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Amino Acid Salts Catalyzed Asymmetric Aldol Reaction of Tryptanthrin: A Straightforward Synthesis of Phaitanthrin A and Its Derivatives

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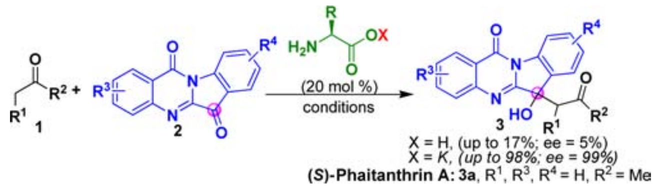
ABSTRACT



The first asymmetric synthesis of (*S*)-Phaitanthrin A and its derivatives via a catalytic aldol reaction of Tryptanthrin and ketones is described, in which the cheap, easily prepared natural amino acid salts exhibited unique catalytic ability; importantly, this methodology tolerates a range of substrates with different substitution patterns. Moreover, the synthetic utility of this strategy was further illustrated by a gram-scale synthesis of Phaitanthrin A.

Natural amino acids, which are wildly found in living organisms, have been one of the most common and important chiral molecules to sustain life. The critical roles they have played in biosynthetic processes inspired organic chemists to spend considerable efforts mimicking functions found in nature. Since Barbas and List reported the proline catalyzed cross-aldol reaction between ketones and aldehydes,[1] a variety of natural amino acids and their analogs were successfully employed as organocatalysts in various asymmetric reactions with high enantiocontrol.[2] In contrast, simple amino acid metal salts, which may take advantage of both organocatalysis and Lewis acid catalysis in asymmetric transformations, have been much less studied. Inspired by the pioneering work of Yamaguchi and co-workers,[3] remarkable advances in the application of amino acid metal salts on the asymmetric aldol reaction,[4] Michael addition,[3,5] and cyanosilylation[6] have been reported. Despite these important contributions, the catalytic ability of amino acid metal salts, which may enable previously inaccessible transformations with

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high efficiency, has not been fully revealed yet. As part of our continuous effort to develop new aldol-type processes,[7] we became interested in the possibility of employing amino acid metal salts to promote the aldol reaction with a challenging type of ketone acceptors, Tryptanthrin,[8] which exhibits low reactivity because of its poor solubility and electrophilicity (Figure 1). Up to now, only a few

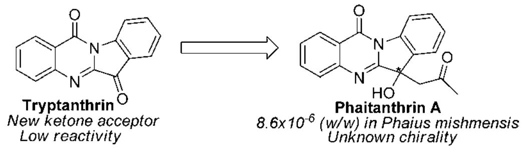
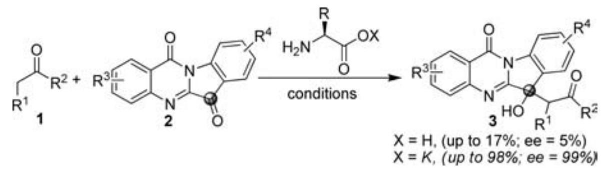


Figure 1. Structures of Tryptanthrin and Phaitanthrin A.

ketone acceptors such as isatin,[9] α-keto esters,[10] α-CF_3-ketones,[11] etc. were successfully involved in catalytic asymmetric aldol reactions; more importantly, the direct aldol reaction of acetone and Tryptanthrin enables a rapid access to Phaitanthrin A (Figure 1), a new type of indoloquinazoline alkaloids isolated from *Phaius mishmensis* which shows promising cytotoxicity against MCF-7, NCI-H460, and SF-268 cell lines.[12] To the best of our knowledge, to date, no asymmetric methods exist for the construction of Phaitanthrin A;[13] besides, the absolute configuration of Phaitanthrin A has not been demonstrated.[12] The biological properties of Phaitanthrin A analogues have been evaluated on their racemic form,[12] hence the availability of a convenient method for the construction of structure-diverse Phaitanthrin A analogues in high optical purity might enable identification of a more selective and potent anticancer lead. Herein, we report the first asymmetric synthesis of (*S*)-Phaitanthrin A and its derivatives via the direct aldol reaction of Tryptanthrin and ketones, in which the cheap, easily prepared natural amino acid salts exhibited unique catalytic ability (Scheme 1).

Scheme 1. Natural Amino Acid Salts Catalyzed Asymmetric Construction of Phaitanthrin A Derivatives



On the basis of previous research on tertiary amine thiourea catalyzed direct aldol reactions,[7] our study commenced with investigating the potential of such chiral bifunctional organocatalysts in promoting the aldol reaction between acetone **1a** and Tryptanthrin **2a**. Unfortunately, the desired product **3a** were obtained with very poor yields and enantioselectivities when either cinchona alkaloid or cyclohexane-1,2-diamine derived double-hydrogen-bonding catalysts were employed in THF (Table 1, entries 1–4). Changing the catalyst to a chiral primary amine–Brønsted acid mixture **4e**, which was identified as the efficient catalytic system in asymmetric aldol reaction involving α-keto esters as acceptors,[10l,m] was also unsuccessful (Table 1, entry 5). A variety of amino acids were next evaluated: under similar reaction conditions, L-proline showed slightly higher enantiocontrol, while L-alanine, L-methionine, and L-phenylalanine exhibited very low catalytic activities (Table 1, entries 6–9). The little but important improvement L-proline afforded inspired us to consider that the amino acid metal salts, which are similar to an amino acid but take advantage of both organocatalysis and Lewis acid catalysis, would be a better choice of catalyst. To test our hypothesis, the L-proline potassium salt was then applied in this reaction. To our delight, a dramatic reaction rate enhancement was observed, leading to the desired product in perfect yield within 12 h albeit with 0% ee (Table 1, entry 10). Inspired by this result, a subsequent full investigation of the influences of either amino acid or cation species was carried out (see Supporting Information). Gratifyingly, the enantioselectivity of **3a** was significantly improved when L-phenylalanine potassium salt **4m** was employed (Table 1, entry 13, 96% yield, 67% ee). Further optimization of reaction conditions indicated that performing the reaction in $CHCl_3$ gave the highest enantioselectivity (Table 1, entry 14), while lowering the reaction temperature to 0 °C was found necessary to improve the enantiocontrol. Finally, as the optimal compromise between reactivity and stereoselectivity, a

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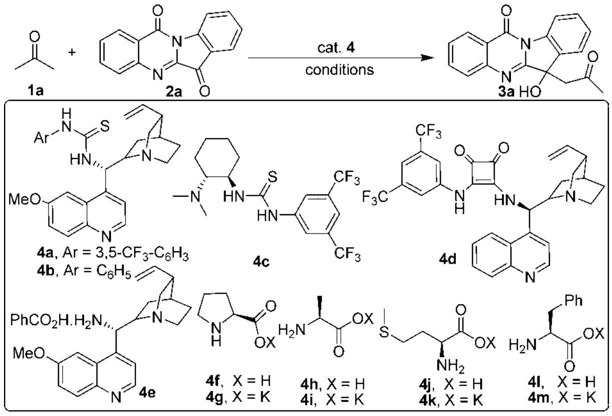
Table 1. Optimization of Reaction Conditions[a]



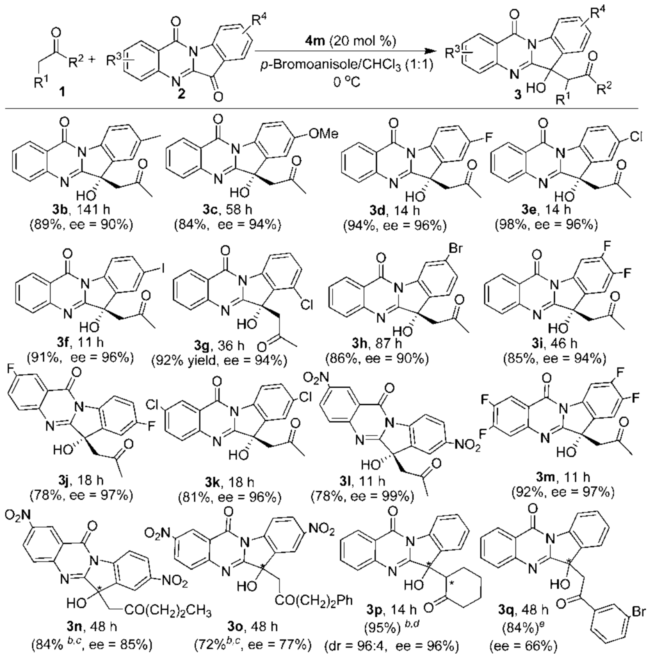
entry	cat.	solvent	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	**4a**	THF	20	24	20	8
2	**4b**	THF	20	24	28	−7
3	**4c**	THF	20	24	22	−5
4	**4d**	THF	20	24	28	−12
5	**4e**	THF	20	24	63	9
6	**4f**	THF	20	24	45	−25
7	**4h**	THF	20	24	nd	nd
8	**4j**	THF	20	24	nd	nd
9	**4l**	THF	20	24	17	5
10	**4g**	THF	20	12	98	0
11	**4i**	THF	20	12	99	−11
12	**4k**	THF	20	12	98	−57
13	**4m**	THF	20	12	96	−67
14	**4m**	$CHCl_3$	20	12	98	−88
15	**4m**	*p*-BMAS	20	12	96	−85
16	**4m**	xylene	20	12	98	−83
17	**4m**	CH_3CN	20	12	trace	-
18[d]	**4m**	*p*-BMAS/$CHCl_3$	20	12	92	−87
19	**4m**	$CHCl_3$	0	12	80	−93
20[d]	**4m**	*p*-BMAS/$CHCl_3$	0	12	98	−92
21[e]	**4m**	*p*-BMAS/$CHCl_3$	0	24	97	−92

[a] Unless otherwise noted, all reactions were carried out with acetone **1a** (0.2 mL), **2a** (0.05 mmol), and catalyst (20 mol %) in 0.6 mL of solvent. [b] Isolated yield. [c] Enantioselectivities were determined by chiral HPLC. [d] 0.3 mL of *p*-bromoanisole (*p*-BMAS) and 0.3 mL of $CHCl_3$ were used as cosolvent. [e] The reaction was carried out with acetone **1a** (0.4 mL), **2a** (0.1 mmol), and catalyst **4m** (20 mol %) in 1.2 mL of solvents (*p*-BMAS/$CHCl_3$ = 0.6 mL/0.6 mL) at 0 °C for 24 h.

mixture of $CHCl_3$ and *p*-bromoanisole (*p*-BMAS) was chosen as the reaction media, affording **3a** with high yield and enantioselectivity (Table 1, entry 19 vs 20).

By adopting the optimal conditions described in Table 1, the generality of the protocol was fully demonstrated by evaluating a variety of Tryptanthrins and ketones. As highlighted in Scheme 2, by employing acetone as the donor, this new method can be applied to a wild range of Tryptanthrins with different substitution patterns. Various electron-donating and -withdrawing substituents at different positions of the aromatic ring are well tolerated, affording the desired aldol products with good yields and enantioselectivities (Scheme 2, **3b**−**3m**, 78% to 98% yield, 90% to 99% ee). For example, a 2,8-dinitro-Tryptanthrin

Scheme 2. Catalytic Asymmetric Synthesis of Phaitanthrin A Derivatives[a]



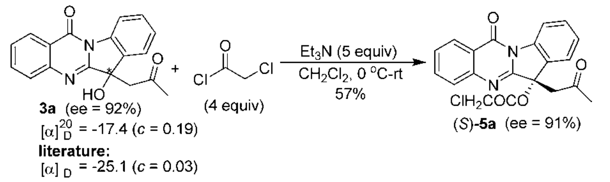
[a] Unless otherwise noted, all reactions were carried out with ketone (0.4 mL), **2** (0.1 mmol), and catalyst **4m** (20 mol %) in 1.2 mL of solvents (*p*-bromoanisole/$CHCl_3$ = 0.6 mL/0.6 mL) at 0 °C; given are isolated yields; enantioselectivities were determined by chiral HPLC. [b] With **4k** (30 mol %) as the catalyst, the reaction was carried out in neat ketone (0.4 mL). [c] At −5 °C. [d] At −20 °C. [e] With **4d** (20 mol %) as the catalyst and 1,4-dioxane (1.2 mL) as the solvent, at 20 °C.

derivative proved to be an excellent participant in such a transformation, leading to **3l** with almost perfect optical purity (99% ee). In addition, other ketone donors were also tested. However, under optimal reaction conditions, more sterically hindered aliphatic ketones such as pentan-2-one, 4-phenylbutan-2-one, and cyclohexanone exhibited low levels of reactivity. Fortunately, performing these reactions in neat ketones with the promotion of catalyst **4k** successfully afforded the desired Phaitanthrin A derivatives with good yields and stereoselectivities (Scheme 2, **3n**−**3p**, up to 96:4 dr, 96% ee). Noticeably, the aromatic ketone was also able to undergo the aldol reaction with Tryptanthrin when **4d** was employed as the catalyst, albeit with relatively lower enantioselectivity (Scheme 2, **3q**, 66% ee).

The absolute configuration of **3a** was assigned by X-ray analysis of compound **5a**, prepared from **3a** by reacting with 4 equiv of 2-chloroacetyl chloride in the presence of Et_3N (Scheme 3). Finally, on the basis of the comparison of the optical rotation of **3a** with literature data for the corresponding natural product,[12] the stereochemistry of the previously unassigned Phaitanthrin A was assigned as an (*S*)-configuration (see Supporting Information).

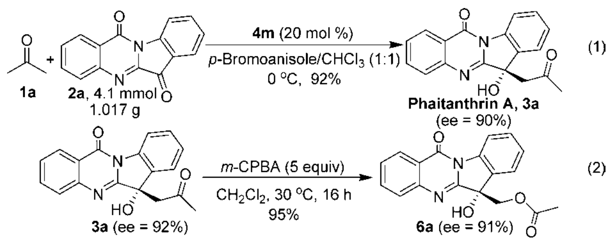
The natural Phaitanthrin A that existed in *Phaius mishmensis* was extremely rare (approximately 8.6×10^{-6} (w/w));[12] thus, a facile and scalable synthesis of this type of compound is of great importance to its further bioactivity evaluation. To demonstrate the synthetic utility of our

Scheme 3. Determination of Absolute Configuration of **3a**



protocol, a gram-scale synthesis of Phaitanthrin A was performed. As shown in Scheme 4 (eq 1), by treatment of **2a** (4.1 mmol) with **1a** under the optimal reaction conditions, the desired product **3a** was obtained in high yield with almost maintained enantioselectivity (92%, ee = 90%).

Scheme 4. Synthetic Utilities of Aldol Reaction



Because of the important anticancer activities the Tryptanthrin-like compounds exhibited, further efforts were made to illustrate the value of this method in the synthesis of biologically relevant compounds. For example, the enantioenriched compound **3a** obtained from the aldol reaction was subjected to a Baeyer−Villiger reaction with *m*-chloroperbenzoic acid as an oxidant, giving **6a** in 95% yield with 91% ee (Scheme 4, eq 2).

Accounting for the high activity and enantiocontrol ability that L-phenylalanine potassium salt exhibited, a possible dual activation mechanism of this new type of aldol transformation is proposed. First, acetone was converted to an enamine in the presence of catalyst **4m** (Figure 2, TS-1), while the Tryptanthrin **2a** was efficiently activated by the potassium ion of the catalyst via chelating with both of the nitrogen and oxygen atoms of the substrate (TS-2 or TS-3); the subsequent nucleophilic attack of enamine to the carbonyl group of tryptanthrin

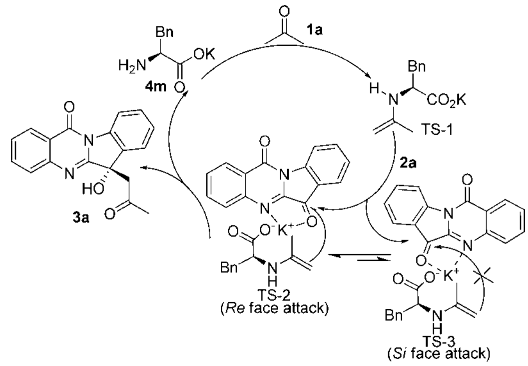


Figure 2. Proposed mechanism of amino acid salt catalyzed asymmetric aldol reaction of Tryptanthrin.

via TS-2 from the *Re* face may be more favorable because of the more suitable position of the electrophilic carbonyl group of **2a** (TS-2 vs TS-3), thus affording the adduct **3a** with the *S* configuration in high optical purity.

In conclusion, a novel amino acid salt catalyzed an asymmetric aldol reaction involving Tryptanthrins as electrophiles was well developed, providing a facile access to (*S*)-Phaitanthrin A and its derivatives in high yields and enantioselectivities; importantly, this methodology tolerates a range of substrates with different substitution patterns. Moreover, the synthetic utility of this strategy was further illustrated by a gram-scale synthesis of Phaitanthrin A. The unique catalytic ability of natural amino acid salts exhibited in this transformation may shed light on the role they played in the formation of related alkaloids existing in nature. Inspired by this success, further studies on the catalytic asymmetric construction of other indoloquinazoline alkaloids are currently underway.

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Supporting Information Available. Experimental procedure, spectral data of compounds **3**, **5**, **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.