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Organocatalytic Enantioselective Strecker Reaction with Seven-Membered Cyclic Imines

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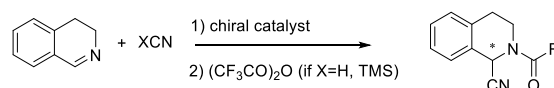
Abstract. A highly enantioselective Strecker reaction with dibenzo[*b,f*][1,4]oxazepines has been described using a dihydroquinine-derived thiourea as organocatalyst. The reaction affords chiral 10,11-dihydrodibenzo[*b,f*][1,4]oxazepine 11-carbonitrile derivatives in excellent yields (up to 99%) and excellent enantioselectivities (up to 98%) under mild reaction conditions.

Keywords: asymmetric catalysis; organocatalysis; Strecker reaction; dibenzo[*b,f*][1,4]oxazepines; α -amino nitriles;

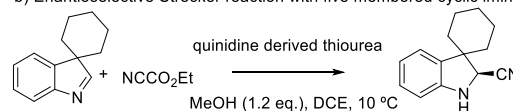
The asymmetric Strecker reaction is one of the most useful and important reactions for carbon-carbon bond formation,^[1] providing enantioenriched α -amino nitriles.^[2] This kind of compounds are very useful building blocks in organic synthesis, because they are precursors for value-added products such as α -amino acids and derivatives,^[3] 1,2-diamines,^[4] or nitrogen heterocycles.^[5] Despite the great achievements and the impressive progress in the enantioselective Strecker reactions, the main examples are focused on acyclic imines,^[6] while the catalytic asymmetric Strecker reactions with cyclic imines are barely studied. The major efforts have been focus in the use of six membered cyclic imines.^[7,8] Several groups have used 3,4-dihydroisoquinoline as electrophile with different cyanide sources (Scheme 1a).^[7] Ma and coworkers, in 2012, described the organocatalytic Strecker reaction of trifluoromethyl-substituted cyclic ketimines with TMSCN.^[8] While Tian reported the reaction with five membered and six membered cyclic imines using ethyl cyanofornate (Scheme 1b).^[9] However, to the best of our knowledge, the catalytic asymmetric Strecker reaction of seven membered cyclic imines has not been reported to date. On the other hand, dibenzo[*b,f*][1,4]oxazepines are a class of nitrogen heterocycle that recently have received great attention from the pharmaceutical

industry due to the widespread biological activities presented in dibenzo[*b,f*][1,4]oxazepine derivatives.^[10] In this context, 11-substituted 10,11-dihydrodibenzo[*b,f*][1,4]oxazepine derivatives play an important role in medicinal chemistry, and several examples of catalytic asymmetric methodologies using dibenzo[*b,f*][1,4]oxazepine derivatives as electrophiles have been described in the literature.^[11,12] However, the enantioselective Strecker reaction with these seven membered cyclic imines have not been described. Herein we present an organocatalytic enantioselective Strecker reaction of seven membered cyclic imines catalyzed by a *Cinchona* alkaloid-based thiourea.^[13]

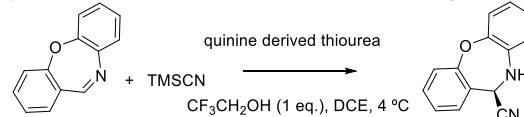
a) Enantioselective Strecker reaction with six membered cyclic imines (ref. 7)



b) Enantioselective Strecker reaction with five membered cyclic imines (ref. 9)



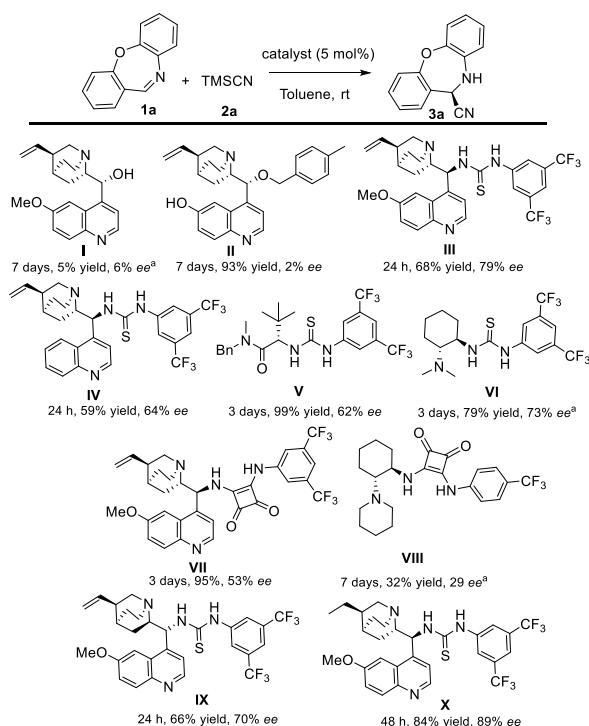
c) Enantioselective Strecker reaction with seven membered cyclic imines (This work)



Scheme 1. Enantioselective Strecker reaction with cyclic imines.

Based on our experience in bifunctional catalysis,^[14] we began our investigations by studying the reaction of dibenzo[*b,f*][1,4]oxazepine **1a** with TMSCN **2a** with various bifunctional organocatalysts in toluene at room temperature (Scheme 2). Quinine (**I**) could not catalyze efficiently the reaction and the product **3a** was obtained with only 5% yield, after 7 days, with 6% *ee*. Cupreine derivative **II** showed higher catalytic activity, leading to product **3a** with a 93%

yield after 7 days, but the product was obtained as a racemic mixture. Next, we tried the reaction using thiourea-based organocatalyst. So, in the presence of quinine-derived thiourea **III**, used by Zhou on asymmetric Strecker reactions with acyclic imines,^[15] the reaction proceed with higher enantioselectivity, obtaining the product **3a** with a promising 79% *ee*. However, cinchonidine-derived thiourea **IV**, was less efficient and a decreasing on the enantiomeric excess was observed. Commercial thioureas, such as the catalysts of Jacobsen^[16] (**V**) and Takemoto^[17] (**VI**) showed good catalytic activity, but in both cases the reaction proceeded with lower enantioselectivity (62% and 73 % *ee*, respectively). We also tried squaramide-based organocatalysts, such as squaramides **VII** and **VIII**, which showed lower catalytic activity and enantioselectivity. Consequently, we returned to the use of thiourea-based organocatalyst. Quinidine-derived thiourea **IX** gave similar yield (66%) than quinine-based thiourea **III**, but lower *ee* (70%). Therefore, the best skeleton of *Cinchona* alkaloids to obtain the higher enantioselectivity is the one present in quinine. Finally, the thiourea **X**, prepared from dihydroquinine, displayed the highest enantiomeric excess and product **3a** was obtained with 84% yield and 89% *ee* after 2 days.



Therefore, we chose catalyst **X** to continue the optimization of the reaction conditions, including the

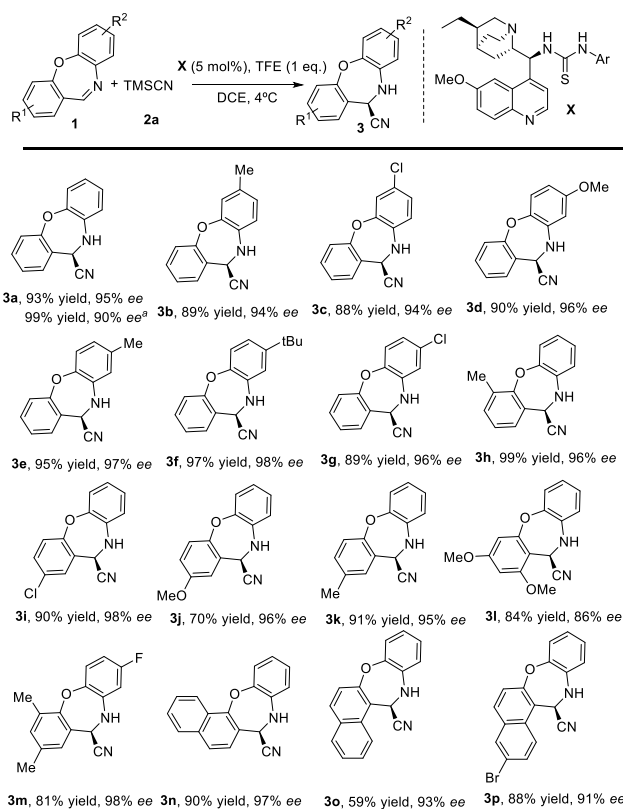
change of cyanide source, solvent, temperatures and additives (Table 1). First, we tried Strecker reaction with other cyanide sources (entries 1-3, Table 1). Ethyl cyanofornate **2b**, was less efficient in this reaction obtaining the α -amino nitrile **3a** with lower yield and enantiomeric excess (entry 2) than TMSCN (entry 1), while with KCN the product **3a** was not formed. Other solvents were also screened (entries 4-12), being toluene (entry 1), dichloromethane (entry 8) and dichloroethane (entry 10) the best solvents. We chose DCE to continue the optimization process, because the enantioselectivity of the reaction was slightly higher. By lowering the reaction temperature to 4 °C (entry 13), the enantioselectivity increased to an excellent 95% *ee*, however the reactivity was much lower and we need 6 days to achieve full conversion. The Strecker product **3a** could be also achieved with good enantiomeric excess when 2 mol% of catalyst **X** was used (entry 14). Finally, we evaluated the addition of alcohols as additives. The addition of 1 equivalent of trifluoroethanol^[18] (entry 15) increase the reactivity, and full conversion was achieved in only 30 hours, while the enantioselectivity was still excellent (95% *ee*). Ethanol was also evaluated as additive (entry 16), with similar results than trifluoroethanol.

Table 1. Optimization of the reaction conditions.^a

Entry	Solvent	T (°C)	t (h)	Y. (%) ^b	<i>ee</i> (%) ^c
1	toluene	rt	48	84	89
2 ^d	toluene	rt	48	77	61
3 ^e	toluene	rt	72	-	-
4	<i>p</i> -xylene	rt	48	98	85
5	Et ₂ O	rt	72	96	85
6	MTBE	rt	96	64	55
7	THF	rt	72	30	9
8	CH ₂ Cl ₂	rt	72	89	90
9	CHCl ₃	rt	24	99	76
10	DCE	rt	48	85	91
11	AcOEt	rt	168	24	62
12	MeOH	rt	72	98	0
13	DCE	4	144	87	95
14 ^f	DCE	4	144	82	93
15 ^g	DCE	4	30	93	95
16 ^h	DCE	4	30	92	94

^{a)} Reaction conditions: 0.1 mmol **1a**, 0.225 mmol **2a**, and **X** (5 mol%) in solvent (1 mL) at rt. ^{b)} Isolated yield after column chromatography. ^{c)} Enantiomeric excess determined by chiral HPLC. ^{d)} NCCO₂Et (**2b**) was used instead of **2a**. ^{e)} KCN (**2c**) was used instead of **2a**. ^{f)} 2 mol% of **X** was used. ^{g)} CF₃CH₂OH (0.1 mmol) was used as additive. ^{h)} CH₃CH₂OH (0.1 mmol) was used as additive.

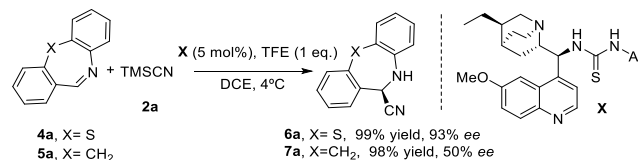
With the optimized reaction conditions in hand (entry 16, Table 1), we proceeded to study the scope of the Strecker reaction of dibenzo[*b,f*][1,4]oxazepines **1** with TMSCN **2a** (Scheme 3). A wide range of substituted cyclic imines **1**, with both electron-donating (MeO, Me, *t*Bu) and electron-withdrawing (Cl, F, Br) substituents at different positions of the two aromatic rings, afforded the corresponding chiral β -amino nitriles **3a–3p** with high yields (up to 99%) and enantioselectivities (up to 98% *ee*). For the cyclic imine **1l**, bearing two methoxy groups in the aromatic ring, a lower enantioselectivity was observed (86% *ee*) probably due to the presence of the methoxy group next to the C=N electrophilic double bond. While with dibenzoxazepine **1m** bearing 3 substituents an excellent 98% *ee* was obtained. Cyclic seven membered imines bearing a naphthyl ring (**1n–1p**), were also suitable for the Strecker reaction, affording the corresponding α -amino nitriles with good yields and high enantiomeric excesses.



Scheme 3. Scope of the Strecker reaction of dibenzoxazepines with TMSCN. Reaction conditions: **1** (0.1 mmol), **2a** (0.225 mmol), TFE (0.1 mmol) and catalyst **X** (5 mol%) in DCE (1 mL) at 4°C for 48-96 h.^{a)} 1 mmol reaction scale.

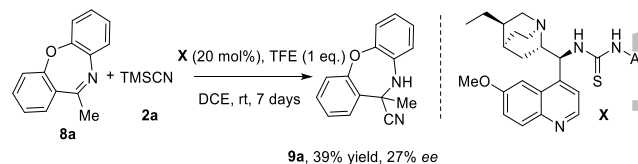
We further studied the Strecker reaction of dibenzo[*b,f*][1,4]thiazepine **4a** with TMSCN (Scheme 4). When the cyclic imine **4a** was used as a substrate, the corresponding α -amino nitrile **6a** was obtained with excellent yield (99%) and high enantiomeric excess (93% *ee*). Moreover, we have tested the reaction with 11*H*-dibenzo[*b,e*]azepine **5a**

(morphanthridine, **5a**), obtaining the corresponding product **7a**, with excellent yield (98%), however with moderate enantioselectivity (50% *ee*). This result shows the importance of the presence of a heteroatom in the seven-membered cyclic imine to obtain high enantioselectivity in the organocatalytic Strecker reaction.



Scheme 4. Asymmetric Strecker reaction with dibenzo[*b,f*][1,4]thiazepine **4a** and 11*H*-dibenzo[*b,e*]azepine **5a**.

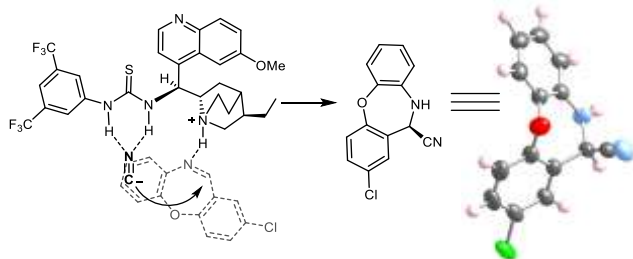
After having proved the efficiency of our methodology for the enantioselective Strecker reaction with seven membered cyclic aldimines, we turned our attention to cyclic ketimines. Unfortunately, when 11-methyl-dibenzo[*b,f*][1,4]oxazepine **8a** was tested under the optimized reaction conditions the α -amino nitrile **9a** was obtained with low yield (39%) and low enantioselectivity (27% *ee*) after 7 days at rt, probably due to steric problems.



Scheme 5. Asymmetric Strecker reaction with seven membered cyclic ketimine **8a**.

The absolute configuration of the stereogenic centre in compound **3i** was determined to be (*R*) on the basis of X-ray crystallographic analysis (Scheme 6); the configuration of the rest of the products **3** were assigned on the assumption of a uniform mechanistic pathway.^[19] A plausible transition-state model is depicted in Scheme 6. The thiourea catalyst is the responsible for the preorientation and the activation of the substrates acting as bifunctional organocatalyst. It is reasonable that TMSCN in the presence of an alcohol (ROH), generates HCN and TMSOR, during the enantioselective Strecker reaction. Therefore, an ammonium salt derived from the dihydroquinine-derived thiourea and HCN can be formed. The cyanide anion can be activated by the thiourea moiety of the catalyst, while the dibenzo[*b,f*][1,4]oxazepine is activated upon formation of a hydrogen bond with the ammonium salt.^[19] The cyanide will be directed to

the *Si*-face of the imine, thus accounting for the observed enantioselectivity.



Scheme 6. Plausible transition-state model and X-ray crystal structure of **3i**.

In summary, we have developed an organocatalytic enantioselective Strecker reaction of TMSCN with dibenzo[*b,f*][1,4]oxazepines, using a dihydroquinine-derived thiourea organocatalyst, obtaining the corresponding chiral α -amino nitriles with excellent yields (up to 99%) and enantioselectivities (up to 98% *ee*). We think that this procedure provides a successful approach for the synthesis of chiral 10,11-dihydrodibenzo[*b,f*][1,4]oxazepine 11-carbonitrile derivatives and expand the repertoire of asymmetric Strecker reactions in organic synthesis.

Experimental Section

General procedure for the enantioselective Strecker reaction

To a solution of the cyclic imine **1a** (19.5 mg, 0.1 mmol) and chiral organocatalyst **X** (2.98 mg, 0.005 mmol) in dichloroethane (1 mL), **2a** (28 μ L, 0.225 mmol) and 2,2,2-trifluoroethanol (7 μ L, 0.1 mmol) were added. The mixture was cooled to 4°C and stirred at this temperature until TLC analysis indicated full conversion of the starting material. Finally, the reaction mixture was directly poured into a column chromatography, using hexane:Et₂O mixtures (8:2 to 7:3) as eluent to afford the product **3aa** (20.6 mg, 0.093 mmol).

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Organocatalytic Enantioselective Strecker Reaction
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