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Catalytic Enantioselective Synthesis of Mariline A and Related Isoindolinones via a Biomimetic Approach

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Abstract: The catalytic enantioselective synthesis of isoindolinones was achieved via the condensation of *ortho*-formyl-arylketones and anilines. In the presence of 1 mol% of a chiral phosphoric acid catalyst, reactions reach completion within 10 minutes and provide products with up to 98% ee. Anilines with an *ortho t*-butyl group form atropisomeric products, enabling the simultaneous generation of axial and point chirality from two achiral substrates. This method was applied to the first synthesis of mariline A.

Isoindolinones are important pharmacophores and form the core of a range of natural products such as mariline A,[1] lennoxamine[2] and pestalochloride A[3] (Figure 1).[4] Largely due to their manifold biological activities, there has been a long-standing interest in the asymmetric synthesis of chiral isoindolinones.[4] However, catalytic enantioselective methods remain underdeveloped. Previous approaches have focused on constructing the lactam moiety via 1,2-addition of nucleophiles to *ortho*-formyl-benzoate-derived imines, with subsequent amide bond forming ring closure.[5] Intramolecular additions of benzamides to *ortho*-olefins, including conjugate additions[6] and an asymmetric aza-Wacker-type cyclization[7] have also been disclosed. Other approaches are known, including the catalytic enantioselective reduction or addition to lactam hemiaminals (not shown).[8] A particularly attractive approach to chiral isoindolinones was recently reported by Schmalz and coworkers who showed that the marine antibiotic pestalone[9] undergoes facile conversion to (±)-pestalachloride A upon exposure to ammonia/ammonium chloride in aqueous dioxane (Figure 1).[10] The same group later showed that this type of reaction is general for a range of amines and *ortho*-formyl-arylketones.[11] Here we report the first catalytic enantioselective version of this valuable transformation.

The proposed mechanism for the formation of isoindolinones from *ortho*-formyl-arylketones **1** and amines involves the initial formation of cyclic bis-hemiaminal **2**, followed by loss of water to give hydroxy-isoindoline intermediate **3**.[11a] The key enantiodetermining step is the tautomerization of **3** to ultimately provide **4**. While not generating a new stereogenic center, the same mechanism is generally thought to be operative in the closely related and well known condensation of amines with *ortho*-phthaldialdehydes,[12] although alternative mechanistic pathways have also been proposed.[13] König, Bringmann and coworkers, who isolated (±)-mariline A and similar natural products, proposed that this type of condensation reaction might in fact represent the biosynthetic pathway to these and other isoindolinones.[1] Schmalz et al. later provided further credence to this proposal by preparing a close analogue of (±)-mariline A from appropriate amine and *ortho*-formyl-arylketone precursors.[11b] It is of interest to note that mariline A and analogues as well as pestalachloride A were isolated from their natural sources in their racemic forms. However, enantiomerically pure mariline A was shown to be configurationally stable.[1]

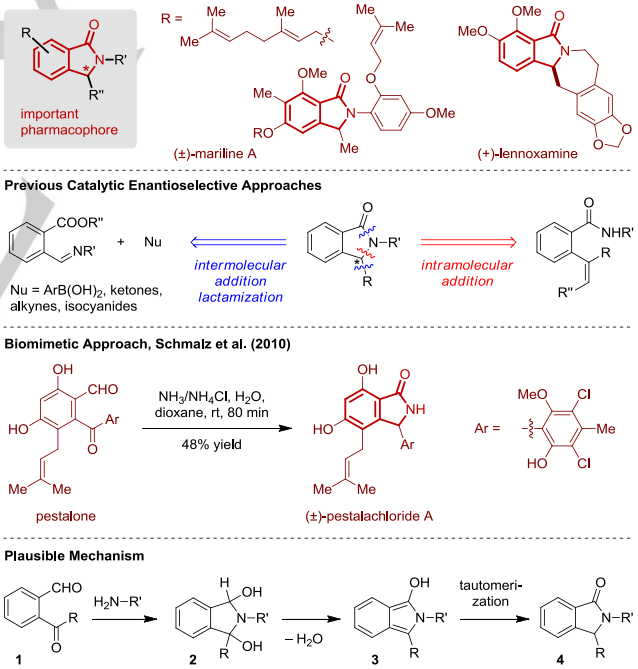

Figure 1. Selected isoindolinone natural products, previous enantioselective approaches, and a potentially biosynthetic pathway to this heterocycle.

We were intrigued by the prospect of developing a catalytic enantioselective variant of this biomimetic condensation reaction.[14] Although the optimized conditions developed by Schmalz et al. involve the use of excess acetic acid in a polar reaction medium, we reasoned that a catalytic amount of a chiral Brønsted acid should suffice to facilitate the key protonation step.[15–17] Considering that the final product is relatively non-basic, product inhibition of the catalytic cycle was not expected to

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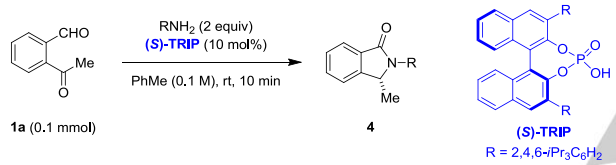
represent a significant problem. To validate this proposal, *ortho*-formyl-arylketone **1a** was tested in combination with various amine-type substrates in the presence of chiral phosphoric acid catalyst (*S*)-TRIP[18] (Table 1). Benzyl carbamate (entry 1) and *tert*-butylamine (entry 2) were unreactive under a range of conditions. Other amines underwent rapid reactions with **1a**. Full conversion of **1a** occurred in less than 10 min in all cases. Prolonged reaction times had no effect on the yields or ee's of the desired isoindolinones **4**. In accord with Schmalz's observations,[11] highly polar polymer-like byproducts are formed in competing side reactions and the outcome of a particular reaction strongly depends on the nature of the amine. Benzyl amine provided product **4c** in moderate yield and low ee (entry 3). Whereas nearly no product **4d** could be detected with parent aniline, again in agreement with findings by the Schmalz group (entry 4),[11] *p*-methoxy aniline provided isoindolinone **4e** in moderate yield albeit racemic form (entry 5). Other electron-rich anilines afforded products in moderate to good yields but with typically low ee's (entries 6–10). A dramatic increase in enantioselectivity was observed with 2-O*t*Bu aniline, allowing for the isolation of product **4k** in 71% yield and 83% ee (entry 11).

Table 1. Initial Evaluation of Amine Component.[a]



entry	R	product	yield (%)	ee (%)
1	Cbz	**4a**	NR	-
2	*t*Bu	**4b**	NR	-
3	Bn	**4c**	44	13
4	Ph	**4d**	trace	-
5	4-MeO-C_6H_4	**4e**	54	0
6	2-MeO-C_6H_4	**4f**	49	10
7	2,4-$OMe_2C_6H_3$	**4g**	66	49
8	2,6-$OMe_2C_6H_3$	**4h**	67	65
9	2,6-$Me_2C_6H_3$	**4i**	88	11
10	3,4,5-$(OMe)_3C_6H_2$	**4j**	70	19
11	2-O*t*BuC_6H_4	**4k**	71	83

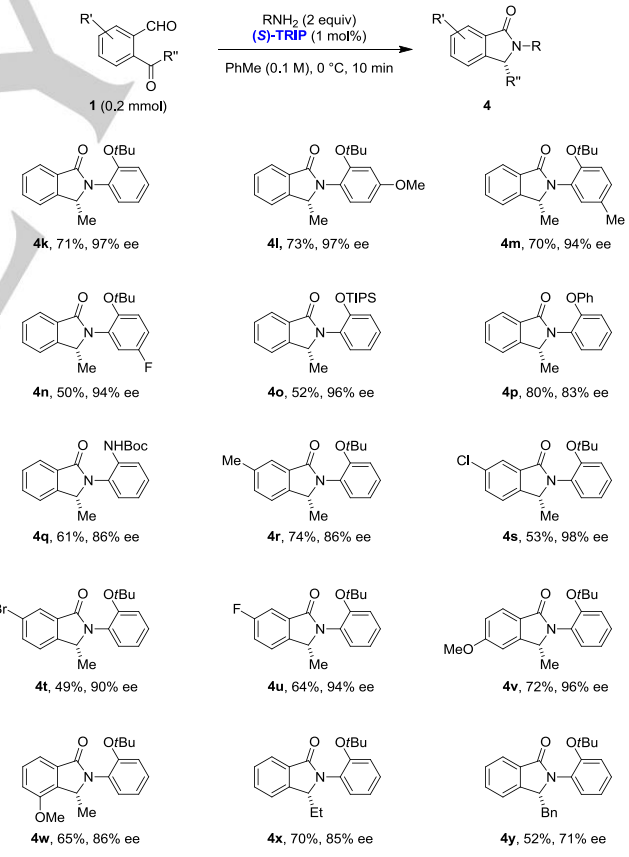
[a] Yields are those of chromatographically purified compounds. The ee values were determined by HPLC analysis; see the Supporting Information for details. NR: no reaction

Utilizing 2-O*t*Bu aniline, other reaction parameters were evaluated next (Table 2). Interestingly, while the reaction generates water as a byproduct, the addition of molecular sieves resulted in a dramatic decrease in the yield and ee of **4k** (entry 2), indicating an important role for water in the overall process.[19,20] A reduction of the reaction temperature to 0 °C brought about a significant increase in ee without apparent effect on the rate of the reaction (entry 3). However, further decreasing the temperature to –20 °C caused a drop in both yield and ee (entry 4). The catalyst loading could be reduced to 1 mol% without adverse effects (entry 5). The reaction was insensitive to moisture; the addition of water had no effect on the results (entry 6). A reduction in catalyst loading to 0.1 mol% still provided product **4k** in excellent ee, albeit in lower yield (entry 7). Variation of the amount of 2-O*t*Bu aniline (entry 8 and 9) or the substrate concentration (10 and 11) provided no obvious further improvements.

Table 2. Optimization of Reaction Parameters.[a]

entry	temp [°C]	**(*S*)-TRIP** (mol%)	concentration [M]	yield (%)	ee (%)
1	rt	10	0.1	71	83
2[b]	rt	10	0.1	54	49
3	0	10	0.1	75	97
4	–20	10	0.1	65	93
5	0	1	0.1	71	97
6[c]	0	1	0.1	72	97
7	0	0.1	0.1	55	92
8[d]	0	1	0.1	74	97
9[e]	0	1	0.1	61	94
10	0	1	0.2	74	96
11	0	1	0.05	68	97

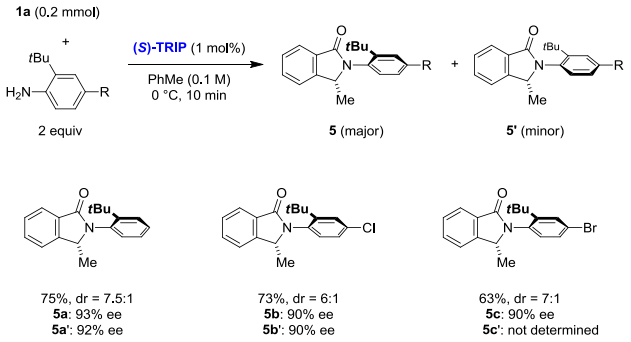
[a] Yields are those of chromatographically purified compounds. The ee values were determined by HPLC analysis; see the Supporting Information for details. [b] In the presence of 4Å MS. [c] 5 equiv of water were added. [d] 4 equiv of 2-O*t*Bu aniline were used. [e] 1.2 equiv of 2-O*t*Bu aniline were used.



Scheme 1. Substrate Scope.

The scope of the isoindolinone formation was explored with a range of *ortho*-formyl-arylketones and primary aromatic amines (Scheme 1). A number of 2-O*t*Bu anilines bearing additional ring-

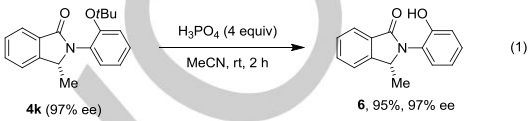
substituents provided products in moderate to good yields and excellent enantioselectivities. 2-OTIPS-aniline underwent the title reaction to form product **40** in excellent ee whereas the use of 2-phenoxyaniline resulted in product **4p** with reduced ee albeit increased yield. *Mono-N*-Boc *ortho*-phenylenediamine also underwent the transformation to form isoindolinone **4q** in good yield and ee. As for the *ortho*-formyl-arylketone component, both electron-donating and electron-withdrawing groups on different ring positions were tolerated, generating isoindolinone products in moderate to good yields and excellent levels of enantioselectivity. Change of the 3-methyl group to ethyl or benzyl was tolerated but led to a slight reduction in enantioselectivity.



Scheme 2. Formation of Atropisomeric Products.

Interestingly, with 2-*t*Bu aniline as the amine component, we observed the formation of diastereomeric products (Scheme 2). Specifically, the two atropisomers **5a** and **5a'** were obtained in a 7.5:1 ratio, both with nearly identical ee (93/92%).[21–23] Similar results were obtained for 2-*t*Bu-4-chloroaniline and 2-*t*Bu-4-bromoaniline. A reaction of **1a** and 2-*t*Bu aniline, performed at room temperature and monitored by ^{1}H-NMR, revealed that **5a'** is the kinetic product which appears to be formed exclusively in the initial stages of the reaction. By the time the reaction reached completion, the ratio of **5a** and **5a'** was found to be 1:9. Over the course of two days this ratio changed to 7:1. Purification of a reaction mixture by column chromatography immediately after consumption of **1a** led to a rapid change of the atropisomeric composition corresponding to the reported values. The major atropisomer **5a** was readily obtainable in pure form via column chromatography. A solution of **5a** that was kept at room temperature for several days showed no sign of **5a'**. Presumably due to lower rotational barriers, atropisomers were not observable for products **4** (Scheme 1).[24] The preferred conformation of products **4** likely corresponds to that of **5**. In fact, this conformation was observed in the X-ray crystal structure of **4s**, which also served to establish its absolute configuration.[25]

As shown in eq 1, removal of the *t*-butyl group in **4k** was readily achieved upon treatment with phosphoric acid, allowing for the isolation of product **6** in excellent yield. Importantly, the ee was unaffected by this transformation.



The title reaction was applied in a relatively straightforward synthesis of mariline A, starting from commercially available benzoic acid derivative **7** (Scheme 3). Key steps include the monobromination of ketone **8** to provide **9** and subsequent regioselective monomethylation to yield intermediate **10**. The key catalytic enantioselective step proceeded in 93% ee.[26]

In summary, we have achieved the catalytic enantioselective synthesis of 3-alkyl isoindolinones via a biomimetic condensation approach, utilizing *ortho*-formyl-arylketones and 2-substituted anilines as starting materials. This method enabled the first enantioselective synthesis of mariline A.

Keywords: asymmetric organocatalysis • Brønsted acid catalysis• mariline A • atropisomerism • isoindolinones

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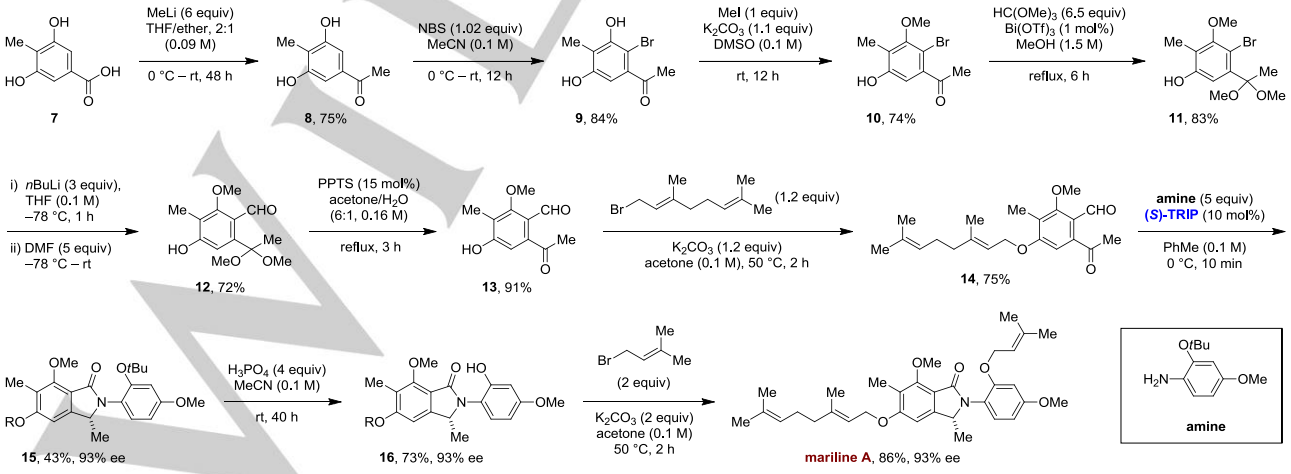

Scheme 3. Enantioselective synthesis of mariline A.

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[24] König and Bringmann et al. recognized the potential role of axial chirality in mariline A. Rotational barriers were calculated to be 11.6 and 14.4 kcal mol^{-1}, respectively, indicating free rotation around the N,C axis. The atropisomer of mariline A corresponding to **5** was calculated to be 2.81 kcal mol^{-1} lower in energy than the atropisomer corresponding to **5a'**. See reference 1.

[25] See the Supporting Information.

[26] Based on analogy to product **4s**, the absolute configuration of mariline A was assigned as (*R*). See the Supporting Information for further discussion.

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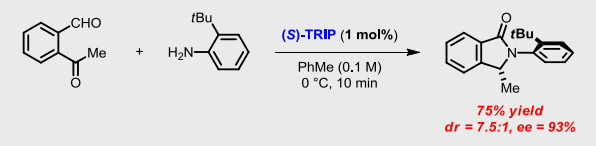

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Catalytic Enantioselective Synthesis of Mariline A and Related Isoindolinones via a Biomimetic Approach

The catalytic enantioselective synthesis of isoindolinones was achieved via the condensation of *ortho*-formyl-arylketones and anilines. In the presence of 1 mol% of a chiral phosphoric acid catalyst, reactions reach completion within 10 minutes and provide products with up to 98% ee. Anilines with an *ortho t*-butyl group form atropisomeric products, enabling the simultaneous generation of axial and point chirality from two achiral substrates. This method was applied to the first synthesis of mariline A.