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Facile Creation of 2-Substituted Indolin-3-ones by Using Primary–Secondary Diamine Catalysts

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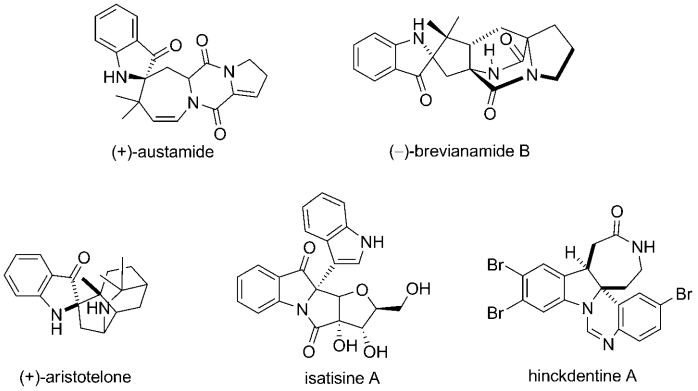
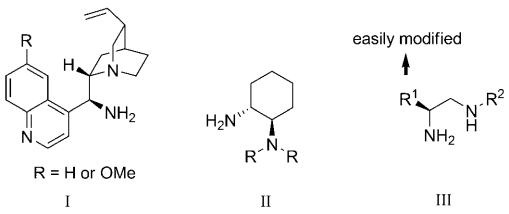
Indolin-3-ones with a chiral center at the 2-position are encountered in a large variety of natural products and can be used in the total synthesis of biologically active alkaloids such as (+)-austamide, (−)-brevianamide B, (+)-aristotelone, isatisine A, and hinckdentine A.[1] Consequently, these structures have been the target of considerable synthetic effort and a variety of preparative methods have already been developed.[2] Among these common methods, the Michael addition[3] has been the most fascinating and powerful reaction.[4] However, the enantioselective versions of this reaction are still surprisingly rare and less exploited.[5] Thus, the development of asymmetric catalytic methods for the construction of chiral indolin-3-ones is particularly appealing.

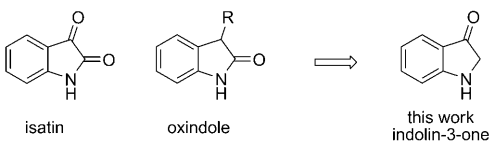


On the other hand, organocatalysis has been one of the most rapidly growing and fruitful research areas in synthetic organic chemistry during the last decade. In modern organocatalysis, the use of chiral secondary amines has proven to be an extremely powerful approach and has dominated the field of amino catalysis.[6] In contrast, less progress has been made in the development of chiral primary amine catalysts. Recently, primary–tertiary diamine catalysts derived from cinchona alkaloids (type I) or 1,2-diamino-cyclohexane (type II) have emerged as readily available, highly versatile, and extremely powerful catalysts in asymmetric synthesis.[7]



Although these catalysts often avoid the need for multiple screening of new catalysts to determine the optimal reaction conditions, they may not always be the best candidates to solve some specific and challenging reactions. Therefore, it is necessary to develop some new chiral amine catalysts. Three facts must be taken into account when preparing these catalysts: 1) the starting material should be commercially available and cheap; 2) the synthesis should be amenable to fine-tuning of the substituents at the nitrogen atoms; and most importantly, 3) the framework can be easily modified. We envisioned that natural α-amino acids would be the starting material of choice.[8] Herein, we describe the use of primary–secondary diamine catalysts derived from natural α-amino acids (type III) in the construction of 2-substituted indolin-3-ones.

Recently, significant progress has been made in the construction of chiral indole motifs by using oxygenated indoles as starting materials (Scheme 1).[9] However, they are more generally focused upon modifications of isatin[10] or oxin-



Scheme 1. Oxygenated indoles. R = H, alkyl, or aryl.

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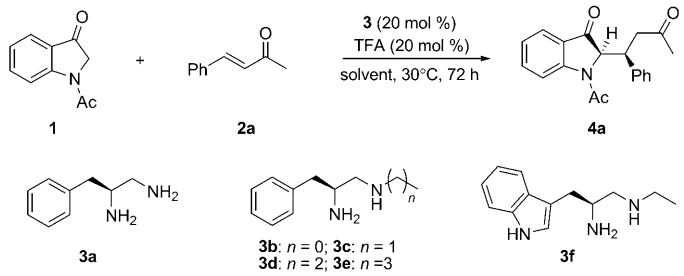
dole[11] at the 3-position; research in transformations of indolin-3-one at the 2-position still remains elusive. Our group have also developed very simple primary–secondary diamine catalysts based on natural amino acids for the asymmetric reactions of α,β-enones. In connection with our interest in developing efficient organocatalytic-constructing chiral indole motifs,[12] we anticipated that this tactic might be applied in the construction of chiral indolin-3-ones catalyzed by a primary–secondary diamine catalyst.

In the exploratory study, we carried out the model reaction of indolin-3-one **1** with enone **2a** to evaluate the catalysts of type III (Table 1). When catalyst **3a** (with two primary amino groups derived from L-phenylalanine) was used,

Table 1. Reaction conditions optimization.[a]



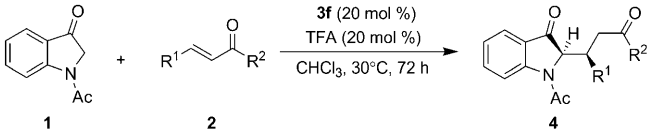
Entry	Catalyst	Solvent	Conversion [%][b]	d.r.[b]	*ee* [%][c]
1	**3a**	$CHCl_3$	71	2:1	21
2	**3b**	$CHCl_3$	81	>20:1	88
3	**3c**	$CHCl_3$	91	>20:1	95
4	**3d**	$CHCl_3$	94	>20:1	90
5	**3e**	$CHCl_3$	90	>20:1	92
6	**3f**	$CHCl_3$	90	>20:1	97
7	**3f**	CH_2Cl_2	91	>20:1	95
8	**3f**	THF	83	>20:1	96
9	**3f**	Et_2O	77	>20:1	91
10	**3f**	CH_3OH	43	>20:1	76

[a] Unless otherwise specified, the reaction was carried out with **1** (0.20 mmol) and **2a** (0.30 mmol) in the presence of an organocatalyst **3** (0.04 mmol), trifluoroacetic acid (TFA) (0.04 mmol), and solvent (1.0 mL) for 72 h. [b] Diastereomeric ratio (d.r.) determined by ^{1}H NMR analysis of the crude mixture. [c] Determined by chiral HPLC on a Chiralpak OD column.

only a low enantioselectivity was achieved (Table 1, entry 1). Fortunately, its monoalkylated analogues **3b**–**3e** provided promising results; the length of the alkyl chain influenced the catalytic activity of **3** and the *N*-ethylated catalyst **3c** gave the best result (Table 1, entries 2–5). Moreover, changing the benzyl group of **3c** to a 3-indolyl group resulted in the optimum catalyst **3f** derived from L-tryptophan (Table 1, entry 6). To further improve the enantioselectivity, several solvents were screened; $CHCl_3$ proved to be the optimal solvent for the reaction (Table 1, entries 6–10). Finally, optimum results were obtained when using catalyst **3f** in combination with CF_3CO_2H in $CHCl_3$ at 30°C for 72 h (Table 1, entry 6).

Encouraged by this promising result, we next investigated the scope and limitations of the reaction under the optimal conditions defined through our model studies. In general, the reaction proceeded smoothly with a wide range of enones. For enones with aromatic substituents, almost optically pure products could be obtained in high yields and excellent diastereo- and enantioselectivities, irrespective of the electronic nature or positions of the substituents on the phenyl ring (Table 2, entries 1–12). Significantly, alterations of the heteroaryl substituents did not impact negatively on

Table 2. Scope of the reaction.[a]



Entry	R^1	R^2	**4**	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	Ph	Me, **2a**	**4a**	85	>20:1	97
2	2-FPh	Me, **2b**	**4b**	87	>20:1	96
3	2-ClPh	Me, **2c**	**4c**	81	>20:1	95
4	2-BrPh	Me, **2d**	**4d**	85	>20:1	96
5	2-MePh	Me, **2e**	**4e**	78	>20:1	95
6	2-MeOPh	Me, **2f**	**4f**	74	>20:1	95
7	3-ClPh	Me, **2g**	**4g**	83	>20:1	96
8	3-BrPh	Me, **2h**	**4h**	80	>20:1	95
9	3-MePh	Me, **2i**	**4i**	75	>20:1	95
10	3-MeOPh	Me, **2j**	**4j**	83	>20:1	96
11	4-ClPh	Me, **2k**	**4k**	72	>20:1	96
12	4-BrPh	Me, **2l**	**4l**	78	>20:1	97
13	2-furyl	Me, **2m**	**4m**	80	4.2:1	92
14	2-thienyl	Me, **2n**	**4n**	80	6.6:1	92
15	Ph	Et, **2o**	**4o**	81	6:1	95
16	$-(CH_2)_3-$, **2p**		**4p**	60	8:1	95
17[e]	n-C_3H_7	Me, **2q**	**4q**	61	2:1	93/90
18[e]	n-C_5H_{11}	Me, **2r**	**4r**	66	1.1:1	94/90

[a] Unless otherwise specified, the reaction was carried out with **1** (0.20 mmol) and **2** (0.30 mmol) in the presence of **3f** (20 mol%) and TFA in $CHCl_3$ (1.0 mL) at 30°C for 72 h. [b] Isolated yield of both diastereoisomers. [c] Determined by ^{1}H NMR analysis of the crude mixture. [d] For analysis of the *ee* values of the products, see the Supporting Information. [e] 30 mol% **3f** and TFA was used.

the enantioselectivity of the reaction (Table 2, entries 13 and 14). No decrease in yield and enantiomeric excess (*ee*) value was observed for the slightly sterically hindered enone **2o**, albeit with slight decrease in diastereoselectivity (Table 2, entry 15).[13] Notably, cyclic enone **2p** also participates well in this reaction; the products could be obtained in moderate yields, with excellent diastereo- and enantioselectivities (Table 2, entry 16). For the less reactive alkyl substituted enones **2q** and **2r**, excellent enantioselectivities could be also obtained, although the corresponding products were obtained with low diastereoselectivities (Table 2, entries 17 and 18).

Finally, the absolute configuration of product **4g** was determined by single-crystal X-ray analysis.[14] This result prompted us to assume a possible mechanism for the asymmetric Michael addition. We envisioned that catalyst **3f** would act in a bifunctional fashion (Figure 1). The primary amine moiety activates the enone **2** via the formation of an

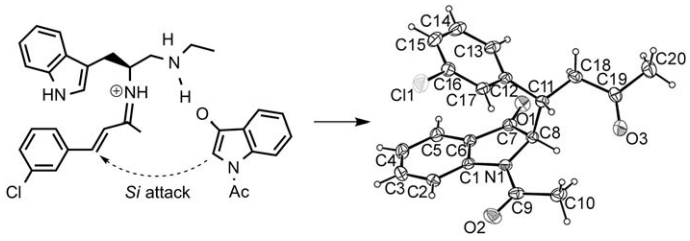


Figure 1. Proposed transition state. Ac = acetyl.

iminum, whereas the secondary amine activates the indolin-3-one **1** by enolization and may also direct its attack to the iminium ion through a hydrogen-bonding interaction. The *Re* face of the enone in this pretransition-state assembly is shielded by the bulky indolyl group, which directs the attack of 1-acetylindolin-3-one **1** towards the *Si* face of the enone **2**. The strong acid additives may play a key role in facilitating the formation of the iminium ion and fostering the regeneration of the catalyst in the hydrolysis of the enamine intermediate after the addition step.

In summary, we have developed a highly enantioselective conjugate addition of 1-acetylindolin-3-one to enones. The reaction is efficiently catalyzed by a readily available primary–secondary amine and gives the corresponding adducts in good yields, moderate to high diastereoselectivities, and excellent enantioselectivities. The high enantioselectivity and broad substrate scope of this transformation make it potentially useful in the synthesis of chiral indolin-3-one derivatives. The synthetic applications of this transformation are currently ongoing in our laboratory.

Experimental Section

General procedure: Indolin-3-one **1** (0.20 mmol) was added to a stirred mixture of enone **2** (0.30 mmol), organocatalyst **3f** (0.04 mmol), and trifluoroacetic acid (TFA, 0.04 mmol) in dry $CHCl_3$ (1.0 mL) at 30 °C. After 72 h, the reaction mixture was directly purified by silica gel chromatography without workup and fractions were collected and concentrated under vacuum to provide the pure desired product **4**.

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Keywords: enantioselectivity · enones · indolin-3-one · michael addition · organocatalysis

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[13] No reactions occurred when more bulky Michael acceptors (such as chalcones) were used as the electrophilic reactant.

[14] CCDC-802614 (**4g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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