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Direct Catalytic Asymmetric Synthesis of β-Hydroxy Acids from Malonic Acid

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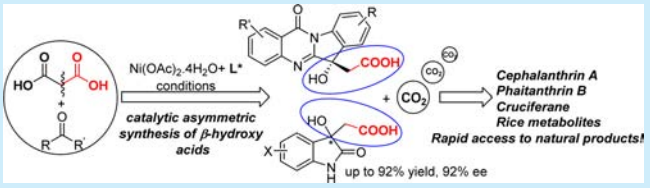
Supporting Information

ABSTRACT: A nickel(II) catalyzed asymmetric synthesis of β-hydroxy acids from malonic acid and ketones was developed, revealing for the first time the synthetic utility of malonic acid in the construction of chiral carboxyl acids; importantly, the synthetic potential of this strategy was further demonstrated by the rapid construction of cephalanthrin A, phaitanthrin B, cruciferane, and rice metabolites.



Enantioenriched β-substituted carboxylic acids are constituents of various biologically active natural products and pharmaceutical compounds as exemplified by cephalanthrin A,[1a] phaitanthrin B,[1b] cruciferane,[1c] and rice metabolites,[1d,e] etc. (Figure 1); thus they have been the focus of extensive

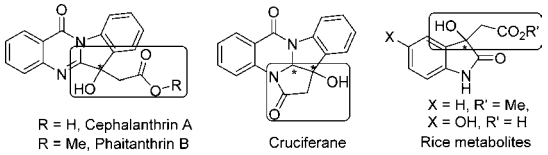


Figure 1. Selected bioactive compounds with chiral β-hydroxy acid structures.

investigation. In the past decades, great achievements have been made in the catalytic synthesis of β-substituted chiral carboxylic acids by asymmetric hydrogenation[2] or intramolecular addition[3] of unsaturated carboxylic acids; besides, desymmetrization[4] or kinetic resolution[5] of β-substituted carboxylic acid derivatives were also achieved. However, the preparation of corresponding carboxylic acid derivatives in these transformations has always limited the substrate scope and product diversity. Alternatively, a different approach to this target is to introduce an acetic acid motif to electrophiles and construct a chiral center simultaneously, which would provide a facile access to structure-diverse β-substituted acids from simple starting materials. More importantly, such methodologies may enable the creation of sterically hindered chiral carboxylic acids with quaternary stereocenters, a significant challenge for catalytic asymmetric synthesis. However, the catalytic asymmetric activation of carboxyl acid donors remains a great challenge, because the high pk_a value of their α-proton makes them difficult to enolize under catalytic or base-free conditions. Very recently, Shimizu and Kanai et al. reported the first example of a direct asymmetric catalytic nucleophilic activation of carboxylic acids in the promotion of 10−20 mol % of BH_3·SMe_2 and 2 equiv of DBU.[6] At the same time, we were also interested in exploring the possibility of constructing β-substituted chiral carboxylic acids by employing activated acetic acid motifs as nucleophiles. Inspired by nature's way to synthesize polyketide and fatty acids,[7] we envisioned that 1,3-dicarboxyl acids, which can cleave a carboxyl group by decarboxylation to produce acetic acid species under mild conditions, would be ideal nucleophilic precursors in the catalytic direct synthesis of β-substituted acids.

Recently, the catalytic asymmetric decarboxylative reactions of β-functionalized acid derivatives (β-keto acids, malonic acid half esters, etc.) have received increasing attention: a number of synthetic methods have been successfully developed to construct ketones, ester derivatives, etc. with high optical purities.[8] In contrast, the 1,3-dicarboxyl acids, though having great potential in the synthesis of chiral carboxyl acids, have never been employed as donors in the catalytic asymmetric decarboxylative transformations. In fact, because of the strong acidity and nucleophilicity of their dicarboxyl group, 1,3-dicarboxyl acids are mainly used for the synthesis of cinnamic acids[9a] and Meldrum's acid[9b] by reacting with different carbonyls; besides, decarboxylative protonation of 1,3-dicarboxyl acids to produce non-nucleophilic acetic acid derivatives may also take place.[8a] Thus, asymmetric synthesis of β-substituted acids via the decarboxylative addition reaction of 1,3-dicarboxyl acids remains a very challenging work. As part of our continuous effort to construct chiral quaternary alcohol derivatives,[10] herein, we wish to report a nickel(II) catalyzed asymmetric synthesis of β-hydroxy acids from malonic acid and ketones, which for the first time revealed the synthetic utility of 1,3-dicarboxyl acids in the construction of chiral carboxyl acids. Importantly, the present methodology enabled a rapid access to cephalanthrin A and phaitanthrin B, new types of indoloquinazoline alkaloids which exhibited promising cytotoxicity against cancer cells.[1a,b] To the best of our knowledge, no catalytic asymmetric methods exist for the construction of these molecules. Besides, the use of this reaction in the facile synthesis of optical active cruciferane and rice metabolites is also described (Figure 2).

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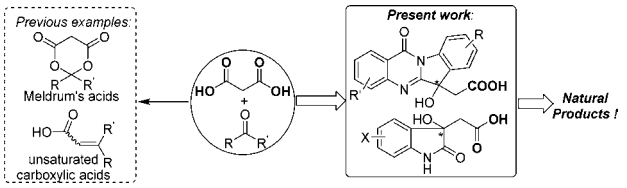
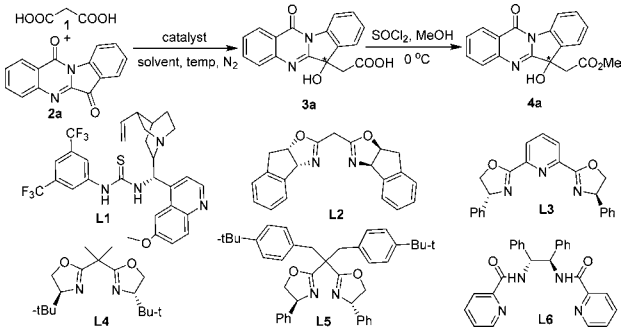


Figure 2. Catalytic asymmetric synthesis of β-hydroxy acids.

In connection with our ongoing researches to explore new catalytic processes for the construction of enantioenriched indoloquinazoline alkaloids,[10b] our study commenced with the direct synthesis of cephalanthrin A via a decarboxylative addition reaction of malonic acid to tryptanthrin. The desired β-hydroxy acid product can be further converted into phaitanthrin B via esterification. However, initial attempt by treatment of tryptanthrin **2a** with 2 equiv of malonic acid **1** in the presence of 20 mol % of quinine-thiourea **L1** proved unsuccessful (Table 1, entry 1), though this organocatalyst was previously identified effective in various decarboxylative addition reactions.[8a,b]

Table 1. Condition Optimization[a]



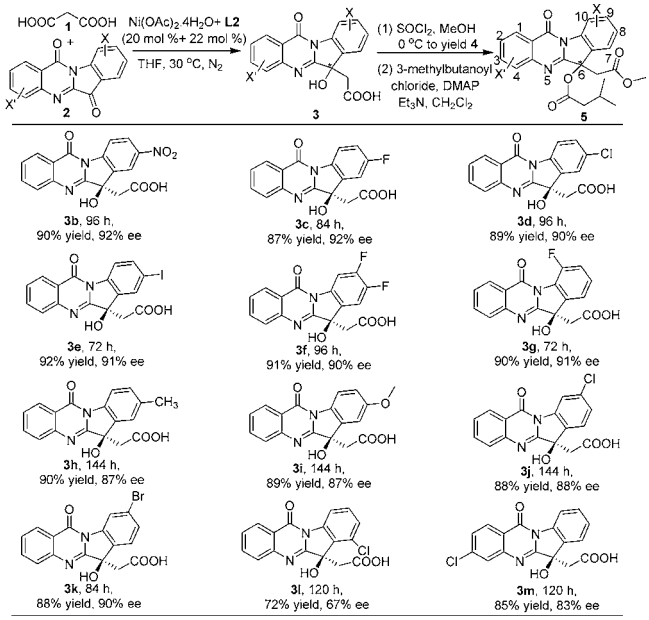
entry	catalyst (20 mol %)	solvent	temp (°C)/ time (h)	yield(%)[b] of **3a**/**4a**, ee[c]
1	**L1**	THF	90/36	
2	$Ni(OAc)_2{\cdot}4H_2O$	THF	90/36	49/–
3	$Ni(OAc)_2{\cdot}4H_2O$/**L2**	THF	90/36	92/90, 76
4[d]	$Ni(OAc)_2{\cdot}4H_2O$/**L2**	THF	90/36	82/86, 74
5	$Ni(OAc)_2{\cdot}4H_2O$/**L3**	THF	90/36	50/89, 4
6	$Ni(OAc)_2{\cdot}4H_2O$/**L4**	THF	90/36	78/88, 2
7	$Ni(OAc)_2{\cdot}4H_2O$/**L5**	THF	90/36	92/94, 26
8	$Ni(OAc)_2{\cdot}4H_2O$/**L6**	THF	90/36	70/91, 41
9	$Ni(OAc)_2{\cdot}4H_2O$/**L2**	toluene	90/36	36/89, rac
10	$Ni(OAc)_2{\cdot}4H_2O$/**L2**	$CHCl_3$	90/36	45/88, 2
11	$Ni(OAc)_2{\cdot}4H_2O$/**L2**	EtOAc	90/36	80/91, 53
12	$Ni(OAc)_2{\cdot}4H_2O$/**L2**	DMSO	90/36	43/87, 37
13	$Ni(OAc)_2{\cdot}4H_2O$/**L2**	THF	40/72	88/91, 89
14	$Cu(OTf)_2$/**L2**	THF	40/72	73/87, 6
15	$Cu(acac)_2$/**L2**	THF	40/72	32/83, 3
16	$NiCl_2{\cdot}6H_2O$/**L2**	THF	40/72	67/93, 26
17	$Ni(OAc)_2{\cdot}4H_2O$/**L2**	THF	30/120	92/91, 90
18[e]	$Ni(OAc)_2{\cdot}4H_2O$/**L2**	THF	30/120	91/90, 88 (>99)

[a]General reaction conditions: **1** (0.4 mmol), **2a** (0.2 mmol), ligand (22 mol %), and catalyst (20 mol %) in 2 mL solvent under the specific temperature. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]For this reaction 10 mol % of catalyst was used. [e]For this reaction 8 mmol **1** and 4 mmol **2a** were used under optimal conditions; the ee value in parentheses was determined after a single recrystallization.

Subsequently, the catalytic abilities of Lewis acids in this reaction were also examined. Fortunately, we were delighted to find the desired β-hydroxy acid **3a** were obtained in 49% yield when 20 mol % of $Ni(OAc)_2.4H_2O$ was employed as catalyst (entry 2). Inspired by this result, investigations to establish an enantioselective version were next carried out (entries 3−8). For chiral HPLC analysis, the β-hydroxy acid product **3a** was converted into corresponding ester **4a** by treatment with thionyl chloride in MeOH. Encouragingly, when (1*R*,2*S*)-(+)-cis-1-amino-2-indanol derived bisoxazoline[11] **L2** was employed as the ligand at 90 °C, the reaction proceeded smoothly and afforded the desired product with high yield and good enantioselectivity of 76% ee (entry 3), and lowering the catalyst loading led to slight decreases in yield and enantioselectivity (entry 4). Further optimization of reaction conditions revealed that THF is the best choice of solvent (entries 8−12), while $Ni(OAc)_2{\cdot}4H_2O$ showed superior catalytic activity compared to other Lewis acids (entries 13−16). Finally, the best compromise between conversion and enantioselectivity was reached when the reaction was carried at 30 °C (entry 17). To ensure the effectiveness of our methodology for synthetic applications, a gram scale reaction was performed (entry 18). By treatment of 4 mmol **2a** with 8 mmol **1** under optimal conditions, the desired **3a** was obtained in good yield and enantioselectivity, which was increased to >99% ee after a single recrystallization.

With these optimized conditions in hand, we then investigated the scope of this catalytic asymmetric decarboxylative reaction. As outlined in Scheme 1, a range of tryptanthrins **2** participated well in the reaction with malonic acid (because of the poor solubility, both the hydroxyl- and carboxyl groups of products were protected before HPLC analysis). In most cases, both the reaction efficiency and the enantioselectivity were found to be less

Scheme 1. Catalytic Asymmetric Decarboxylative Addition of Malonic Acid and Tryptanthrin[a]



[a]All reactions were carried out with **1** (0.4 mmol), **2** (0.2 mmol), **L2** (22 mol %) and $Ni(OAc)_2{\cdot}4H_2O$ (20 mol %) in 2 mL THF at 30 °C for the specific time; given are isolated yields; enantioselectivities were determined by chiral HPLC, the hydroxyl- and carboxyl groups of **3** were protected before HPLC analysis.

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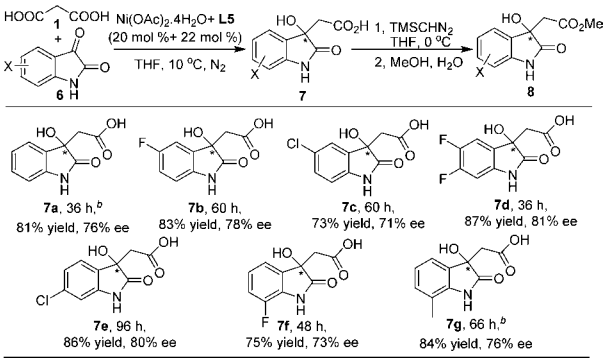
dependent on the substituent of tryptanthrins. For example, substitution at the 8-, 9-, and 10-positions with electron-donating or -withdrawing groups all resulted in good yields and ee values of 87−92% and 87−92%, respectively (Scheme 1, **3b**−**3k**); while substitution at 3-position of tryptanthrin led to a slight decrease in the ee value (Scheme 1, **3m**). However, when more sterically hindered tryptanthrin was employed as electrophile, much lower yield and enantioselectivity were observed (**3l**, 72%, 67% ee).

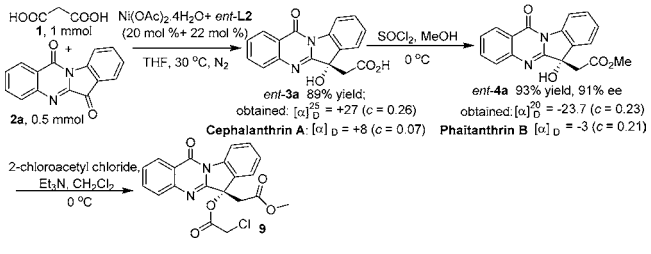
Encouraged by the good results achieved above, we wished to extend the application of this methodology to the reaction of malonic acid and isatins **6**, which may enable the asymmetric synthesis of 2-(3-hydroxy-2-oxoindolin-3-yl) acetic acids **7** and their esterified derivatives **8**, key structures of metabolites isolated from rice bran.[1d,e] Further optimization of reaction conditions indicated that changing the ligand to **L5** and decreasing the temperature to 10 °C were necessary to improve the enantioselectivity. Finally, we were pleased to find that a variety of isatins reacted smoothly with malonic acid under modified reaction conditions, affording 2-(3-hydroxy-2-oxoindolin-3-yl) acetic acids **7** with moderate to good yields and optical purities (Scheme 2, **7a**−**7g**, up to 87%, 81% ee).

Scheme 2. Catalytic Asymmetric Decarboxylative Addition of Malonic Acid and Isatin[a]



[a]Unless otherwise noted, all reactions were carried out with malonic acid **1** (0.4 mmol), isatin **6** (0.2 mmol), **L5** (22 mol %), and $Ni(OAc)_2{\cdot}4H_2O$ (20 mol %) in 2.0 mL of THF at 10 °C; given are isolated yields. Enantioselectivities were determined by chiral HPLC; the carboxylic group of **7** was protected before HPLC analysis. [b]The reaction was carried out at 30 °C.

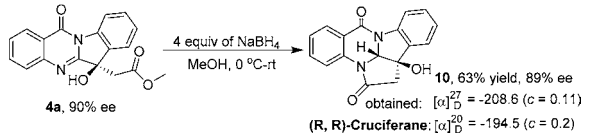
Scheme 3. Determination of Absolute Configuration of Cephalanthrin A and Phaitanthrin B



The absolute configuration of cephalanthrin A and phaitanthrin B was assigned as (*S*)-configuration by X-ray analysis of compound **9**, prepared from ent-**4a** by reacting with 2-chloroacetyl chloride (Scheme 3);[12] however, the optical rotation values of ent-**3a** and ent-**4a** obtained in our experiments was not strictly consistent with the literature data of cephalanthrin A[1a] and phaitanthrin B.[1b]

Given the importance of indoloquinazoline alkaloids and the limited methods for their preparation, further efforts were made to illustrate the value of this method in the synthesis of (*R*,*R*)-cruciferane **10**, an enantioenriched form of pyrrolo[2,3-*b*]indolo-[5,5a,6-b,a]quinazoline type racemic natural product from the root of *Isatis indigotica*.[1c] By treatment with $NaBH_4$,[13] the enantioenriched compound **4a** was converted to (*R*,*R*)-cruciferane **10** in 63% yield and 89% ee (Scheme 4).[14] The absolute configuration of **10** was confirmed by comparing the obtained data with literature values.[1c]

Scheme 4. Asymmetric Synthesis of (*R*,*R*)-Cruciferane



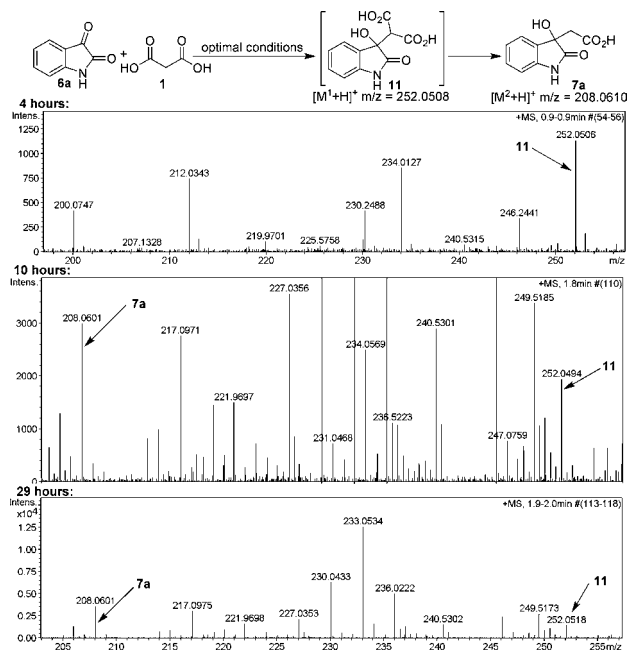


Figure 3. HRMS analysis of the reaction between **1** and **6a**.

To gain insight into this decarboxylative process, a time-course high resolution mass spectroscopy (HRMS) analysis of the reaction between isatin **6a** and malonic acid **1** under optimal conditions was carried out. As shown in Figure 3, after the reaction had proceeded for 4 h, not the desired product **7a** but a peak at *m*/*z* 252.0506 was detected, revealing that the nucleophilic addition of malonic acid to isatin is the first step of the whole transformation (Figure 3, **11**); while prolonging reaction time led to an increased abundance of the peak at *m*/*z* 208.0601 accompanied by the decrease of intermediate **11**, confirmed the decarboxylative process of unstable intermediate **11** which afforded the desired *β*-hydroxy acid product **7a**.

On the basis of these results obtained above, an asymmetric aldol-decarboxylation mechanism of the present transformation was proposed (Figure 4): first, anion exchange between the chiral nickel acetate complex and malonic acid afforded a nickel−malonic acid complex, which was capable of enolization to generate the nucleophilic intermediate I slowly, thus enabled the subsequent asymmetric addition of nickel malonic acid complex

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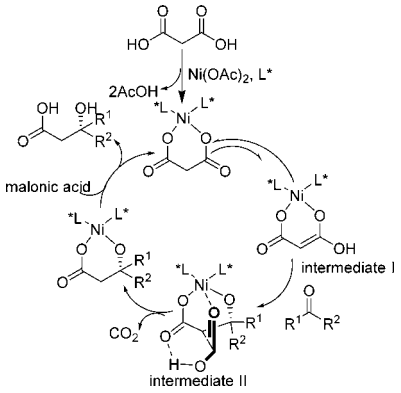

Figure 4. Proposed mechanism for the catalytic asymmetric synthesis of β-hydroxy acid from malonic acid.

to active ketones; then the resulting adduct cleaved CO_2 to produce the desired β-hydroxy acid in an enantioenriched form.

In summary, we have developed an enantioselective aldol-decarboxylation reaction between malonic acid and different kinds of ketones, providing a facile access to β-hydroxy acids with good enantiopurity and structural diversity. The application of the resulting β-hydroxy acids in the convenient synthesis of optically active cephalanthrin A, phaitanthrin B, (*R*,*R*)-cruciferane and rice metabolites enhances the importance of this asymmetric decarboxylative reaction. Importantly, this study indicates that the Lewis acid promoted asymmetric activation of malonic acid can also be applied to the enantioselective synthesis of other types of carboxylic acids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02891.

Experimental procedures and detailed characterization data of all new compounds(PDF)
X-ray crystal details for **9** (CIF)

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Author Contributions

‡H.G. and Z.L. contributed equally.

Notes

The authors declare no competing financial interest.

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■ NOTE ADDED AFTER ASAP PUBLICATION

An extra hydrogen atom on the oxygen atom of carbonyl of oxindole was deleted in the TOC/Abstract graphic; the correct version reposted on November 25, 2015.

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