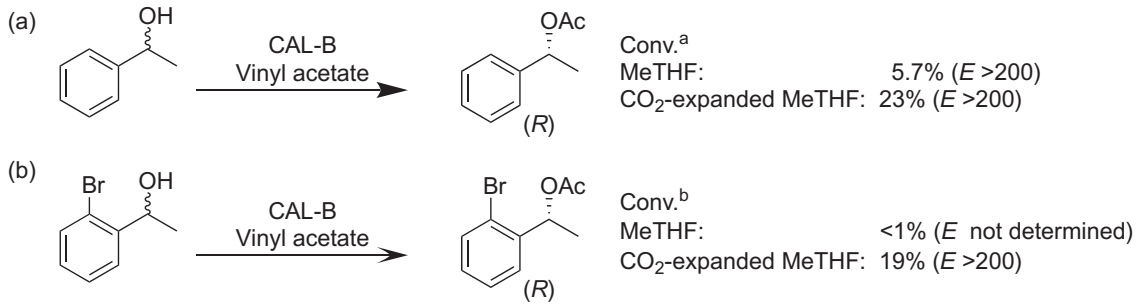


Fig. 1. CAL-B-catalyzed transesterification of 1-phenylethanol and 1-(2′-bromophenyl)ethanol in CO_2-expanded MeTHF [27,32,33]. [a]Reaction conditions: substrate (0.40 mmol), vinyl acetate (0.53 mmol), Novozym 435® (10 mg), MeTHF (10 mL) or CO_2-expanded MeTHF (10 mL, MeTHF concentration 10% v/v, 6.0 MPa), 20 °C, 1 h [32]. [b]Reaction conditions: substrate (0.10 mmol), vinyl acetate (0.53 mmol), Novozym 435® (10 mg), MeTHF (10 mL) or CO_2-expanded MeTHF (10 mL, MeTHF concentration 10% v/v, 6.0 MPa), 20 °C, 5 h [33].

various *ortho*-substituted 1-phenylethanol analogs **1a**-**7a** in CO_2-expanded MeTHF and CO_2-expanded hexane (Fig. 2). **1a**-**5a** were used to examine the *ortho* substituent effect, while **6a** and **7a** were selected to examine the potential of this reaction to synthesize chiral **6b** and **7b**, key intermediates of NEK2 kinase inhibitor [34,36] and c-Met/ALK inhibitor (Crizotinib), [37,38] respectively. The activities of CAL-B were found to be significantly higher in both CO_2-expanded MeTHF and CO_2-expanded hexane than in the corresponding neat liquids without expansion with CO_2.

Results and discussion

CAL-B-catalyzed transesterification of various *ortho*-substituted 1-phenylethanol analogs **1a**-**7a** in MeTHF and in CO_2-expanded MeTHF was examined at 50 °C. As shown in Table 1, the reaction in CO_2-expanded MeTHF showed higher conversion than those in neat MeTHF for the reaction of **1a**-**5a**. However, the reactions of **6a** and **7a**, to afford the pharmaceutical intermediates, hardly proceeded both in MeTHF and in CO_2-expanded MeTHF. For the reaction of **1a**-**5a** in CO_2-expanded MeTHF, the smaller the size of the substituents are, the better the conversions were. As listed in Table S2, the similar effect of size of *ortho* substituents can be seen for other reactions such as the dynamic kinetic resolution of *ortho*-substituted 1-phenylethanol analogs by CAL-B and dicarbonylchlorido (pentabenzylcyclopentadienyl)ruthenium in toluene [7] and hydrolysis of *ortho*-substituted 1-phenylethyl acetate analogs by *Bacillus subtilis* esterase (*Bs*E) [39]. It can be also seen for other biocatalytic reactions such as oxidation of *ortho*-substituted benzaldehyde analogs by *Geotrichum candidum* aldehyde dehydrogenase [40] and bovine lens aldehyde dehydrogenase [41], and asymmetric reduction of *ortho*-substituted acetophenone analogs by a mutant W288A of *G. candidum* acetophenone reductase (*Gc*APRD) [15]. On the other hand, the enantioselectivities were excellent for all reactions proceeded in CO_2-expanded MeTHF; *ee* of transesterification products of **1a**-**5a** was >99% (*R*) regardless of the kind of substituents. The excellent enantioselectivity of CAL-B was also reported for transesterification in CO_2-expanded MeTHF using other types of substrates such as 1-adamantylethanol, 1-(1-naphthyl)ethanol, 2-octanol, etc. [27,32,33] and for transesterification in supercritical carbon dioxide using *meta*- and *para*-substituted 1-phenylethanol analogs such as 1-(3′-trifluoromethylphenyl) ethanol and 1-(4′-bromophenyl) ethanol [42]. Therefore, the excellent enantioselectivity of CAL-B was not affected when the conversion was improved by expanding the solvent by CO_2.

Then, the kind of solvents to be expanded by CO_2 was investigated for the CAL-B-catalyzed transesterification of **3a**. Since CO_2 expanded MeTHF was reported to be best among the biobased solvents tested for the transesterification of 1-adamantylethanol by CAL-B (γ-valerolactone, diethyl carbonate, MeTHF, 2-methylfuran, *p*-cymene, (+)-limonene and (−)-limonene) [32], conventional

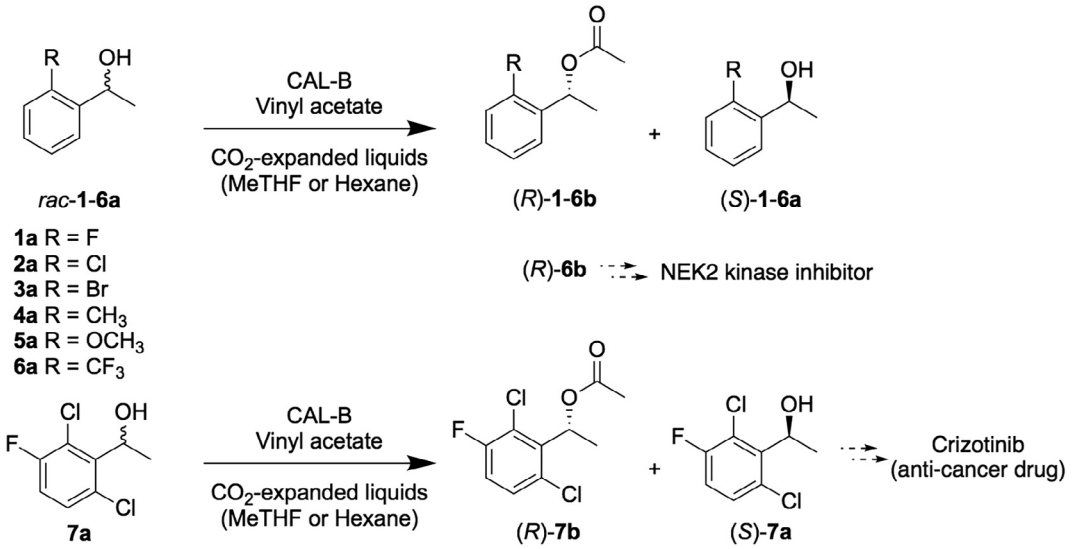
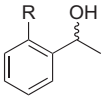
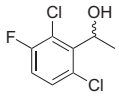


Fig. 2. CAL-B-catalyzed transesterification of *ortho*-substituted 1-phenylethanol analogs (**1a-7a**) in CO_2-expanded liquids [34,36–38].

Table 1
Comparison of CAL-B-catalyzed transesterification of *ortho*-substituted 1-phenylethanol analogs in MeTHF and in CO_2-expanded MeTHF.

Substrate			Solvent	Product	Conv.[a] (%)	ee_p (%)
	R = F	**1a**	MeTHF	**1b**	2.0	N.d.
			CO_2-expanded MeTHF		24	>99
	Cl	**2a**	MeTHF	**2b**	<1	N.d.
			CO_2-expanded MeTHF		11	>99
	Br	**3a**	MeTHF	**3b**	<1[b]	N.d.
			CO_2-expanded MeTHF		5.6[b]	>99
	CH_3	**4a**	MeTHF	**4b**	<1	N.d.
			CO_2-expanded MeTHF		9.1	>99
	OCH_3	**5a**	MeTHF	**5b**	1.2	N.d.
			CO_2-expanded MeTHF		18	>99
	CF_3	**6a**	MeTHF	**6b**	<1	N.d.
			CO_2-expanded MeTHF		<1	N.d.
		**7a**	MeTHF	**7b**	<1	N.d.
			CO_2-expanded MeTHF		<1	N.d.

Reaction conditions: **1a-7a** (0.10 mmol), vinyl acetate (0.20 mmol), Novozym 435® (10 mg), MeTHF (10 mL) or CO_2-expanded MeTHF (10 mL, MeTHF concentration 5% v/v, 6.0 MPa), 50 °C, 0.50 h. N.d.: not determined due to low conversions observed. ee_p: Enantiomeric excess of the product.
[a] The reactions were stopped at low conversion to show differences between the two media.
[b] Similar results shown in Fig. 1 were reported using different conditions [33].

solvents were also investigated in this study. Generally, hydrophobic solvents have been reported to be suitable for lipase-catalyzed transesterification [43,44]. For example, hexane was reported to be best among the solvents tested for the transesterification of 1-phenylethanol by CAL-B (vinyl acetate, THF, diisopropyl ether, chloroform, toluene, hexane, and isooctane) [45]. Based on these reports, *p*-cymene, hexane, THF, and vinyl acetate were chosen for the investigation for CAL-B-catalyzed transesterification of **3a** at 50 °C. As shown in Table S3, CO_2 expanded hexane gave the best result, followed by CO_2 expanded *p*-cymene. When the reactions in solvents without expansion by CO_2 were compared, hexane also gave the best result, followed by *p*-cymene. The preliminary experiment using MeTHF, hexane, *p*-cymene, diethyl carbonate, and cyclopentyl methyl ether (CPME) at 20 °C also resulted in hexane being the best. The hydrophobicity of hexane, as well as *p*-cymene, is considered to be suitable for the reaction, and CO_2 may exert the additional positive effect.

Then, a conventional excellent solvent for CAL-B-catalyzed reaction, hexane, was used instead of MeTHF for the transesterification of **1a-7a** at 50 °C. The results are shown in Table 2. The reactions in CO_2-expanded hexane gave better conversions than those in neat hexane for all substrates tested. The conversions in neat hexane and CO_2-expanded hexane were also higher than those in neat MeTHF and CO_2-expanded MeTHF (Table 1), respectively. It is probably due to the high hydrophilicity of MeTHF as reported in other lipase-catalyzed reactions [44]. For **1a-3a**, as the steric hindrance of substituents are larger, the acceleration effects were more profound. Importantly, the enantioselectivities of reactions were excellent for all of the reactions proceeded except for **6a**.

The effect of temperature on CAL-B-catalyzed transesterification of **3a** in CO_2-expanded hexane was investigated. As shown in Fig. 3, the conversion increased from 20 °C to 50 °C, and the highest conversion was observed at 50 °C (23%), which is in agreement with the reported optimum temperature of CAL-B-catalyzed

Table 2
Comparison of CAL-B-catalyzed transesterification of *ortho*-substituted 1-phenylethanol analogs in hexane and in CO_2-expanded hexane.

Substrate			Solvent	Product	Conv.[a] (%)	ee_p (%)
	R = F	**1a**	Hexane	**1b**	30	>99
			CO_2-expanded hexane		46	>99
	Cl	**2a**	Hexane	**2b**	16	>99
			CO_2-expanded hexane		30	>99
	Br	**3a**	Hexane	**3b**	9.0	>99
			CO_2-expanded hexane		23	>99
	CH_3	**4a**	Hexane	**4b**	11	>99
			CO_2-expanded hexane		27	98
	OCH_3	**5a**	Hexane	**5b**	29	>99
			CO_2-expanded hexane		42	>99
	CF_3	**6a**	Hexane	**6b**	<1	N.d.
			CO_2-expanded hexane		1.2	N.d.
	CF_3	**6a**	Hexane	**6b**	13[b]	58
			CO_2-expanded hexane		41[b]	58
		7a	Hexane	**7b**	<1	N.d.
			CO_2-expanded hexane		<1	N.d.
		7a	Hexane	**7b**	<1[b]	N.d.
			CO_2-expanded hexane		2.0[b]	N.d.

Reaction conditions: **1a-7a** (0.10 mmol), vinyl acetate (0.20 mmol), Novozym 435® (10 mg), hexane (10 mL) or CO_2-expanded hexane (10 mL, hexane concentration 5% v/v, 6.0 MPa), 50 °C, 0.50 h. ee_p: Enantiomeric excess of the product.
[a] The reactions were stopped at low conversion to show differences between the two media.
[b] 24 h.

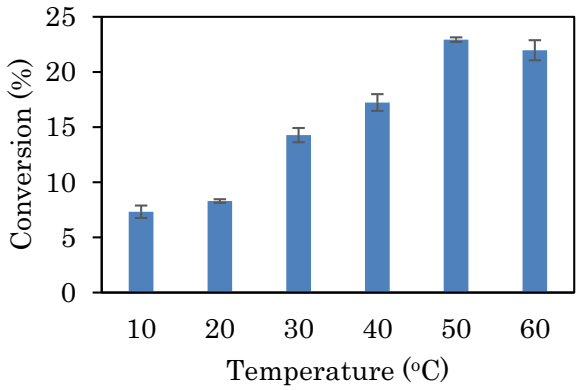


Fig. 3. Effect of temperature on CAL-B-catalyzed transesterification of 1-(2′-bromophenyl)ethanol **3a** in CO_2-expanded hexane. Reaction conditions: **3a** (0.10 mmol), vinyl acetate (0.20 mmol), Novozym 435® (10 mg), CO_2-expanded hexane (10 mL, hexane concentration 5% v/v, 6.0 MPa), 0.50 h. Enantiomeric excess of the product ee_p > 99% (R) under all temperatures examined.

transesterification [46–48]. The enantioselectivities of reactions were excellent (ee_p > 99% (*R*)), regardless of the reaction temperature.

CAL-B-catalyzed transesterification of **1a**-**7a** was also investigated using liquid CO_2 as a solvent at 20 °C. The reaction temperature using liquid CO_2 can be set only below the critical temperature of CO_2 (31.1 °C) [24]. As shown in Table S2, the reactions in liquid CO_2 at 20 °C gave lower conversions than those in CO_2-expanded hexane at 50 °C due to the difference in reaction temperature. However, the reactions of **2a**-**5a** in liquid CO_2 at 20 °C gave higher conversions than those in hexane at 20 °C. Therefore, the presence of a large concentration of CO_2 in the solvent is important for the CAL-B-catalyzed transesterification.

The CAL-B activity toward *ortho*-substituted 1-phenylethanol analogs, which was low in neat organic solvents, was enhanced in both CO_2-expanded liquids tested (MeTHF and hexane). The mechanism of the CO_2 induced acceleration can be hypothesized that CO_2 induces enhanced transport properties [25–27] and improved flexibility of enzymes [49–52]. Particularly, the solvent-exposed residues α5, the pseudo-lid covering the entrance of the active site, has high fluctuations in CO_2 and thus allows the lipase more tolerant to sterically hindered substrates with *ortho*-substitutions [49–52]. Additionally, a plausible reason for the difference in the degree of acceleration between the two solvents, of which more drastic are found for MeTHF than for hexane, is that CO_2 increases the hydrophobicity of MeTHF, whereas neat hexane is hydrophobic, so that the hydrophobicity of hexane does not change significantly by the expansion with CO_2.

Conclusion

CO_2-expanded liquids were proven to be promising alternative solvents for CAL-B-catalyzed transesterification of sterically hindered *ortho*-substituted 1-phenylethanol analogs. This research will lead to the further development of biocatalysis in CO_2-expanded liquids using different kinds of substrates and/or enzymes in the future, especially to diminish the detrimental effect of the *ortho* substituents.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2020.152424.

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