Synthetic Methods

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Multistep Phase-Switch Synthesis by Using Liquid–Liquid Partitioning of Boronic Acids: Productive Tags with an Expanded Repertoire of Compatible Reactions**

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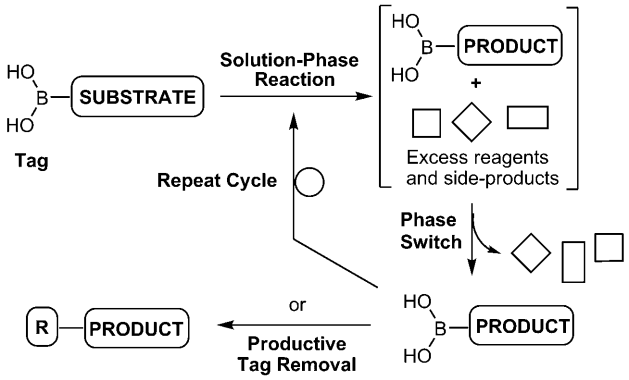
In memory of Keith Fagnou (1971–2009)

There are increasing environmental pressures to improve the sustainability of reaction processes in synthetic organic chemistry. In response to these demands, new techniques and strategies are needed to accelerate and facilitate the synthesis and isolation of organic compounds while minimizing the consumption of solvents and chromatographic supports that contribute to the waste stream. Indeed, much of the wastes produced in organic reactions originate from the extensive use of silica gel and solvents employed in chromatographic purification steps. Phase-switching strategies are very attractive as a means to avoid chromatography.[1] In phase-switch chemistry, reactions take place conveniently under homogeneous conditions, and product separation is facilitated by a liquid–liquid partition or a precipitation/filtration operation. Phase trafficking is possible through functionalizing the substrate or reagents with a phase "tag". Several ingenious phase-switching strategies were developed and employ various tags such as perfluoroalkyl groups,[2] polyethylene glycol chains,[3] metal chelators,[4] H-bonding receptors,[5] polymerizable norbornene groups,[6] polyaromatics,[7] phosphonium salts,[8] and others.[9] Whereas many of these strategies have been used for tagging reagents or catalysts, only a few were employed for tagging substrates and even fewer allowed for multistep syntheses to be implemented. In all of these methods, however, the requirement for a phase tag creates two chemically unproductive steps: attachment of the tag to the substrate, and detagging of the product at the end. The latter operation destroys the phase tag and often leaves an undesired remnant (or "trace") on the desired product. Recently, we have introduced a less invasive phase-switching strategy involving the boronic acid functionality as a built-in, productively convertible phase tag (Scheme 1).[10] Rather than cleaving the extraneous tag at the end of a synthetic sequence, as in other phase-switch systems, the boronic acid can be derivatized productively using the wide range of selective transformations known for this class of compounds.[11] Owing to the commercial availability of hundreds of functionalized boronic acids, which can serve as potential substrates in many synthetic applications, this atom-economical phase-switch system can also circumvent the tag-attachment step. Moreover, as boronic acids react only under specific conditions (e.g., transition-metal activation),[11] their use as inert tags should be compatible with a wide range of chemical transformations.



Scheme 1. Concept of phase-switch synthesis using boronic acids as productive tags.

Our first-generation system employed the diethanolaminomethyl polystyrene (DEAM-PS) resin[12] to phase-switch boronic acids through solid-phase immobilization.[10] Although this system proved suitable, the use of a solid support requires extensive solvent washes after each immobilization operation, and the scalability is limited compared to strategies based on liquid–liquid partitioning. We envisioned the development of a liquid–liquid, water–organic phase-switching system that would exploit the known ability of boronic acids to form strong water-soluble complexes with polyols at high pH (Scheme 2).[13] For this application, we sought a polyol additive that would be polar enough to efficiently phase-switch hydrophobic boronic acids into an aqueous phase. The additive should also be completely insoluble in organic solvents so as to avoid contamination of the organic layer. This strategy, illustrated in Scheme 2, allows excess reagents and nonpolar side-products to be eliminated with ease at the end of the reaction. Therefore, upon

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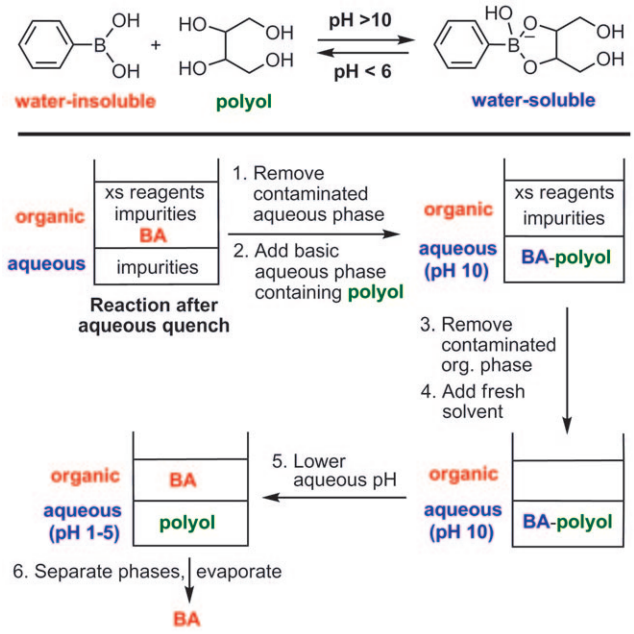
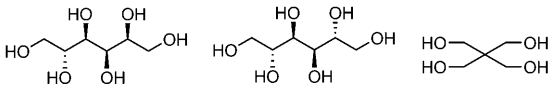


Scheme 2. Liquid–liquid phase-switching of boronic acid tagged compounds (**BA**) by using a polyol additive.

Table 1: Optimization of phase-switching conditions for partitioning boronic acids between ethyl acetate and water.[a]



sorbitol mannitol pentaerythritol

Entry	**Ar**-B(OH)$_2$	Additive (conc.)	Base (conc.)	Removal [%][b]
1	4-PhC_6H_4-	none	none	0
2	4-PhC_6H_4-	none	NaOH (1.0 M)	0
3	4-PhC_6H_4-	fructose (1.0 M)	NaOH (1.0 M)	88
4	4-PhC_6H_4-	sorbitol (1.0 M)	NaOH (1.0 M)	89
5	4-PhC_6H_4-	sorbitol (1.0 M)	Na_2CO_3 (1.0 M)	97 (95)
6	4-PhC_6H_4-	mannitol (1.0 M)	Na_2CO_3 (1.0 M)	91
7	4-PhC_6H_4-	fructose (1.0 M)	Na_2CO_3 (1.0 M)	93 (94)
8	4-PhC_6H_4-	$C(CH_2OH)_4$ (1.0 M)	Na_2CO_3 (1.0 M)	56
9	4-PhC_6H_4-	PVA (1.0 M)	Na_2CO_3 (0.2 M)	3
10	4-PhC_6H_4-	sorbitol (0.2 M)	Na_2CO_3 (1.0 M)	76 (79)
11	4-MeC_6H_4-	sorbitol (1.0 M)	Na_2CO_3 (1.0 M)	– (91)
12[c]	4-MeC_6H_4-	sorbitol (1.0 M)	Na_2CO_3 (1.0 M)	– (93)
13[d]	4-MeC_6H_4-	sorbitol (1.0 M)	Na_2CO_3 (1.0 M)	– (88)
14	2-*i*PrC_6H_4-	sorbitol (1.0 M)	Na_2CO_3 (1.0 M)	– (82)
15	2-naphthyl	sorbitol (1.0 M)	Na_2CO_3 (1.0 M)	– (99)
16	3-BnOC_6H_4-	sorbitol (1.0 M)	Na_2CO_3 (1.0 M)	– (92)
17	4-$MeO_2CC_6H_4$-	sorbitol (1.0 M)	Na_2CO_3 (1.0 M)	– (87)
18	4-pyridinyl	sorbitol (1.0 M)	Na_2CO_3 (1.0 M)	– (< 5)

[a] Assay conditions (see the Supporting Information for details). For UV measurements: 0.1 mmol of boronic acid was partitioned between 1.0 mL of the aqueous phase and 1.0 mL of the organic phase with additives and base specified in the table. For the mass recoveries, a typical scale of 100 mg boronic acid was used and the reacidification was stopped at pH 2. Unless indicated otherwise, the organic phase is ethyl acetate. [b] Measured by UV spectrophotometric reading of the organic phase using a premeasured calibration curve. Numbers in brackets refer to the mass recovery yields. [c] Organic phase is diethyl ether. [d] Organic phase is dichloromethane. PVA = polyvinyl alcohol.

completion of a reaction, the aqueous layer from the work-up is first removed, and then the phase-switching polyol-containing aqueous alkaline solution is added, which transfers the boronic acid to water as a polar boronate adduct. The contaminated organic phase is removed, and a new and clean organic layer is added. Upon acidification of the aqueous phase, the polyol–boronic acid complex dissociates to return the boronic acid product into the clean organic phase. The polyol additive remains in the aqueous layer and pure product can be recovered simply by evaporation of the organic layer. This reaction cycle can be repeated as desired, or terminated through a chemically productive conversion of the boronic acid tag as part of either a target-oriented or a diversity-oriented synthesis. Moreover, methods are known to effect protodeboronation of arylboronic acids, so that this system can also serve as a traceless phase-switching strategy for accessing arenes.[14]

The ability of different polyol additives to phase-switch the hydrophobic biphenylboronic acid from ethyl acetate to water was rapidly evaluated by UV spectrophotometry (Table 1, entries 1–10). The hexol sorbitol, an inexpensive (ca. 25 USD/kg) and nontoxic commodity chemical, was found to be the most efficient at a pH of 10 and over (entry 4). Additional optimization identified sodium carbonate as a preferred and milder base (entry 5) over sodium hydroxide (entry 4), which led to a partial hydrolysis of ethyl acetate. Mass yield recovery experiments (shown in brackets) validated the UV assays and confirmed the efficiency of these phase-switching conditions (ca. 95% recovery). Both phases are homogeneous and a five minute agitation time is sufficient for complete phase switching. Decomplexation and return of the boronic acid to a fresh organic phase was found to be effective with a reacidification in a pH range of 1–5. Other carbonates (e.g. K_2CO_3) can be employed, and, especially if emulsions occur, other solvents like diethyl ether and dichloromethane are suitable provided the boronic acid is soluble (entries 11–13). The efficiency of the phase switching appears to be quite general for all arylboronic acids, but may be hampered slightly by very hindered *ortho* substituents (entry 14). As shown with the effective recovery of 4-methoxycarbonylphenylboronic acid (entry 17), these phase-switch conditions do not appear to cause significant hydrolysis of carboxyesters. The only limitation is that of small amphoteric derivatives such as 4-pyridinylboronic acid (entry 18), which is soluble in water over the pH range of 1–12.

A series of larger-scale experiments addressed the issue of minimal consumption of solvent and sorbitol for practical applications. On multigram scales, only a small excess (>1.35 equiv) of sorbitol is required. For example, phase-switching of 4.0 g (32 mmol) of PhB(OH)$_2$ (dissolved in only 40 mL of ethyl acetate) with 50 mL of 1.0 M aqueous sorbitol (50 mmol) containing 1.0 M Na_2CO_3 led to a 95% recovery yield. In the absence of sorbitol, the recovery yield was approximately 10%. The efficiency of each step in the optimal phase-switching process can be visualized using the blue-colored azulene-2-boronic acid (Figure 1).[14] As depicted in Figure 1, this experiment confirms that both a

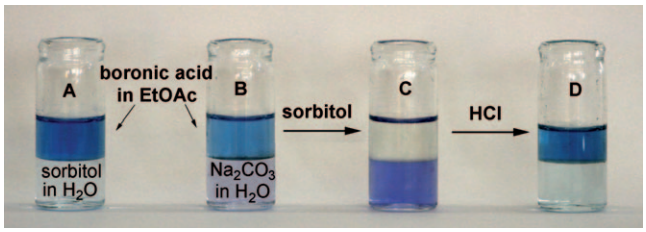


Figure 1. Phase-switching of blue-colored azulene-2-boronic acid. A) Partition of azulene-2-boronic acid between ethyl acetate and a neutral sorbitol-containing aqueous phase. B) Partition between ethyl acetate and aqueous sodium carbonate phase. C) Partition between ethyl acetate and basic sorbitol-containing aqueous phase. D) Partition between ethyl acetate and a re-acidified sorbitol-containing aqueous phase.

basic pH and sorbitol are needed for efficient phase-switching of the boronic acid from the organic to the aqueous phase.

For this phase-switch synthetic approach to be generally applicable, the phase switching must be highly chemoselective. To this end, a control experiment was performed whereby a mixture including *p*-tolylboronic acid and nine other organic compounds with different functional groups was subjected to the optimal phase-switching conditions. The comparison of proton NMR spectra between the initial mixture (Figure 2A) and the pure, recovered (Figure 2B) boronic acid (88% mass recovery) clearly demonstrates the high chemoselectivity of this phase-switch system.

A general phase-switching system employing boronic acids as phase tags must be complemented with a broad repertoire of chemical transformations tolerant of this functionality. Although aliphatic boronic acids tend to oxidize rapidly under atmospheric conditions, most alkenyl and arylboronic acids are bench-stable powders that can be stored in closed bottles at ambient temperature for months.[16] The high chemical stability of arylboronic acids is supported by reports describing their inertness to harsh transformations such as aromatic nitration, benzylic bromination, and periodate oxidations.[16] A systematic examination of their tolerance to different reaction conditions, however, seems nonexistent. Therefore, we have executed a number of simple transformations of model unprotected boronic acids with a phase-switch purification. It is remarkable that oxidations of alcohols, carbonyl reductions (Scheme 3a), carbodiimide-promoted esterification and amidation (Scheme 3b and c), carbonyl addition reactions with organometallic reagents, a Wittig olefination, and even a sequence of aldehyde alkynylation and alkyne-azide cycloaddition (Scheme 3d) can all be realized to isolate the expected products in good to high yields and acceptable homogeneity after a simple phase-switch purification. In the case of polar or basic products such as triazoles (Scheme 3d; last reaction equation), more extractions may be necessary. No starting material was left in any of these examples of reactions, thereby eliminating the need for further purification of products by silica chromatography. In the Wittig reaction of *p*-boronobenzaldehyde, removal of the phosphine oxide by-product was greatly facilitated by the phase-switch operation, giving after evaporation the pure acrylate product.

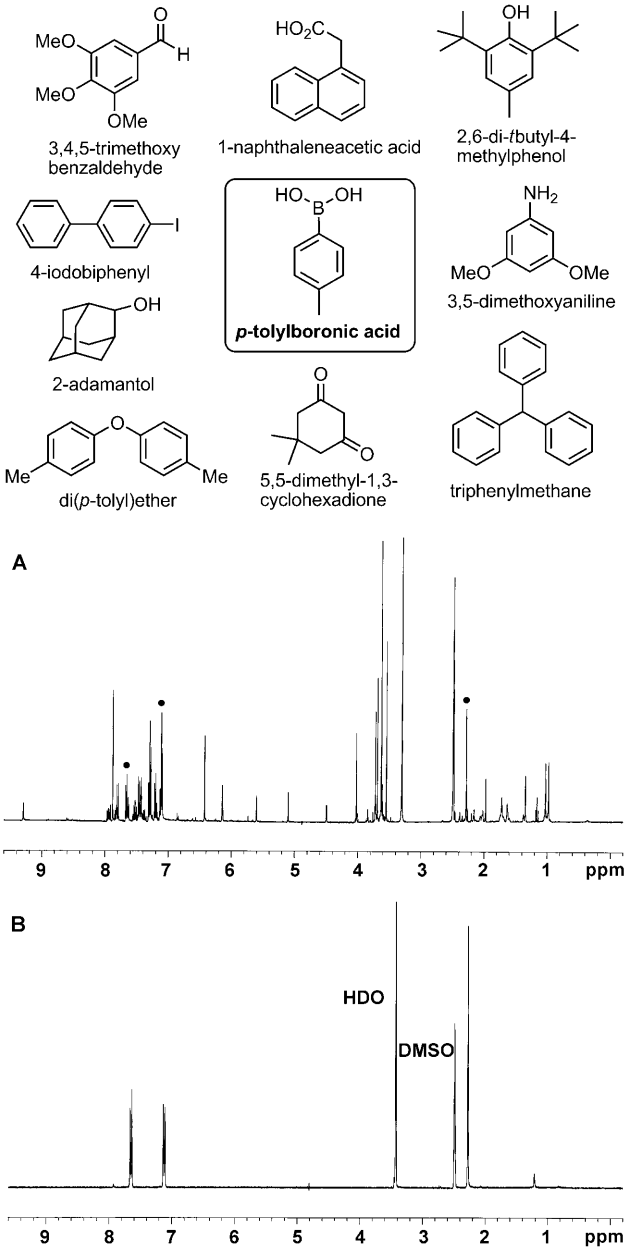
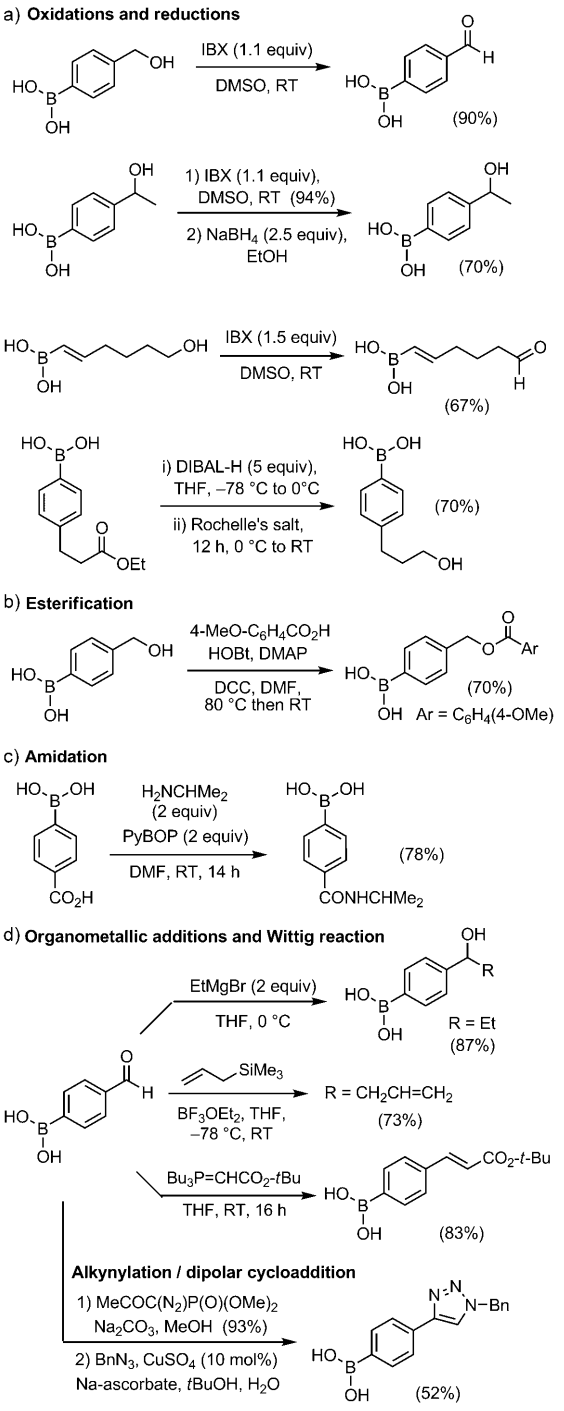


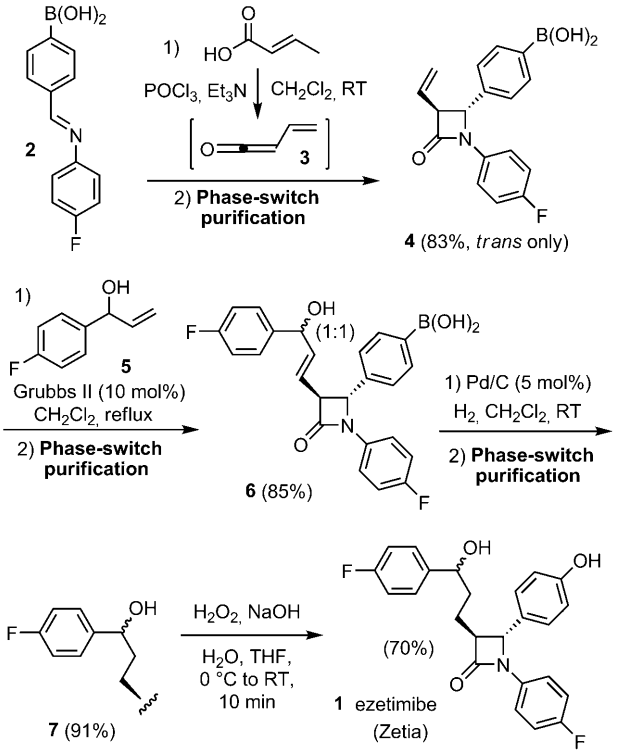
Figure 2. Comparison of ^{1}H NMR spectra for the purification of *p*-tolylboronic acid from a 10-compound mixture. A) ^{1}H NMR spectra of an equimolar mixture of 10 compounds including *p*-tolylboronic acid (peaks indicated with a dot). B) ^{1}H NMR spectra of recovered *p*-tolylboronic acid after phase-switching (1 M sorbitol/1 M Na_2CO_3), back-switching in ethyl acetate by reacidification (pH 3) of the aqueous phase and a basic aqueous wash to remove the rest of the carboxylic acid.

In the planning of a phase-switch synthesis, the initial substrate is selected from a broad choice of commercial boronic acids to circumvent the need for a tag-attachment step. That functionality is preserved as a built-in phase tag until the last step of productive tag removal. To demonstrate the value of this productive phase-switch concept in target-oriented synthesis and to additionally expand the repertoire of suitable reaction conditions, we put it to test toward a



Scheme 3. Selection of optimized reaction conditions compatible with free boronic acids. Note: In all cases only phase-switch purification was performed to give yields of isolated products in acceptable purity. No silica chromatography was required. Bn = benzyl, PyPOP = benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate, DCC = dicyclohexylcarbodiimide, DIBAL-H = diisobutylaluminum hydride, DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, HOBt = 1-hydroxybenzotriazole, IBX = *o*-iodoxybenzoic acid, THF = tetrahydrofuran.

racemic synthesis of ezetimibe, **1** (Zetia), a commercial antihyperlipidemic drug (Scheme 4).[17] The chosen route to ezetimibe emphasizes the possibility of using the boronic acid



Scheme 4. Phase-switch synthesis of ezetimibe (Zetia). Silica gel chromatography was performed only after the final step.

tag as a masked hydroxy group. Therefore, Schiff base **2** (generated by condensation of commercially available *p*-boronobenzaldehyde with *p*-fluoroaniline) was reacted with the ketene **3** derived from crotonic acid to give the desired *trans*-configured β-lactam product **4** in very good yield after a simple phase-switch purification. The latter underwent a high-yielding alkene cross-metathesis with racemic alcohol **5**, and subsequent hydrogenation of the resulting allylic alcohol **6** afforded the saturated intermediate **7** in high yield. No starting material remained in any of these reactions, thereby circumventing purification of products by silica chromatography. The final step of productive tag removal was realized by B–C bond oxidation to yield ezetimibe (**1**) in good yield after the only chromatographic purification of the entire sequence. Although it was obtained as a separable mixture of diastereomers resulting from the carbinol center, this short synthesis demonstrates the suitability of this phase-switch synthesis concept for preparing highly functionalized molecules in multiple steps while circumventing chromatographic purifications.

In summary, we have described a novel phase-switch system involving a productive phase tag for use in multistep organic synthesis. This system, based on a pH-driven liquid–liquid partitioning, exploits the ability of sorbitol to complex and transfer boronic acids reversibly from an organic solvent to water at high pH. The boronic acid functionality represents a convenient phase tag because of its widespread commercial availability, ease of handling, and its compatibility with several reaction conditions like alcohol oxidations, ester and ketone reductions, amide and ester coupling, organometallic

additions, Wittig olefinations, alkene metathesis, catalytic hydrogenations, and cycloadditions. Most importantly, boronic acids can be converted selectively into a wide variety of useful products to terminate the synthetic cycle concomitantly with the detagging operation. Other attractive features of this concept, such as ease of purification and solvent economy, were highlighted in a multistep synthesis of the antihyperlipidemic drug ezetimibe.

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