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Organocatalytic Enantioselective Amination of 2-Substituted Indolin-3-ones: A Strategy for the Synthesis of Chiral α-Hydrazino Esters

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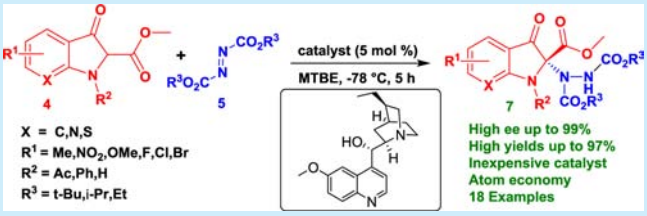
Supporting Information

ABSTRACT: An efficient enantioselective α-amination of 2-substituted 3-indolinones has been achieved for the first time using hydroquinidine as a chiral catalyst through an aza-Michael reaction. The desired α-hydrazino esters are obtained in excellent yields with high enantiomeric excess leading to a quaternary stereocenter with a broad substrate scope.



Indoline alkaloids are widely distributed in nature and known to exhibit a wide spectrum of biological activities.[1] In particular, 2,2-disubstituted indolin-3-one is frequently found in various natural products such as secoleuconoxine, scholarisine, cephalinone B, mitomycins, and so forth.[2] The mitomycins are a class of natural products that exhibit potent antitumor activities.[3] Furthermore, the indolin-3-one core is present in indole alkaloids such as mersilongine, melodinine, leuconoxine, minfiensine, and so forth.[2] Therefore, indolin-3-ones have received special attention due to their inherent biological activities and their occurrence in biologically active natural products (Figure 1).

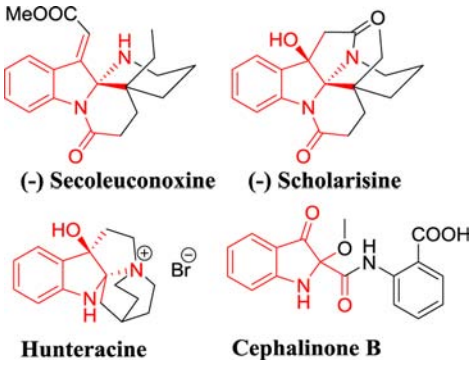


Figure 1. Indoline natural products.

However, the creation of a quaternary chiral center at the C2 position of 3-indolinone-2-carboxylates, especially with a nitrogen source, is a challenging task for synthetic organic chemists. Inspired by the structural complexity and biological importance of indoline alkaloids, we initiated the enantioselective α-hydrazination of 2-substiuted 3-indolinones. However, a few methods have been reported for the organocatalytic asymmetric synthesis of 2,2-disubstituted indoline-3-one derivatives from 3-indolinone-2-carboxylates and α,β-unsaturated systems.[4] During the past decade, elegant methods have been reported for direct asymmetric α-amination[5] of active carbonyl compounds with azodicarboxylates and nitrosobenzene using different chiral organocatalysts.[5l−o] In most cases, 1,3-dicarbonyls,[5f,g] α-branched cyclic ketones,[5a] cyclic aromatic ketones,[5b] and oxindoles[5d,e] have been used as Michael donors in enantioselective amination reactions (Figure 2). However, there have been no reports on the direct asymmetric hydrazination of 3-indolinone-2-carboxylates derivatives using azodicarboxylates.

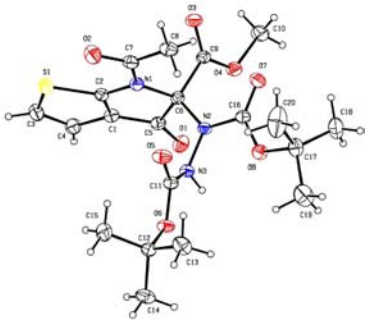


Figure 2. ORTEP diagram of **7k**.

We herein report a novel strategy for the enantioselective α-hydrazination of 2-substituted 3-oxoindoline, 7-azaindolin-3-one, 1*H*-benzo[*f*]indol-3(2*H*)-one, and 5,6-dihydro-4*H*-thieno-[2,3-*b*]pyrrol-4-one using azodicarboxylate as a nitrogen source and hydroquinidine[6] as a chiral catalyst (Table 1). At first, we screened the aza-Michael addition of 1-acetyl-3-oxoindoline-2-carboxylate[8a] (**4a**) with di-*tert*-butyl azodicarboxylate (**5a**) using

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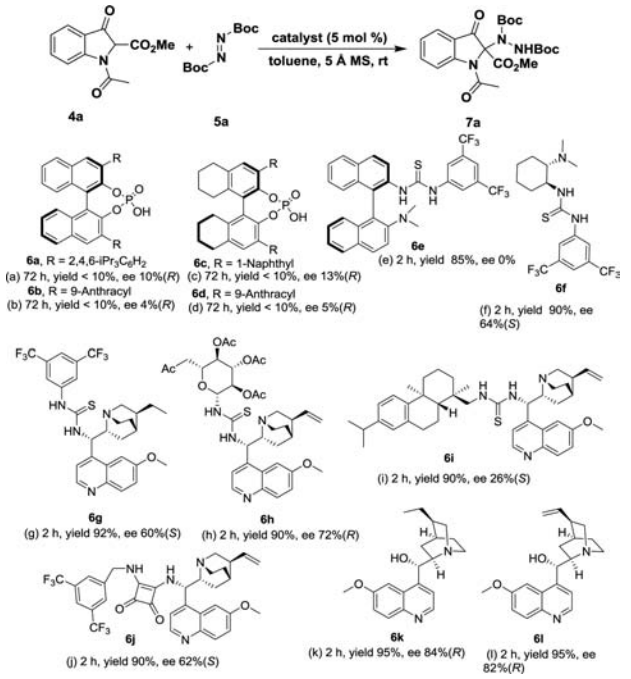
Table 1. Catalyst Screening in the Enantioselective Amination of α-Substituted 3-Oxoindolines[a]



entry	catalyst	solvent	t (°C)	time (h)	yield[b] (%)	ee[c] (%)
m	**6k**	anisole	rt	5h	90	82(R)
n	**6k**	xylene	rt	5h	90	82(R)
o	**6k**	DCE	rt	5h	90	72(R)
p	**6k**	toluene	0 °C	5h	96	88(R)
q	**6k**	MTBE	0 °C	5h	96	90(R)
r	**6k**	MTBE	−20 °C	5h	97	96(R)
s	**6k**	MTBE	−20 °C	5h	97	97[d](R)
t	**6k**	MTBE	−20 °C	5h	97	97[e](R)
u	**6k**	**MTBE**	**−78 °C**	**5h**	**97**	**99**(R)

[a]All reactions were performed with 0.21 mmol of **4a**, 0.27 mmol of BocN=NBoc, and 5 Å MS (50 mg) in 4 mL of solvent. [b]Isolated yields after column chromatography. [c]Enantiomeric excess determined by chiral HPLC analysis. [d]Performed without MS. [e]Slow addition of BocN=NBoc for 1 h.

chiral phosphoric acid catatysts[7] (Table 1, **6a**−**d**).[7] The reaction was conducted at 25 °C for 72 h in toluene. Unfortunately, the desired product (**7a**) was formed only in minor amounts with poor enantioselectivity (Table 1, entries a−d). Therefore, we attempted the above reaction using bifunctional thiourea catalysts. The desired product was formed in 85% yield in 2 h at 25 °C using the catalyst **6e** (entry e)[9] without asymmetric induction. However, with the use of Takemoto's chiral tertiary amine-thiourea catalyst (**6f**),[10] the desired product was obtained in excellent yield (**90%**) with moderate enantioselectivity (64%, entry f). We made several efforts to enhance the enantioselectivity.

Further reaction was carried out using thiourea-hydroquinine catalyst (**6g**).[11] Though the corresponding product was obtained in excellent yield (92%), there is no further improvement in enantiomeric excess (60%, entry g). A little improvement in asymmetric induction (72%, entry h) was noted when the reaction was performed using the catalyst (**6h**).[12] Surprisingly, the ee was diminished to 26% (entry i using the catalyst **6i**).[13] Though the reaction proceeded well with squaramide-quinidine catalyst (**6j**),[14] the corresponding product **7a** was obtained with moderate (62%) ee. Through the use of the hydroquinidine catalyst (**6k**), the enantioselectivity was improved to 84% without decreasing yield (95%, entry k). However, a slight decrease in ee (82%, entry l) was noted with the quinidine catalyst (**6l**). Simultaneously, we examined the reaction in different solvents such as anisole, xylene, and DCE (entries m−o, respectively). The results revealed that the use of MTBE at 0 °C gave product **7a** in 96% yield with good enantioselectivity (90% ee, entry q). Next, we studied the effect of temperature on the reaction rate. The reaction was quite successful at −20 °C in MTBE, affording product **7a** in 97% yield with 96% ee (entry r). A slight enhancement in enantioselectivity was observed by conducting the reaction without molecular sieves at −20 °C (97% ee, entry s). The slow addition of azodicarboxylate (**5a**) over 1 h at −20 °C also did not improve the asymmetric induction (entry t). After screening several catalysts under various reaction conditions, we found that the reaction proceeded well at −78 °C in MTBE in excellent yield (97%) and enantiomeric excess (99% ee) (Table 1, entry u; 97%). The substrate scope was examined under optimized conditions. Initially, we evaluated the viability of substrates bearing various substituents on the aromatic ring of 3-oxoindolines such as electron-donating, electron-withdrawing, and neutral groups. The presence of a halide on the aromatic ring at different positions (e.g., 6-F, 6-Cl, 5-Br) is compatible under the present reaction conditions (Scheme 1, **7b**, **7d**, **7e**; 98−99% ee). The substrate bearing an electron-withdrawing nitro group on the aromatic ring (5-NO_2) afforded product **7h** in relatively lower yield (84%) with 97% ee. The substrates having electron-donating groups such as 4-methyl-, 7-methyl-, and 5,6-dimethoxy- on the aromatic ring (**4j**, **4n**, **4p**, respectively) were less reactive at low temperature (−78 °C), and the corresponding products were obtained with slightly lower enantiomeric excess compared to that of the electron-deficient substrate (**4h**). In the case of the 7-methyl derivative (**4j**), the reaction was complete after 18 h at room temperature, and the corresponding product **7j** was isolated in 84% yield with 94% ee. In the case of substrates bearing 4-methyl- and 5,6-dimethoxy- groups (**4n**, **4p**), the respective products (**7n** and **7p**) were isolated in moderate yields and enantiomeric excess (Scheme 1, **7n**, 90% ee; **7p**, 85% ee).

Furthermore, the substituents on the azodicarboxylate had a considerable impact on asymmetric induction. For example, ethyl and isopropyl azodicarboxylates gave the desired products in relatively lower enantiomeric excess (91 and 87% ee, respectively) compared to that of di-*tert*-butyl azodicarboxylate (Scheme 1, **7g**, **7m**). Next, we studied the effect of substituents on the nitrogen atom of 3-oxoindolines, The substrate without any protection on nitrogen was found to be less effective at −78 °C over 24 h. A drastic change in ee was observed (Scheme 1, **7q**; 70% ee). This method works well even with the substrate-bearing phenyl group on nitrogen (Scheme 1, **7c**; 99% ee, 94% yield).[8b] This method is compatible with chloroacetyl-protected 3-oxoindoline (**4f**), affording product **7f** with 98% ee.

The substrate scope was further extended to heteroaromatic and polyaromatic fused systems. Under optimized conditions, the substrate (**4l**), i.e., methyl 3-oxo-2,3-dihydro-1*H*-benzo[*f*]-indole-2-carboxylate, gave desired product **7l** in 92% yield with 91% ee. However, methyl 1-acetyl-3-oxo-2,3-dihydro-1*H*-pyrrolo[2,3-*b*]pyridine-2-carboxylate afforded product **7o** in relatively low yield with slightly lower selectivity (85 and 86% ee, respectively). The reaction was complete after 12 h at room temperature. Furthermore, the reaction between methyl 6-

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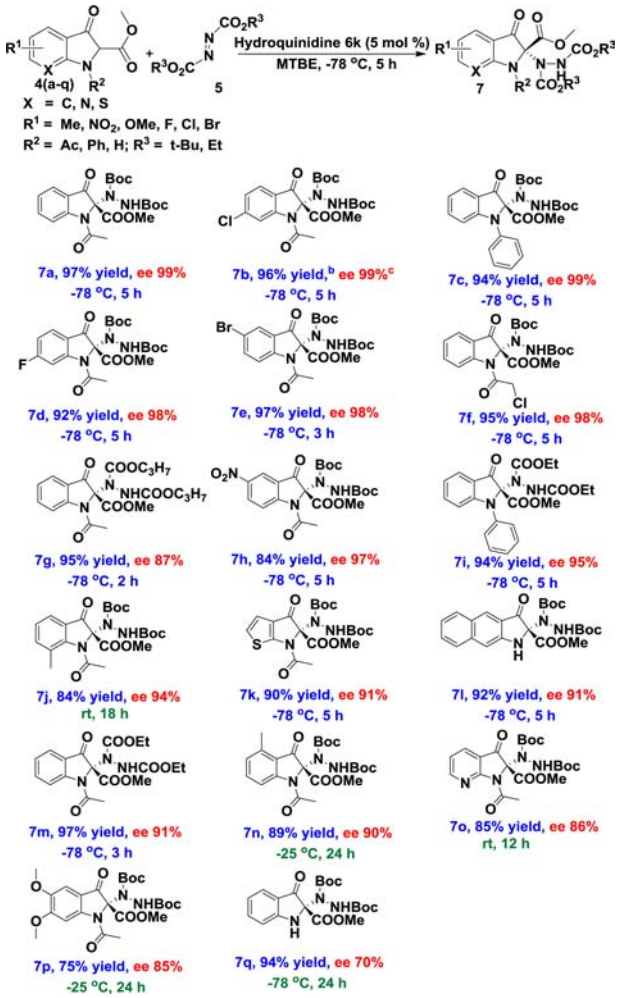
Scheme 1. Substrate Scope[a]



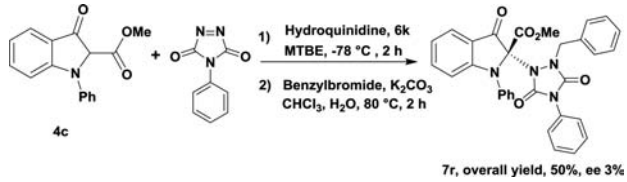
[a]All reactions were performed with 1.0 equiv of compound **4**, 1.2 equiv of compound **5**, and catalyst (5 mol %) in MTBE (0.05 M). [b]Isolated yields after column chromatography, [c]Enantiomeric excess determined by chiral HPLC analysis.

acetyl-4-oxo-4,5,6,6a-tetrahydro-3a*H*-thieno[2,3-*b*]pyrrole-5-carboxylate and *tert*-butyl azodicarboxylate at −78 °C gave product **7k** in 90% yield with 91% ee after crystallization in methanol. The crystal form of **7k** showed high enantiomeric excess (91% ee). The structure and absolute configuration of products **7** were determined by single-crystal X-ray crystallography (Figure 2).[15]

To further expand the scope of Michael acceptor, we examined the reactivity of 4-phenyl-3-*H*-1,2,4-triazole-3,5(4*H*)-dione as a nitrogen source. The reaction proceeded in low yield (**50%**) without stereoselectivity (Scheme 2, **7r**; 3% ee) under optimized reaction conditions.

In summary, we have developed a novel strategy for α-hydrazination of 3-oxoindolines using azodicarboxylate and simple hydroquinidine as a catalyst. This method provides the α-aminated products in good to excellent yields and enantiomeric purity (up to 99% ee). In contrast to previous approaches, this strategy is applicable to a wide range of substrates. The end products are integral parts of different natural products and biologically active molecules. Further developments are in progress to expand the scope of this method.

Scheme 2. Scope to 4-Phenyl-3*H*-1,2,4-triazole-3,5(4*H*)-dione[a]



[a]The reaction was performed with **4c** (0.10 g, 0.37 mmol), triazole (0.78 g, 0.45 mmol), and hydroquinidine (5 mol %) in 8 mL of MTBE.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03473.

Crystallographic file of **7c** (CIF)
Crystallographic file of **7k** (CIF)
Copies of ^{1}H,^{13}C NMR spectra, and HPLC data of products along with ORTEP diagrams of **7c** and **7k** (PDF)
PLATON report (PDF)

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Notes

The authors declare no competing financial interest.

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(15) CCDC 1478278 contains supplementary crystallographic data for structure **7k**, and CCDC 1478277 contains supplementary crystallographic data for the structure **7c**. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk.

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