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Amano-PS-IM-catalyzed mechanochemical enzymatic acylative kinetic resolution of secondary alcohols

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Mechanochemical enzymatic acylative kinetic resolution of secondary alcohols using ball milling represents a highly efficient and sustainable approach for the synthesis of chiral esters and alcohols with high enantioselectivity. Previously reported protocols have predominantly relied on lipase B from Candida antarctica (CALB). However, its relatively high cost and its applicability restricted to methyl-substituted secondary alcohols leave significant room for improvement in terms of practicality, sustainability, and substrate scope. Herein, we report a mechanochemical protocol for acylative kinetic resolution catalyzed by less-expensive Amano lipase PS-IM (immobilized on diatomaceous earth). A broad range of secondary alcohols were efficiently converted to the corresponding acylated products in high yields with excellent enantioselectivities, through the careful optimization of the mechanochemical conditions. Notably, this protocol is applicable to ethyl- and other longer alkyl-substituted secondary benzylic alcohols, which are scarcely reactive under conventional CALB-catalyzed conditions.

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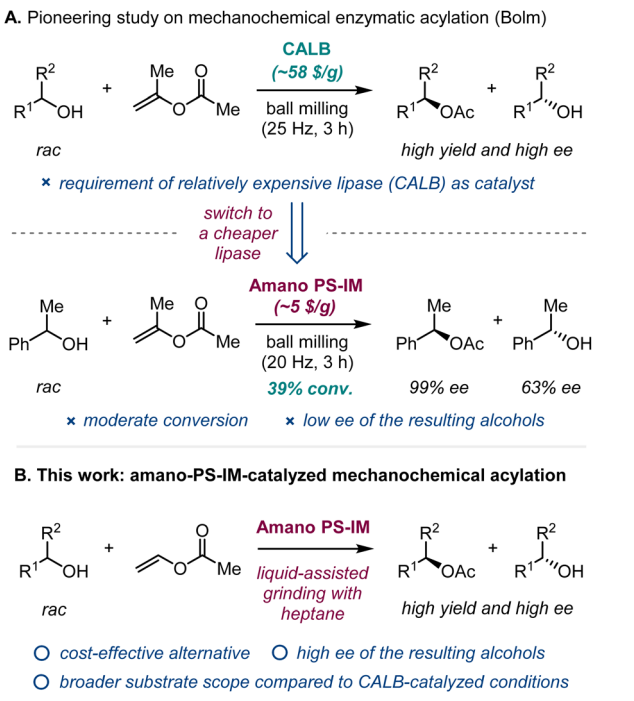
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Mechanochemical organic synthesis using ball milling has attracted significant attention because of its practical advantages, including faster reaction kinetics than those achieved through traditional solution-based techniques, reduced use of potentially harmful solvents, and simplified experimental procedures.[1,2] More recently, mechanochemical enzymatic reactions have emerged as particularly promising approaches for achieving selective organic synthesis under sustainable conditions.[3] To date, a wide range of enzymatic transformations have been explored under mechanochemical conditions as a part of the ongoing transition toward green chemistry.[3,4]

Among mechanochemical enzymatic transformations, acylation of alcohols is a well-established reaction that demonstrates the utility of enzymatic catalysis under solvent-minimized, mechanochemical conditions.[5–8] Bolm and Hernández reported the first mechanochemical protocol for the acylative kinetic resolution of secondary alcohols (Scheme 1).[5] Followed by this pioneering achievement, they demonstrated that this mechanochemical enzymatic system is applicable to the selective esterification of primary alcohols in lignin model compounds.[6] Although these are significant achievements, the reported reactions rely on lipase B from Candida antarctica (CALB) as the enzymatic catalyst, which is associated with a substantial catalyst cost.[5–8] However, a more cost-effective alternative such as Amano PS-IM (immobilized on diatomaceous earth), which is approximately an order of magnitude less expensive,[9] has been reported to exhibit diminished catalytic activity and enantioselectivity under Bolm's conditions.[5] Indeed, Amano PS-IM exhibits lower



Scheme 1 Mechanochemical enzymatic acylative kinetic resolution.

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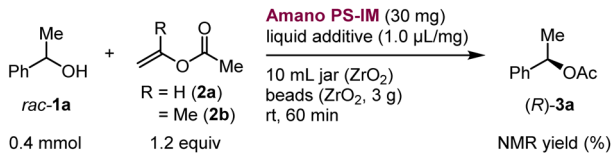
reactivity and stereoselectivity than CALB even under conventional solution-based conditions.[10]

To introduce practical and cost-effective biocatalytic processes, we envisioned that fine-tuning the mechanochemical parameters and additives would enable the development of a mechanochemical acylative kinetic resolution using less-expensive Amano PS-IM. Moreover, Amano PS-IM is expected to offer an expanded substrate scope, as it possesses greater structural flexibility within its catalytic pocket than CALB.[11] Here, we report that an appropriate choice of milling conditions as well as a liquid-assisted grinding (LAG) additive[12] enable the Amano-PS-IM-catalyzed highly efficient acylative kinetic resolution of secondary alcohols under mechanochemical conditions. A variety of chiral acylated products and chiral alcohols were obtained in good yields with excellent enantioselectivities comparable to those achieved with reported CALB-catalyzed protocols.[5] Notably, this protocol is applicable to ethyl and other alkyl-substituted secondary benzylic alcohols, which are scarcely reactive in conventional CALB-based acylation systems.[13]

Initially, we optimized the mechanochemical conditions using enzymatic catalyst Amano PS-IM for the acylative kinetic resolution of 1-phenylethanol [(*rac*)-**1a**] (Table 1). All reactions were performed in a Retsch MM400 mixer mill (ZrO_2 milling jar: 5 mL; ZrO_2 beads:[14] *ca.* 2 mm in diameter, *ca.* 20 mg per bead; 3 g total, *ca.* 150 beads), and all reagents were purchased from common commercial suppliers and used as received. Guided by conventional solution-phase protocols,[10,13] the mechanochemical reaction was first performed at 25 Hz for 60 min using (*rac*)-**1a** (0.4 mmol), vinyl acetate (**2a**, 1.2 equiv.), and Amano PS-IM (30 mg) (entry 1). Under these conditions, the desired ester (*R*)-**3a** was obtained in a moderate yield (33%), consistent with previously reported results.[5] Replacing vinyl acetate with isopropenyl acetate (**2b**) did not enhance the reaction efficiency (entry 2). Notably, decreasing milling frequency improved the yield of (*R*)-**3a** (entries 3 and 4). In particular, milling at a low frequency of 5 Hz afforded (*R*)-**3a** in 43% yield (entry 4). Although further mechanistic studies are warranted, we infer that higher milling frequencies may disrupt the higher-order structure of Amano PS-IM, resulting in reduced efficiency. Owing to its greater structural flexibility compared to CALB,[11] Amano PS-IM appears more sensitive to mechanical stimulation, necessitating careful optimization of mechanochemical conditions to maintain sufficient catalytic activity in the ball mill. Next, the effects of LAG were examined. Although the addition of hexane (1.0 μL mg^{-1}) had a negligible impact on the reaction outcome, the use of heptane under identical conditions led to significant improvement, affording (*R*)-**3a** in 49% yield with excellent enantioselectivity (96% ee, entry 6). In contrast, relatively polar solvents, such as tetrahydrofuran (THF) and *N*,*N*-dimethylformamide (DMF), under LAG conditions, resulted in inferior performance to that achieved upon using heptane (entries 7 and 8). It should be noted that heptane, which gave the best performance, is a more environmentally benign solvent than THF and DMF, further enhancing the attractiveness of this transformation. Furthermore, increasing the milling frequency to 15 Hz in the presence of heptane led to a slight decrease in the yield (46%, entry 9), indicating that lower milling frequencies were more favorable for Amano-PS-IM-catalyzed enzymatic transformation.

Subsequently, we evaluated a solid alcohol substrate, 1-(naphthalen-1-yl)ethan-1-ol [(*rac*)-**1b**], under the optimized reaction conditions for liquid substrate (*rac*)-**1a** (Table 2). This comparison was motivated by the fact that solid-state substrates often exhibit lower reactivity than liquid substrates under mechanochemical conditions.[2a,d] In fact, the reaction of (*rac*)-**1b** afforded the corresponding acylated product (*R*)-**3b** in a lower yield (entry 1, 16%). We then examined the effects of jar

Table 1 Preliminary optimization of the Amano-PS-IM-catalyzed acylation of *rac*-**1a** under mechanochemical conditions[a]



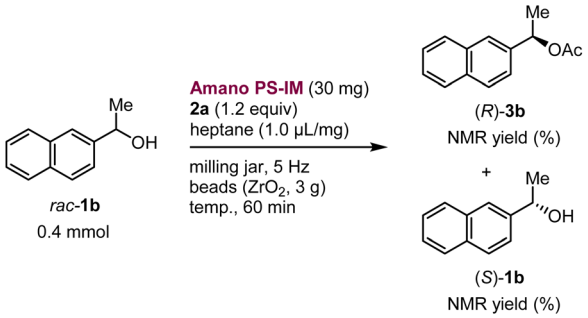
Entry	**2a** or **2b**	Milling frequency (Hz)	Liquid additive	Yield (%) of (*R*)-**3a**[b]	ee of (*R*)-**3a**[c]
1	**2a**	25	None	33	—
2	**2b**	25	None	12	
3	**2a**	15	None	39	—
4	**2a**	5	None	43	—
5	**2a**	5	Hexane	41	—
6	**2a**	5	Heptane	49	96
7	**2a**	5	THF	46	—
8	**2a**	5	DMF	40	—
9	**2a**	15	Heptane	46	—

[a] Conditions: **1a** (0.4 mmol), **2** (0.48 mmol), Amano PS-IM (30 mg), and a liquid additive (1.0 μL mg^{-1}) were added to a ZrO_2 ball mill jar (10 mL) with ZrO_2 beads (3 g). [b] Determined by ^1H NMR analysis of the crude reaction mixture using an internal standard. [c] Determined by high-performance liquid chromatography (HPLC) analysis.

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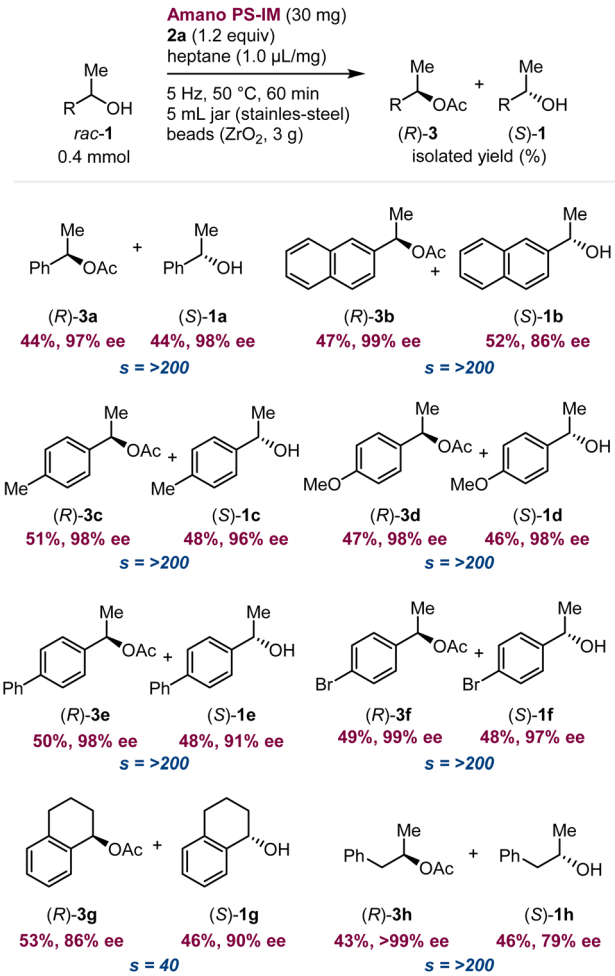
Table 2 Optimization of the Amano-PS-IM-catalyzed acylation of solid alcohol *rac*-**1b** under mechanochemical conditions[a]



Entry	Milling jar	Temp. (°C)	Yield (%) of (*R*)-**3b**[b]	ee of (*R*)-**3b**[c]	Yield (%) of (*S*)-**1b**[b]	ee of (*S*)-**1b**[c]
1	ZrO_2 (10 mL)	rt	16	—	79	—
2	SS (5 mL)	rt	35	—	67	—
3	SS (5 mL)	35	34	—	65	
4	SS (5 mL)	50	48	99	52	86

[a] Conditions: **1a** (0.4 mmol), **2** (0.48 mmol), Amano PS-IM (30 mg), and heptane (1.0 μL mg^{-1}) were added to a ball mill jar (10 mL) with ZrO_2 beads (3 g). [b] Determined by ^1H NMR analysis of the crude reaction mixture using an internal standard. [c] Determined by HPLC analysis. SS = stainless steel.

Table 3 Substrate scope[a]



[a] Conditions: **1** (0.4 mmol), **2a** (0.48 mmol), Amano PS-IM (30 mg), and heptane (1.0 μL mg^{-1}) were added to a stainless-steel jar (5 mL) with ZrO_2 beads (3 g). Isolated yields are shown. Enantiomeric excess values were determined by HPLC analysis.

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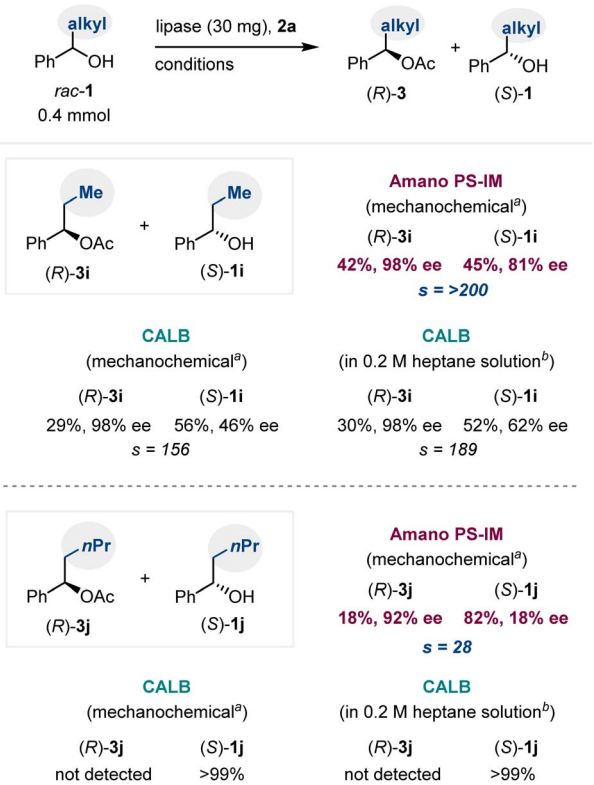
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materials (entry 2). The use of a stainless-steel (SS) jar (5 mL) instead of a ZrO_2 (10 mL) jar improved the yield (entry 2, 35%). Next, the effect of reaction temperature was investigated (entries 3 and 4). A commercially available temperature-controllable heat gun was placed directly above the ball-milling jar to control the reaction temperature.[2f] In the absence of external heating, the internal temperature after 60 min of ball milling was approximately 30 °C (entry 3). We found that higher temperatures using heat gun provided better efficiency, and the reaction at 50 °C afforded (*R*)-**3b** in 48% yield with excellent enantioselectivity (99% ee, entry 4).

Using the optimized mechanochemical conditions and Amano PS-IM as the enzymatic catalyst, we investigated the substrate scope, primarily focusing on methyl-substituted secondary alcohols (Table 3). Overall, the scope of this method is comparable to that of the previously reported mechanochemical protocol employing CALB.[5] In addition to substrates **1a** and **1b**, *para*-methyl-, *para*-methoxy-, and *para*-phenyl-substituted substrates (**1c–e**) afforded the corresponding products [(*R*)-**3c**–(*R*)-**3e**] in excellent yields (47–51%) with high enantioselectivities (98% ee for all cases). A substrate bearing bromo substituent **1f** was well tolerated, yielding the desired product (*R*)-**3f** with excellent enantioselectivity (99% ee). This protocol was also applicable to a cyclic alcohol **1g**, delivering (*R*)-**3g** with high enantioselectivity (86% ee). Moreover, a non-benzylic substrate **1h** underwent efficient enzymatic kinetic resolution with excellent enantioselectivity (>99% ee). The selectivity factors (*S* values) for these reactions exceeded 200 in most cases (see the SI for details).[15] Notably, the resulting alcohols were obtained in high yields and excellent enantioselectivities across the substrate set, highlighting the high efficiency of this mechanochemical kinetic resolution approach.

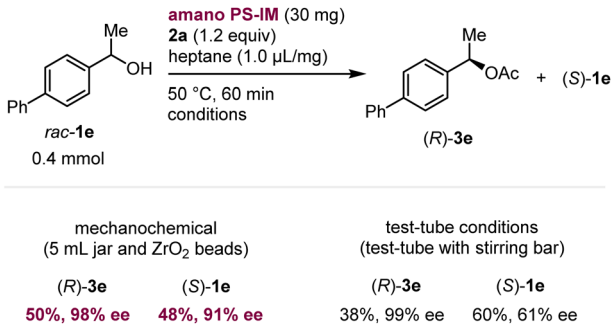
To demonstrate the synthetic utility of this protocol, substrates with longer alkyl chains were examined (Table 4). Amano-PS-IM has greater structural flexibility within its catalytic pocket than CALB, indicating the possibility of an expanded substrate scope.[11] However, this advantage has not yet been demonstrated in a synthetic context. Under the newly developed mechanochemical conditions, the reaction of ethyl-substituted secondary alcohol **1i** catalyzed by Amano PS-IM afforded the desired product (*R*)-**3i** in good yield (42%) with excellent enantioselectivity (98% ee). In contrast, both CALB-catalyzed mechanochemical conditions and solution-phase conditions using heptane as the solvent (0.2 M) resulted in substantially lower yields (29% and 30%, respectively) although high enantioselectivity was obtained in both cases (98% ee).[13] We next investigated a more demanding longer-alkyl-substituted alcohol, **1j**, which is a particularly challenging substrate for enzymatic acylative kinetic resolution. Indeed, to

Table 4 Substrate scope[a,b]



[a] Conditions: **1** (0.4 mmol), **2a** (0.48 mmol), lipase (30 mg), and heptane (1.0 μL mg^{-1}) were added to a stainless-steel jar (5 mL) with ZrO_2 beads (3 g) at 50 °C for 60 min. Isolated yields are shown. [b] Conditions: **1** (0.4 mmol), **2a** (0.32 mmol), CALB (30 mg), and heptane (0.2 M) at 30 °C for 6 h. Isolated yields are shown. Enantiomeric excess values were determined by HPLC analysis.

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Scheme 2 Control experiment.[a] [a]Conditions: **1e** (0.4 mmol), **2a** (0.48 mmol), Amano PS-IM (30 mg), and heptane (1.0 μL mg^{-1}). Isolated yields are shown. Enantiomeric excess values were determined by HPLC analysis. Additional details of the experimental conditions are provided in the SI.

the best of our knowledge, successful CALB-catalyzed acylation of such substrates has not been reported.[13] Pleasingly, the desired product (*R*)-**3j** was obtained under the Amano-PS-IM-catalyzed mechanochemical conditions, whereas no reaction occurred when the CALB catalyst was employed under mechanochemical or solution-based conditions. Collectively, these results clearly demonstrate the enhanced substrate scope and synthetic utility of the Amano-PS-IM-catalyzed protocol.

To highlight the role of ball milling, a control experiment was performed by conducting the reaction in a sealed tube equipped with a stirring bar (Scheme 2). Under these conditions, the desired product (*R*)-**3e** was obtained in a lower yield (38%) than that obtained under mechanochemical conditions (50%). Consequently, the resulting alcohol (*R*)-**1e** exhibited reduced enantiomeric excess (61% ee). These results underscore the essential contribution of the mechanochemical conditions to the efficiency of the present Amano-PS-IM-catalyzed protocol.

In conclusion, we developed an Amano-PS-IM-catalyzed mechanochemical enzymatic acylative kinetic resolution of secondary alcohols. Although inexpensive Amano PS-IM has been reported to exhibit low catalytic performance under mechanochemical conditions, we demonstrated that the optimization of mechanochemical parameters and liquid additives enables highly efficient acylative kinetic resolution. Under the optimized conditions, a broad range of secondary benzylic alcohols were transformed to the corresponding acylated products in high yields with excellent enantioselectivities. Importantly, this protocol is applicable to ethyl- and other longer-alkyl-substituted secondary benzylic alcohols, which are unreactive under conventional CALB-catalyzed conditions. Overall, the present study suggests that the judicious optimization of mechanochemical reaction parameters can unlock the use of diverse enzymatic catalysts, thereby enabling solvent-minimized, green transformations that are difficult or inaccessible under traditional solution-based conditions.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the supplementary information (SI). Supplementary information is available. See DOI: https://doi.org/10.1039/d6mr00028b.

Acknowledgements

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