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Chemoselective esterification of α-hydroxyacids catalyzed by salicylaldehyde through induced intramolecularity†

Cite this: *RSC Advances*, 2013, **3**, 1976

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Received 26th November 2012,
Accepted 28th November 2012

DOI: 10.1039/c2ra23068b

www.rsc.org/advances

A new, direct and chemoselective esterification of α-hydroxyacids was developed using a reversible covalent-binding strategy. By taking advantage of acetal chemistry, simple aldehydes can be used to efficiently catalyze the esterification of α-hydroxy carboxylic acids in the presence of β-hydroxyacid moieties or other carboxylic acids in amounts equal to or in excess of the alcohols. A diverse array of α-aryl, α-alkyl, α-heteroaryl, and functionalized α-hydroxyacids were smoothly esterified with 1° and 2° alcohols catalyzed by 10 mol% inexpensive and commercially available salicylaldehyde, furnishing the resultant esterification products in 83–95% yields after a simple basic aqueous workup to remove the unreacted hydroxyacids. In addition, the salicylaldehyde can be recovered through vacuum distillation or silica gel purification, thereby meeting the standards of green chemistry. A mechanistic study proved that the formation of covalent adduct **III** during our proposed catalytic cycle (Scheme 1A) is responsible for the real catalysis.

Introduction

Conceptually inspired by enzymatic processes, catalysis though induced intramolecularity utilizing a reversible multiple covalent binding strategy is considered one of the important tools and future directions for conducting sustainable organic syntheses.[1] In reactions for which either the catalytic functional group or functionalized substrates are rigidly tethered through reversible covalent interactions, a large amount of entropy must be expended in advance. Therefore, such entropic loss can be utilized to accelerate the subsequent chemical transformation, allowing the intermolecular processes to proceed in an intramolecular manner with an inherently low energy cost and efficient energetic discrimination of competing transition states in the rate-determining step. This can result in high levels of regio-, chemo-, and stereoselective induction and enhanced reaction rates.[2] By taking advantage of the high tendency of formation and relatively low activation barriers for bond-forming equilibration of hemiacetals, hemithioacetals, or carbinolamines,[3] carbonyl compounds (aldehydes and ketones) can act as enzyme-mimicking catalysts.[4] This strategy provides a great opportunity to allow pre-association of the reaction counterparts to form a highly reactive transient geometry and thermodynamically stable transition state. As a consequence, bimolecular reactions can be achieved through fast and stereoselective unimolecular processes that allow for pre-modification of designed intermediate structures.[1,2,5] Recently, a remarkable demonstration of temporary intramolecularity in Cope-type hydroaminations has shown the possibility of using simple aldehydes as catalytic tethering functionalities to achieve highly challenging intermolecular transformations in a catalytic and enantioinductive manner.[6]

Many early applications using carbonyl compounds (aldehydes or ketones) as catalytic platforms have focused on the hydrolysis and transesterification of functionalized esters such as activated esters of amino acids and α-hydroxyesters.[7] However, the actual catalysis proceeded through the generation of a five-membered cyclic intermediate (dioxolanone), triggered by the reversible nucleophilic addition of the *gem*-hydroxyl group of the hemiacetal to the reacting carbonyl group (Scheme 1A). Nevertheless, the pursuant elimination that was conjectured as the rate-determined step strongly relied on the leaving capability of the alcohol component of the ester (*i.e.* the alkoxide). Therefore, applications using this strategy seem limited and only applicable to activated esters; furthermore, synergistic assistance of a general base in close proximity to the catalytic site is required.[5,7] In contrast to those carbonyl-catalyzed enzyme-mimicking hydrolysis reactions, the direct construction of ester bonds of hydroxyacids using acidic boric and boronic acids as reversible covalently-bonding units have shown the complementary applications of induced intramolecularity.[8] The cyclic acyloxyboronate species is naturally, reversibly, and covalently formed as an activated

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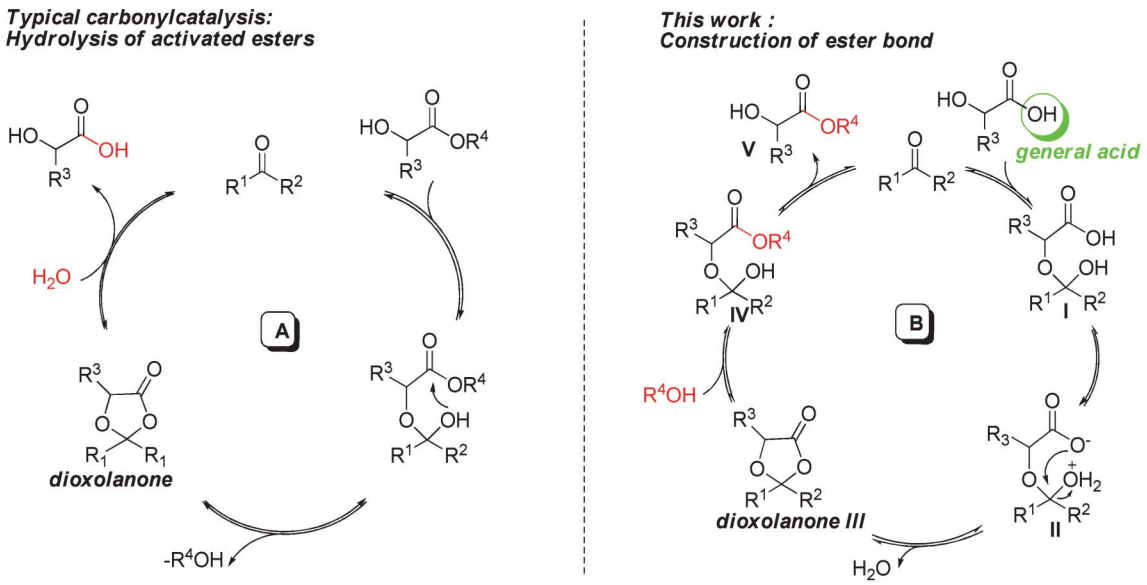
† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c2ra23068b

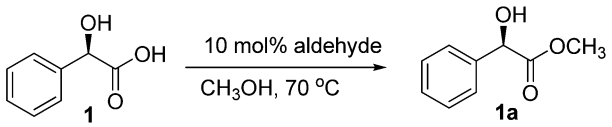


Scheme 1

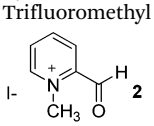
electrophilic intermediate with very low energetic requirements during such equilibrating processes between bifunctional α-hydroxyacids and boric (or boronic) acids, thereby facilitating the subsequent nucleophilic acyl substitution and water-expelling turnover processes.

In this regard, we wished to take advantage of the glycosidic lysozyme catalysis[9] associated with the related acetal hydrolysis chemistry.[10] The carboxylic acid group of the α-hydroxyacid would serve as a general acid and self-catalyze acetal formation with the carbonyl catalyst, which would be followed by cyclic acylal (dioxolanone) intermediate formation with participation of the ionized carboxylate anion (Scheme 1B). This would allow intramolecular facilitation of the subsequent nucleophilic esterification,[11] if such a proposed equilibrium exists. In this article, we describe the chemo- and site-selective catalysis of directed esterification of α-hydroxyacids under relatively mild and metal-free conditions using simple aromatic aldehydes, especially salicylaldehyde, by manipulating the reversible acetal bond formation and subsequent cyclic dioxolanone-generating equilibria between bifunctional α-hydroxyacids and carbonyl catalysts. This method may provide another chance to circumvent the inherent harshness, difficulty, and inefficiency of classical esterification reactions.[8,12] This strategy also fully demonstrates an application contrary to traditional aldehyde catalysis and illustrates the power of induced intramolecularity. In addition, the aldehyde catalysts can be conveniently recovered by simple distillation or chromatographic purification, and the use of transition metal catalysts can be avoided, thereby meeting the standards of current innovation toward green organic synthesis.

Table 1 Catalyst **1** screening[a,b]



1 **1a**

Entry	Aldehyde	Time (h)	Yield (%)[c]
1	Benzaldehyde	24	62(11)[d]
2	4-Nitrobenzaldehyde	24	13
3	Pentafluorobenzaldehyde	24	5
4	Pyridine-2-carboxaldehyde	24	8
5	2-Benzloxyacetaldehyde	24	28
6	2-Phenylacetaldehyde	24	13
7	*tran*-2-Hexenal	24	43
8	4-Methoxy-benzaldehyde	24	75(20)[d]
9	2,6-Dimethoxybenzaldehyde	24	68(12)[d]
10	Salicylaldehyde	18	92(28)[d]
11	3-Hydroxybenzaldehyde	24	76
12	4-Nitro-salicyladehyde	24	60
13	4-Methoxysalicyladehyde	18	87
14	2,4,6-Trihydroxybenzaldehyde	24	79
15	Tetrahydro-4*H*-pyran-4-one	48	6
16	Cyclohexanone	48	11
17	Trifluoromethyl phenyl ketone	48	35
18		24	82(5)[d]
19[e,f]	Salicylaldehyde	18	90 (**1b**)
20[e,g]	Salicylaldehyde	15	92 (**1c**)

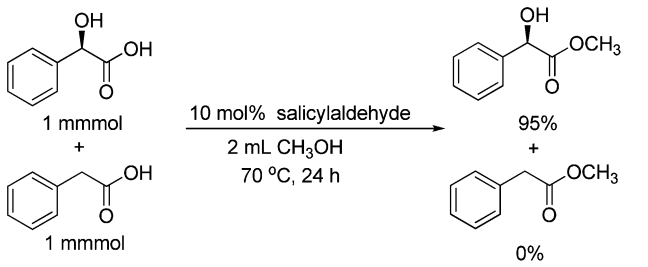
[a] Reaction conditions: 10 mol% aldehyde, (*R*)-mendalic acid (1 mmol) in 1 mL CH_3OH at 70 °C. [b] Reaction progress was monitored by TLC, ^1H NMR spectroscopy, and GC analysis. [c] Yield of isolated product. [d] Reaction was conducted at room temperature (25 °C). [e] Reaction was conducted at 80 °C. [f] EtOH was used instead of CH_3OH. [g] *iso*-PrOH was used instead of CH_3OH.

Results and discussion

Catalyst screening

Initial attempts were guided by the model esterification of (*R*)-mandelic acid with methanol as the solvent in the presence of 10 mol% of aldehydes at 70 °C, and the results are shown in Table 1. To our delight, only 10 mol% of benzaldehyde allowed the reaction to proceed at 70 °C, albeit with a moderate yield (62%, Table 1, entry 1), while only 11% yield of **1a** was obtained at room temperature after 24 h (Table 1, entry 1, parentheses). Notably, esterification product **1a** was obtained as an enantiomerically pure material (determined by chiral HPLC analysis), suggesting that no racemization occurred under the reaction conditions. Interestingly, highly activated electron-deficient aldehydes such as 4-nitrobenzaldehyde and pentafluorobenzaldehyde failed to promote this condensation to a significant extent (Table 1, entries 2 and 3). In addition, 2-formylpyridine with a basic nitrogen atom proximate to the reaction center, which was employed to catalyze the hydroxyl-directed methanolysis of activated glycolate,[7] also proved ineffective (Table 1, entry 4), implying that our reaction mechanism is not through a general base or nucleophilic mechanism. Aliphatic aldehydes activated by α-benzyloxy or phenyl groups provided negligible activity in this condensation (Table 1, entries 5 and 6). An α,β-unsaturated alkenyl aldehyde showed a slight improvement in yield, but was still unsatisfactory (Table 1, entry 7). Surprisingly, electron-rich 4-methoxybenzaldehyde was found to be highly active, furnishing ester **1a** in 75% yield at 70 °C and 20% yield at room temperature within 24 h (Table 1, entry 8). The dimethoxy analog was less efficacious, yet still very active (68% yield, Table 1, entry 9).

It appears that an acidic phenol group proximate to the carbonyl does play a significant role in this catalytic condensation, as judged by the remarkable improvement in the yield for the reaction using salicylaldehyde (18 h, 92% yield, entry 10) relative to that of the analogous reaction catalyzed by 3-hydroxybenzaldehyde (24 h, 76% yield, entry 11). However, the analog with an electron-withdrawing nitro substituent was less efficacious than the parent salicylaldehyde (24 h, 60% yield, Table 1, entry 12). The salicylaldehyde possessing an electron-donating methoxy group at C-4 and water-soluble 2,4,6-trihydroxybenzaldehyde were catalytically comparable to salicylaldehyde, but showed no significant improvement in yield (Table 1, entries 13 and 14). Both 4-heterocyclohexanone and cyclohexanone, which were efficient catalysts for the hydrolysis of functionalized amides under strong alkaline conditions,[13] were found to be inactive, even at prolonged reaction times (Table 1, entries 15 and 16). A ketone catalyst possessing a strong electron-withdrawing trifluoromethyl group (CF_3) was slightly more efficient than the cyclic ketones and a prolonged reaction time was required to achieve a moderate yield (48 h, 35%, Table 1, entry 17). While basic 2-formylpyridine showed poor catalytic ability, ionic, water soluble, methylated *N*-methylpyridinium-2-carboxaldehyde iodide salt **2** was found to have catalytic efficiency comparable to that of salicylaldehyde, furnishing product **1a** in 82% yield at 70 °C within 24 h (Table 1, entry 18). However, it was not very efficient at room temperature (Table 1, entry 18, parentheses) compared with benzaldehyde, 4-methoxybenzaldehyde, 2,6-dimethoxybenzaldehyde, and salicylaldehyde (entries 1, 8, 9, and 10, parentheses). Other alcohols, such as ethanol and isopropanol, can also be used as protic nucleophiles using salicylaldehyde as the catalyst at higher temperature (80 °C) to furnish ethyl mandelate **1b** and *iso*-propyl mandelate **1c** in 90% and 92% yield, respectively (Table 1, entries 19 and 20). Interestingly, the reaction rate of the more sterically hindered isopropanol was faster than primary alcohols, probably because of the decreased rate of the competing acetal (or hemiacetal) formation of isopropanol and mandelic acid with the catalyst. However, the current protocol did not proceed well with 3° alcohols such as *tert*-butanol, even at prolonged reaction times, presumably due to the steric hindrance of 3° alcohols. It is worth mentioning that most of the carbonyl catalysts can be recovered through high vacuum distillation after completion of the reaction under mild heating (50 °C) and the pure mandelates (as judged by spectroscopic analysis) can be obtained upon washing the crude product with aqueous bicarbonate to remove the unreacted carboxylic acid or *via* chromatographic purification, if necessary. Ionic catalyst **2** can easily be recovered though precipitation by addition of a less polar solvent or from the water layer after aqueous work up. In order to examine the chemoselectivity of the present salicylaldehyde catalysis, equimolar amounts of mandelic acid and 2-phenyl acetic acid were mixed with 2 mL methanol in the presence of 10 mol% salicylaldehyde at 70 °C for 24 h. It was found that mandelic acid was quantitatively converted to the corresponding methyl ester **1a**, while no esterification product of 2-phenyl acetic acid was detected (Scheme 2). This result suggests that a high level of chemoselectivity can be achieved in our catalytic system, even in the presence of excess amounts of alcohol.

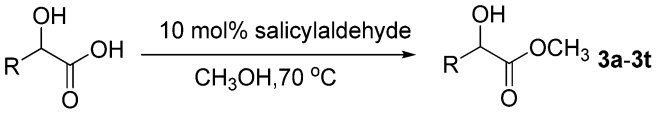


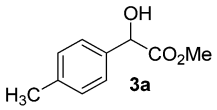
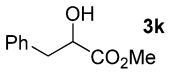
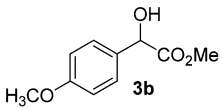
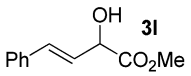
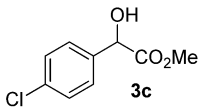
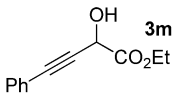
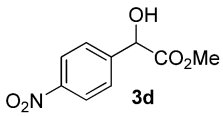
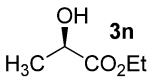
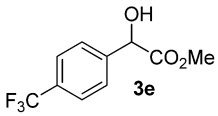
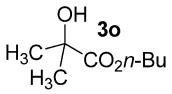
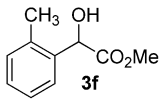
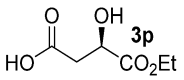
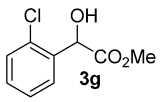
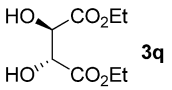
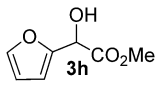
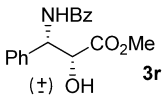
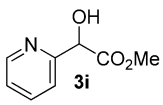
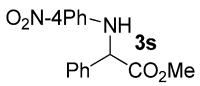
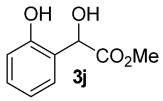
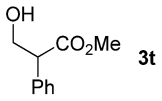
Scheme 2 Chemoselective esterification of mandelic acid in the presence of 2-phenylacetic acid catalyzed by salicylaldehyde

The scope of functional group compatibility

With these promising results in hand, our attention turned to the examination of the substrate scope of the reaction (Table 2). Salicylaldehyde readily promoted the esterification of a range of mandelic acid derivatives with various electronic and steric demands in concentrated methanolic solution at 70 °C (Table 2, entries 1–7). In general, substrates bearing electron-withdrawing groups (*e.g.* 4-Cl, 4-NO_2, and 4-CF_3, entries 3–5) were more reactive than those with electron-donating groups (*e.g.* 4-CH_3 and 4-CH_3O, entries 1 and 2). The

Table 2 Substrate scope[a,b]



Entry	Product	Time (h)	Yield (%)[c]	Entry	Product	Time (h)	Yield (%)[c]
1	 **3a**	18	90	11	 **3k**	12	95
2	 **3b**	24	91	12	 **3l**	12	91
3	 **3c**	14	93	13[d]	 **3m**	8	93
4	 **3d**	14	90	14[d,e]	 **3n**	28	85
5	 **3e**	12	93	15[f]	 **3o**	36	92
6	 **3f**	20	92	16[d,e]	 **3p**	14	89
7	 **3g**	16	90	17[d,e]	 **3q**	36	89
8	 **3h**	18	89	18	 **3r**	20	90
9	 **3i**	48	48	19	 **3s**	30	23
10	 **3j**	30	82	20	 **3t**	48	<5

[a] Reaction conditions: 10 mol% aldehyde, α-hydroxyacid (1 mmol) in 1 mL CH_3OH at 70 °C. [b] Reaction progress was monitored by TLC and ^1H NMR spectroscopy analysis. [c] Yield of isolated product. [d] Reaction was conducted at 80 °C. [e] EtOH was used instead of CH_3OH. [f] *n*-BuOH was used instead of CH_3OH and the reaction was conducted at 100 °C.

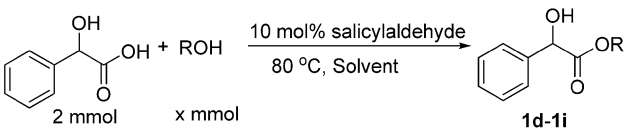
influence of steric hindrance on the reaction rate was pronounced for 2-substituted phenyl derivatives (compare entries 1 and 3 with entries 6 and 7). The esterification rates of the 2-chloro- and 2-methyl-substituted mandelic acids were slightly lower than the corresponding 4-substituted analogs. The reaction was also compatible with a heteroaryl-containing mandelic acid system to afford the highly biologically active **3h** within 18 h (89% yield, entry 8).[14] However, the esterification of a pyridyl-derived substrate was somewhat sluggish, probably because the basic nitrogen atom neutralized the acidic proton of the phenol group of salicylaldehyde or the mandelic acid, thus inhibiting the proposed acetal formation equilibrium and minimizing the yield (48%, entry 9). It was found that a slightly longer reaction time was required in the case of the *ortho*-substituted phenol substrate, owing to the competing reaction between the phenol group of the substrate and the carboxylic acid group of the α-hydroxyacid with the catalyst (30 h, 82%, entry 10).

The substrate class was further extended to α-hydroxyacids possessing α-benzyl, α-alkenyl, α-alkynyl, and α-alkyl groups. In general, α-benzyl, α-alkenyl (*trans*-PhCH=CH), and α-alkynyl (PhC≡C) analogs were more reactive than α-aryl and α-alkyl analogs (entries 11, 12, and 13). Their salicylaldehyde-catalyzed esterifications could be completed in 8–12 h. Furthermore, the conjugated alkene and triple bond remained intact without isomerization or rearrangement. In marked contrast, substrates bearing α-alkyl groups, such as lactic acid and 2-hydroxy-2-methylpropanoic acid, were less reactive in methanol; however, ethyl lactate **3n** (80 °C, 28h, 85% yield, entry 14) and *n*-butyl 2-hydroxy-2-methylpropanoate **3o** (100 °C, 36h, 92% yield, entry 15) could be obtained, albeit with prolonged reaction times and elevated temperatures, in the corresponding higher-boiling alcohols. With dicarboxylic acids framework, L-malic acid, the ethylation was ultimately regioselective for the carboxylic group proximate to the α-hydroxy moiety to provide monoester **3p** in 89% yield within 14 h (entry 16). It is notable that neither a significant improvement of the yield of monoester **3p** nor diester formation were observed when the reaction was extended to 24 h, which fully demonstrates the unique chemoselectivity of this aldehyde catalysis for α-hydroxyacids. In contrast, the esterification of tartaric acid was slower, even at 80 °C (36 h, 89% yield, entry 17), probably because of the fast formation of the acetal of the diol moiety of tartaric acid and the carbonyl group, which inhibited the formation of the proposed reactive intermediate **III**. Furthermore, the esterification of pharmaceutically active *N*-benzoyl-3-phenylisoserine (*i.e.* the taxol C-13 side chain)[15] led to methylated ester **3r** in 90% yield within 20 h, suggesting that β-branching substitution did not influence the catalytic efficiency of salicylaldehyde (compare entry 18 with entry 11). Notably, the methylation of phenyl glycine derivative 2-(4-nitrophenylamino)-2-phenylacetic acid was inefficacious, even though the amino group was protected with an electron-deficient *para*-nitrophenyl group, and amino ester **3s** was obtained in only 23% yield after a prolonged reaction time (entry 19). Finally, the reaction of a β-hydroxyacid (tropic acid) was inefficient with a long reaction time (<5% yield, 48h, entry 20), which again demonstrates the promising chemoselectivity of our catalytic system.

Concentration effects

It was found that the concentration and solvent effects largely influenced the yields of the direct esterification of α-hydroxyacids catalyzed by boronic acids. Whereas excess α-hydroxyacid accelerated the reaction, excess alcohol suppressed the reaction because of the competing coordination of both substrates and alcohols with the boron center.[8] Thus, we evaluated the solvent and concentration effects in our system using 10 mol% salicylaldehyde as the catalyst with different ratios of mandelic acid and alcohols (Table 3). The evaluation of other solvents in the esterification reaction of mandelic acid catalyzed by 10 mol% salicylaldehyde was undertaken at 80 °C and the amount of *n*-butanol was reduced to 5 equivalents. We found that nonpolar solvents such as toluene, cyclohexane, and heptane were tolerated at high molar concentration (2 M),[16] and toluene was optimal (Table 3, entries 1–3). On the effects of the concentration of the alcohol, expectedly, the reaction rate and yield increased when the amount of the alcohol used in toluene was decreased. The best molar ratio of mandelic acid to *n*-butanol was 1 : 1 (Table 3, entry 5), whereas the reaction rate was inhibited when the mandelic acid/*n*-butanol molar ratio was less than 1 : 1 (Table 3, compare entries 1 and 4 with 5). This phenomenon was probably due to the competition between formation of the hemiacetal of mandelic acid and that of excess *n*-butanol with the carbonyl group of the catalyst.[7] In contrast, the reactions of bulky alcohols proceeded more smoothly with a 1 : 1 molar ratio of mandelic acid to alcohol (Table 3, compare entries 5 and 6), and the rate of competition of mandelic acid for aldehyde decreased as the size of the alcohol moiety increased. The esterification of less nucleophilic benzyl alcohol was also proved efficacious in 14 h with nearly quantitative conversion (Table 3, entry 7), while a more basic long-chain aliphatic alcohol required an elevated temperature (100 °C) and a prolonged reaction time (Table 3, entry 8). The reaction of a sterically hindered 2° alcohol also proceeded smoothly to

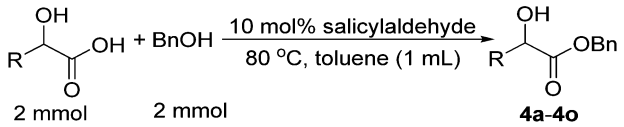
Table 3 Concentration effects[a]



Entry	Solvent/R_2OH	Time (h)	Yield (%)[b]
1	Toluene/*n*-BuOH (5 eq)	16	87 (**1d**)
2	Cyclohexane/*n*-BuOH (5 eq)	24	80 (**1d**)
3	Heptane/*n*-BuOH (5 eq)	18	84 (**1d**)
4	Toluene/*n*-BuOH (2 eq)	14	89 (**1d**)
5	Toluene/*n*-BuOH (1.0 eq)	12	93 (**1d**)
6	Toluene/*i*-Armyl (1.0 eq)	10	95 (**1e**)
7	Toluene/BnOH (1.0 eq)	14	94 (**1f**)
8[c]	Toluene/$CH_3(CH_2)_{16}CH_2OH$ (1.0 eq)	30	81 (**1g**)
9[c]	Toluene/Ph_2CHOH (1.0 eq)	20	90 (**1h**)
10[d]	Toluene/*cis*-PhCH=$CHCH_2OH$ (1.0 eq)	24	87 (**1i**)

[a] All reactions were conducted in 1 mL solvent in the presence of 10 mol% salicylaldehyde and 2 mmol mandelic acid at 80 °C. [b] Isolated yield. [c] Reaction temperature: 100 °C. [d] Reaction temperature: 120 °C (reflux).

Table 4 Esterification of equal amounts of benzyl alcohol and α-hydroxyacids[a]



2 mmol 2 mmol **4a-4o**

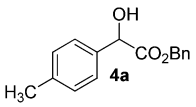
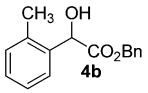
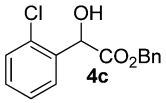
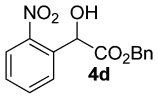
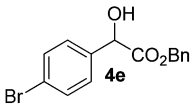
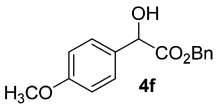
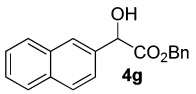
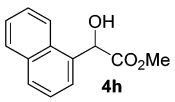
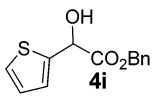
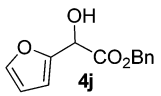
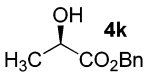
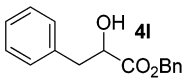
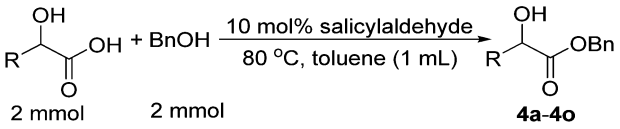
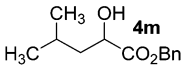
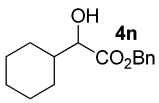
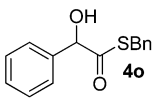
Entry	Product	Time (h)	Yield (%)[b]
1	 **4a**	10	90 (**4a**)
2	 **4b**	12	91 (**4b**)
3	 **4c**	8	93 (**4c**)
4	 **4d**	8	92 (**4d**)
5	 **4e**	8	94 (**4e**)
6	 **4f**	14	90 (**4f**)
7	 **4g**	10	94 (**4g**)
8	 **4h**	12	90 (**4h**)
9	 **4i**	8	95 (**4i**)
10	 **4j**	10	93 (**4j**)
11[c]	 **4k**	18	85 (**4k**)
12[c]	 **4l**	15	88 (**4l**)

Table 4 (*Continued*)



2 mmol 2 mmol **4a-4o**

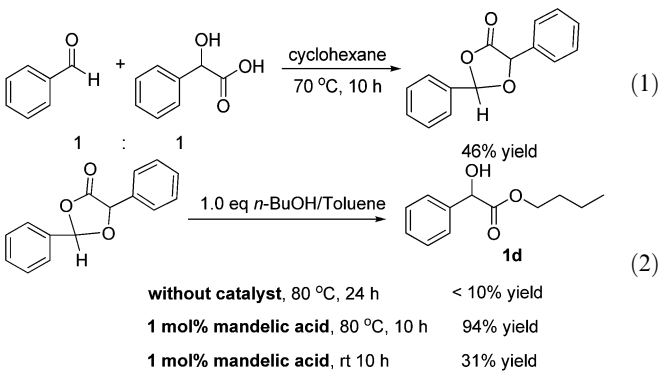
Entry	Product	Time (h)	Yield (%)[b]
13[c]	 **4m**	20	87 (**4m**)
14[c]	 **4n**	24	91 (**4n**)
15[d]	 **4o**	8	93 (**4o**)

[a] All reactions were conducted in 1 mL toluene in the presence of 10 mol% salicylaldehyde at 80 °C. [b] Isolated yield. [c] Reaction temperature: 100 °C. [d] The dilute benzylthiol in toluene (10 mL) was slowly added to the reaction mixture of mandelic acid and salicylaldehyde over 7 h at 60 °C *via* syringe pump.

furnish product **1h** in 90% yield within 20 h at 100 °C (Table 3, entry 9). The more challenging α,β-unsaturated cinnamyl alcohol also afforded a high product yield, albeit at the cost of a higher reaction temperature (Table 3, entry 10). Based on these results, it is noteworthy that the use of excess alcohol is not necessary, and more complex alcohols were applicable using our protocol.

We further demonstrated the more challenging benzylation of a series of α-hydroxyacids under the optimal conditions (2 M in toluene, 80 °C) catalyzed by 10 mol% salicylaldehyde in the presence of 1.0 equivalents benzyl alcohol (Table 4). In all cases, except those involving α-alkyl-substituted hydroxyacids, benzylation proceeded smoothly at 80 °C to afford the corresponding benzyl esters **4a**–**4j** in 90–95% yields at short reaction times (8–14 h, entries 1–10). In general, similar to the corresponding methylation (Table 2), α-aryl substrates bearing electron-withdrawing groups were more reactive than those with electron-donating groups. Also, the *ortho*-substituted aryl substrates were less reactive than the *para*-substituted substrates (compare entry 1 with entry 2). The steric effect was also pronounced for naphthyl-containing analogs; the 2-naphthyl (*i.e.* 3,4-/*m*,*p*-benzo-fused) system was more reactive than the 1-naphthyl (*i.e.* 2,3-/*o*,*m*-benzo-fused) system (entries 7 and 8). The benzylation of heteroaryl-containing systems such as the thiophene and furfural derivatives (entries 9 and 10) are even faster than α-aryl systems, presumably because of their high solubilities under such reaction conditions. Although a higher temperature (100 °C) was required for α-alkyl substituted systems, higher product yields were obtained, even in the cases of sterically hindered isobutyl

and cyclohexyl systems (85–91% yield, entries 11–14). Moreover, the thioesterification was also compatible, even at 60 °C to afford thioester **4o** in 93% yield within 8 h (entry 15). However, slow addition of the dilute toluene solution of benzylthiol (0.1 M) was essential to avoid formation of the extremely stable thioacetal of salicylaldehyde, which would interrupt the proposed catalytic equilibrium during the reaction.



(1)

(2)

Mechanistic study

With these results in hand, we were keen to validate our proposed reaction mechanism in Scheme 1B. In order to examine whether the designed equilibrium actually exists, we first set about trying to validate the existence of the intermediary dioxolanone, **III**. We conducted a reaction with a 1 : 1 ratio of benzaldehyde/mandelic acid in refluxing cyclohexane (70 °C) in the absence of any acidic catalyst or alcohol for 10 h (eqn (1)). Gratifyingly, the corresponding dioxolanone **III** was isolated with 46% yield as a spectroscopically pure solid, after extracting the unreacted mandelic acid with basic aqueous solution (see the Experimental section). This result had several mechanistic implications: (1) the hydroxyl group of the bifunctional mandelic acid serves as a directing group that rapidly and reversibly reacts with the carbonyl group of the catalyst to generate hemiacetal **I**; (2) the neighboring carboxylic acid group of mandelic acid then acts as a general acid and protonates the *gem*-hydroxyl of hemiacetal **I** to generate protonated species **II**; (3) the resulting ionized carboxylate reversibly and covalently participates in the next water-expelling step, which consequently facilitates the formation of kinetically competent cyclic dioxolanone **III**. However, such productive equilibrium is not favored at room temperature; therefore, a moderate energy requirement (heating) is essential to achieve this equilibrium.[17]

We further examined the reactivity of dioxolanone **III** toward alcoholysis with *n*-butanol (1.0 equivalent) in the presence or absence of mandelic acid in toluene. In the absence of mandelic acid, the alcoholysis was quite slow even at 80 °C, whereas esterification product **1d** was obtained in 94% yield at 80 °C and 31% yield at room temperature within 10 h when a catalytic amount of mandelic acid (1 mol%) was added to the reactions (eqn (2)). These results again suggested that a general acid catalysis provided by the carboxylic acid group of mandelic acid is crucial for the subsequent nucleophilic acyl substitution of **III** by the alcohols. Consequently, hemiacetal **IV** is produced and dissociation of the α-hydroxyester from **IV** liberates product **V**, regenerating the carbonyl catalyst. A similar hydrolysis of a dioxolanone intermediate promoted by an acidic proton was also observed in a detailed mechanistic study of the alcoholysis of activated esters catalyzed by 2-formylpyridine (general base), which coincides with our observations in eqn (2).[7] It should be noted that the final product-releasing step is irreversible, since the released α-hydroxyester did not undergo hydrolysis or transesterification at 80 °C in the presence of 10 mol% salicylaldehyde in aqueous ethanol.[18]

In view of the previous studies on the detailed mechanism concerning substituent effects in the intramolecular hydrolysis of hydroxyacid-derived acetals, electron-donating substituents on the aromatic ring of the acetal (*i.e.* a methoxy group) accelerate the hydrolysis rates, owing to the resonance stabilization of the oxocarbonium transition state.[19] In contrast, electron-withdrawing substituents (such as nitro or halide groups) strongly decelerate the hydrolysis because they deactivate the partially positive intermediate (Fig. 1, **A**). In addition, the *ortho*-hydroxy substituent can serve as a general acid itself, spontaneously catalyzing the hydrolysis of the phenolic acetal through an intramolecular hydrogen-bonding activation from the acidic phenolic proton. This leads to the development of a resonance-assisted equilibration between the phenol and *o*-quinone methide,[20] thereby remarkably accelerating the hydrolysis of the phenolic acetal (Fig. 1, **B**). These results are consistent with our observations of the electronic effect of the catalyst; that is, electron-rich aromatic aldehydes, especially salicylaldehyde with an *ortho*-hydroxy group, proved most efficient, as summarized in Table 1. We further postulate that in the case of salicylaldehyde catalysis, the phenolic proton also acts as a general acid and can intramolecularly activate the carbonyl group of the aldehyde and dioxolanone intermediate **III** synergistically with the α-hydroxyacid (Fig. 2), thus more efficiently catalyzing the formation of dioxolanone **III** and the subsequent nucleophilic acyl substitution of **III** with the alcohol. Moreover, the resonance-assisted equilibrium between the phenol and *o*-quinone methide facilitates the expulsion of water from **II**, release of the product **V** from **IV**, and regeneration of the catalyst. Although cationic pyridyl-derived catalyst **2** does not possess any Brønsted-acid characteristics, it is comparable to the efficient catalyst salicylaldehyde in the esterification reaction. This is probably because its cationic pyridinium structure stabilizes the oxonium ion proximate to the aromatic nitrogen atom by inductive electron-withdrawing or resonance effects,[21] thereby facilitating the manipulation of our proposed esterification using acetal chemistry.

Conclusion

In summary, we have documented a successful example using simple and inexpensive salicylaldehyde for the efficient and highly chemoselective direct esterification of functionalized α-hydroxyacids with excess amounts of volatile alcohols. We have also demonstrated that the current method is applicable

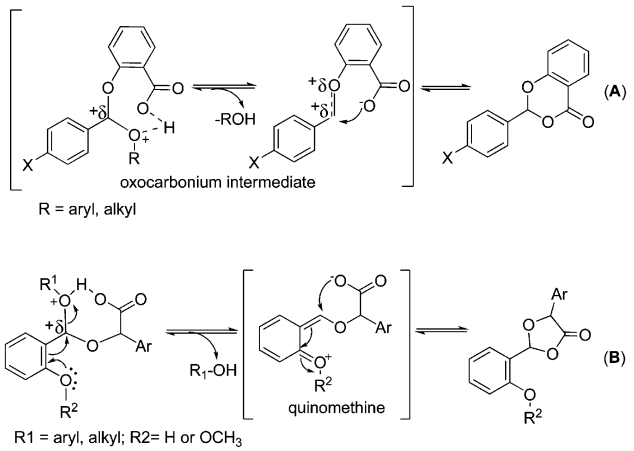


Fig. 1 Stabilization of the oxocarbonium transition state though resonance-assisted equilibration.

in an atom-efficient version of the reaction performed with equimolar amounts of α-hydroxyacids and complex alcohols in concentrated solutions in toluene. Application involving chemoselective esterification of α-hydroxyacid in the presence of β-hydroxyacid backbones in the same molecule (malic acid) or other simple acids fully demonstrates the potential value of this enzyme-mimicking catalytic protocol in the synthesis of other complex multifunctionalized esters. Mechanistic studies indicate that the turnover step is likely the formation of dioxolanone **III** during the reaction, which was triggered by self-catalysis of the α-hydroxyacid (general acid catalysis). In addition, the *ortho*-phenolic proton assistance of the salicylaldehyde and the resonance-assisted equilibration between the phenol and *o*-quinone methide are both responsible for the catalytic turnover. Notably, the catalyst is easily recovered *via* high-vacuum distillation or chromatographic purification after the reaction. Thus, the new approach meets the criteria for green chemical reactions, and this augurs well for its potential application in pharmaceutical chemistry and asymmetric catalysis.

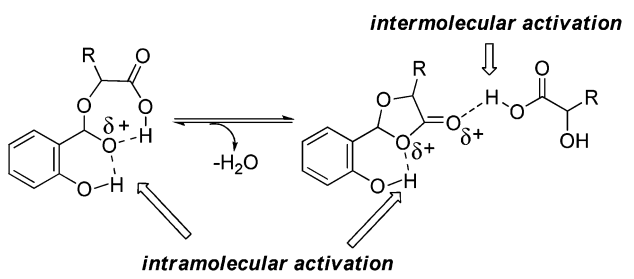


Fig. 2 Synergistic activation of the carbonyl of dioxolanone **III** through intramolecular hydrogen bonding of the phenolic proton and intermolecular hydrogen bonding of the carboxyl group of the α-hydroxyacid.

Experimental

The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using a JEOL JVM EX400 spectrometer (400 MHz, ^1H; 100 MHz, ^{13}C) and Bruker AVANCE 500 spectrometer (500 MHz, ^1H; 125 MHz, ^{13}C), with $CHCl_3$ as an internal reference. Electron-impact (ESI) mass spectra were recorded using a Thermo Finnigan spectrometer equipped with LCQ Advantage ionization and a SpectraSYSTEM detector system. Analytical GC was carried out using an Agilent 6890C GC system equipped with an Agilent DB-WAX column (30 m × 0.25 mm × 0.25 mm). Analytical TLC plates were visualized under UV light, or by spraying with phosphomolybdic acid (PMA) or $KMnO_4$ staining agents. All the reactions were performed under a nitrogen or argon atmosphere, and the end products were isolated as pure materials. Aldehyde **2**,[22] racemic *N*-benzoyl-3-phenylisoserine,[23] 2-(4-nitrophenylamino)-2-phenylacetic acid,[24] and α-substituted α-hydroxyacids[25] were prepared according to the literature reports. (*R*)-Mandelic acid, racemic 4-bromomandelic acid, (*R*)-lactic acid, racemic 2-hydroxyl-2-methyl-propanoic acid, racemic tropic acid, L-tartaric acid, and L-malic acid were purchased from Aldrich or Acros and used without further purification. All the liquid aldehydes and alcohols used in this study were distilled under reduced pressure from anhydrous $CaSO_4$ or activated magnesium metal before use. All products except **1i** are known compounds,[26] and they were identified by comparing their physical and spectra data with those reported in the literature (see ESI† for details).

Representative procedure for the esterification of α-hydroxyacids catalyzed by salicylaldehyde (Table 2)

(*R*)-Mandelic acid (**1**, 153 mg, 1 mmol) was dissolved in methanol (1.0 mL) in a 5 mL single-neck round-bottomed flask. Salicylaldehyde (12.2 mg, 11 μL, 0.10 mmol) was added to the flask *via* a syringe, at room temperature under a nitrogen atmosphere. The resulting mixture was heated to 70 °C, and the reaction progress was monitored by TLC, ^1H NMR spectroscopy, and GC analysis. After completion of the reaction, the mixture was gradually cooled to room temperature, and the organic solvent was evaporated to give the crude product. The salicylaldehyde was recovered through vacuum distillation using a Kügelrohr apparatus (1 torr, 50 °C). The remaining material was extracted with ethyl acetate (20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL × 2), dried with Na_2SO_4, and filtrated. Evaporation of the organic solvent provided pure methyl mandelate **1a** (153 mg, 92% yield). ^1H NMR (400 MHz, $CDCl_3$): δ 7.43–7.33 (m, 5H), 5.18 (d, J = 5.2, 1H), 3.76 (s, 3H), 3.45 (d, J = 5.6, 1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.1, 138.2, 128.6, 128.5, 126.6, 72.9, 53.0; MS $C_9H_{10}O_3$ (EI, 166) 166 (M^+, 13), 107 (100), 79 (51), 77 (43), 40 (12); TLC R_f 0.32 (EtOAc/hexane, 1/3); GC conditions: Agilent DB-WAX column (30 m × 0.25 mm × 0.25 mm), flow rate: 1 mL min^{-1}; 90 °C, 1 min; 10 °C min^{-1} to 140 °C; retention time (t_R) 19.78 min; internal standard: 1,3,5-trimethylbenzene. HPLC for racemic methyl mandelate: t_R 27.4 min (*R*, 50%), 31.2 min (*S*, 50%) (CHIRALCEL AD-H, *i*-PrOH/hexane, 6 : 94, 1.0 mL min^{-1}, λ = 254 nm). $[\alpha]_D^{24}$ −142 (*c* 1.0, MeOH) for 99% ee (lit. $[\alpha]_D^{20}$ -144 (*c*

1.0, MeOH) for (*R*)). The absolute configuration was deduced to be *R* according to the sign of the optical rotation.[26]

Representative procedure for the esterification of mandelic acid with *n*-butanol catalyzed by salicylaldehyde in toluene (concentration study, Table 3, entry 5)

To a 5 mL single-necked round-bottomed flask was added mandelic acid (306 mg, 2 mmol) in 1 mL toluene at room temperature under a nitrogen atmosphere. Solutions of *n*-butanol (149 mg, 184 μL, 2 mmol) and salicylaldehyde (24.4 mg, 22 μL, 0.20 mmol, 10 mol%) were added successively *via* syringe. The resulting mixture was heated to 70 °C and the reaction progress was monitored by TLC and ^{1}H NMR spectroscopy analysis. After completion of the reaction, the salicylaldehyde was recovered through vacuum distillation using a Kügelrohr apparatus (1 torr, 50 °C). The remaining material was extracted with ethyl acetate (20 mL) and the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL × 2), dried with Na_2SO_4, and filtrated. Evaporation of the organic solvent provided pure *n*-butyl mandelate **1d** (387 mg, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.34 (m, 5H), 5.16 (d, J = 5.2, 1H), 4.15 (m, 2H), 3.57 (d, J = 5.6, 1H, OH), 1.56 (m, 2H), 1.26 (m, 2H), 0.85 (t, J = 7.2, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 138.4, 128.5, 128.3, 126.5, 72.8, 66.0, 30.3, 18.8, 13.5; MS $C_{12}H_{16}O_3$ (EI, 208) 208 (M^+, 21), 191 (58), 107 (100), 79 (62), 77 (47); TLC R_f 0.28 (EtOAc/hexane, 1 : 5).[26]

Representative procedure for the esterification of α-hydroxyacids with benzyl alcohol catalyzed by salicylaldehyde in concentrated toluene (Table 4)

To a 5 mL single-necked round-bottomed flask was added α-hydroxyacid (2 mmol) in 1 mL toluene at room temperature under a nitrogen atmosphere. Solutions of benzyl alcohol (216mg, 208 μL, 2 mmol) and salicylaldehyde (24.4 mg, 22 μL, 0.20 mmol, 10 mol%) were added successively *via* syringe. The resulting mixture was heated to 70 °C and the reaction progress was monitored by TLC and ^{1}H NMR spectroscopy analysis. The salicylaldehyde was recovered through vacuum distillation using Kügelrohr apparatus (1 torr, 50 °C). The remaining material was extracted with ethyl acetate (20 mL) and the organic layer was purified by column chromatography on a shot pad of silica gel (hexane/EtOAc = 1 : 5) to provide the pure benzyl mandelate **1f** (455 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43–7.30 (m, 7H), 7.21–7.19 (m, 2H), 5.24 (d, J = 12.0, 1H), 5.22 (d, J = 5.2, 1H), 5.14 (d, J = 12.0, 1H), 3.41 (d, J = 5.2,1H, OH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.5, 138.2, 135.0, 128.6, 128.5, 128.4, 127.9, 126.6, 73.0, 67.6; MS $C_{15}H_{14}O_3$ (EI, 242) 242 (M^+, 4), 226 (12), 107 (100), 92(18), 90(24), 80(12), 79(19), 77(11); TLC R_f 0.34 (EtOAc/hexane, 1 : 5); Mp: 96–98 °C.[26]

Synthesis of dioxolanone III from mandelic acid and benzaldehyde (eqn (1))

Mandelic acid (608 mg, 4 mmol) was placed in a 10 mL single-neck round-bottom flask and benzaldehyde (415 μL, 2 mmol) in cyclohexane (5 mL) was added to the flask *via* a syringe, at room temperature under nitrogen atmosphere. The resulting mixture was refluxed (70 °C) for 10 h. The reaction mixture was gradually cooled to room temperature, and the organic solvent and unreacted benzaldehyde were evaporated under vacuum to give the crude product. The crude product was dissolved in ether (30 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL × 2) to remove the unreacted mandelic acid. The organic layer was dried with Na_2SO_4 and filtrated. Evaporation of the organic solvent provided pure 2,5-diphenyl-[1,3]dioxolan-4-one (dioxolanone **III**, 442 mg, 46% yield), with 99.6% *cis* isomers. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.43 (m, 10H), 6.57 (s, H), 5.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 134.3, 133.3, 130.7, 129.3, 128.79, 128.75, 127.0, 126.8, 103.2, 77.19; MS $C_{15}H_{12}O_3$ (EI, 240) 240 (M^+, 16), 151(32) 105 (100), 93(23), 90(24), 79(43), 77(76); Mp: 102–104 °C.[27]

Synthesis of *n*-butyl mandelate 1d from dioxolanone III (eqn (2))

To a dry 25 mL, two-necked round-bottomed flask was added 2,5-diphenyl-[1,3]dioxolan-4-one (dioxolanone **III**, 240 mg, 1.0 mmol), *n*-butanol (82 mg, 102 μL, 1.1 mmol), and 1 mol% mandelic acid (1.5 mg, 0.01 mmol) in anhydrous toluene (10 mL) under a nitrogen atmosphere. The reaction mixture was heated at 80 °C for 10 h. The mixture was cooled to room temperature, washed with saturated aqueous $NaHCO_3$ (10 mL × 2), dried with Na_2SO_4, and filtrated. Evaporation of the organic solvent gave pure *n*-butyl mandelate **1d** (196 mg, 94% yield).

Acknowledgements

We acknowledge the financial contribution extended by the National Science Council of the Republic of China (NSC-100-2113-*M*-145-001-MY2). We also thank the mass laboratory of National Taiwan Normal University and the NMR laboratory of National Sun Yat-sen University for assistance in the NMR spectra measurements.

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