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Organocatalytic enantioselective Strecker reaction of cyclic trifluoromethyl-ketoimines

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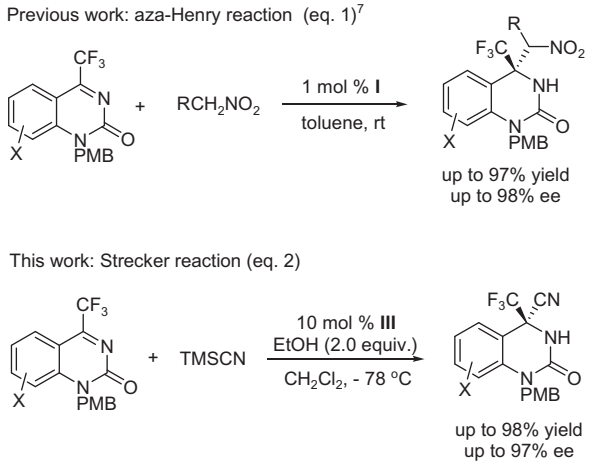
ABSTRACT

A quinine thiourea promoted enantioselective Strecker reaction of cyclic ketoimines with TMSCN has been developed. The process affords new enantioenriched trifluoromethyl dihydroquinazolinones in high yields and with high enantioselectivities.

The Strecker reaction is a powerful tool for C–C bond formation.[1,2] Furthermore, the versatile nitrile groups can be conveniently transformed into a variety of new functionalities, which are highly valuable for the diversity oriented synthesis. Inspired by Harada's pioneering work,[3] asymmetric Strecker reactions have been realized in a catalytic fashion.[1,2] Recently, impressive organocatalytic enantioselective processes have been made.[1,4] However, the substrates of the electrophiles have been largely restricted to aldimines.[1,4] Limited success on enantioselective Strecker reactions with ketoimines[5] has been observed because of their lower reactivity and difficulty in control of enantiofacial selectivity. Furthermore, even for ketoimines, intensive studies have been focused on the methyl ketoimines.[4i,5a–g] Only two cases using trifluoromethyl ketoimines are reported by Enders and Zhou recently.[5h,i] However, to our knowledge, cyclic trifluoromethyl ketoimines have not been explored for organocatalytic asymmetric Strecker reactions so far.[6]

Recently we have developed a chiral quinine derived thiourea **I** catalyzed highly enantioselective aza-Henry reaction of trifluoromethyl 2(*1H*)-quinazolinones with nitroalkanes (Scheme 1, Eq. 1).[7] In addition, the reaction has been successfully applied as a key step in the efficient synthesis of anti-HIV drug DPC 083. In our continuing effort on the exploration of the medicinally valuable molecular architectures for the synthesis of structurally diverse, biologically interesting chiral trifluoromethyl dihydroquinazolinones,[8] we conceived that the use of TMSCN as nucleophiles could produce new functionalized compounds, which may be useful for biological studies. Herein we wish to report the study outcomes. Notably, highly enantioselective addition of TMSCN to cyclic trifluoromethyl quinazolinone ketoimines has been achieved under mild reaction conditions in high yields and with high enantioselectivities.

A model reaction between trifluoromethylquinazolin-2(1*H*)-one (**1a**) (1.0 equiv) and TMSCN (2.0 equiv) in the presence of **I**,[9,10] a catalyst used in our aza-Henry reaction, in CH_2Cl_2 at rt



Scheme 1. Organocatalytic enantioselective aza-Henry and Strecker reactions.

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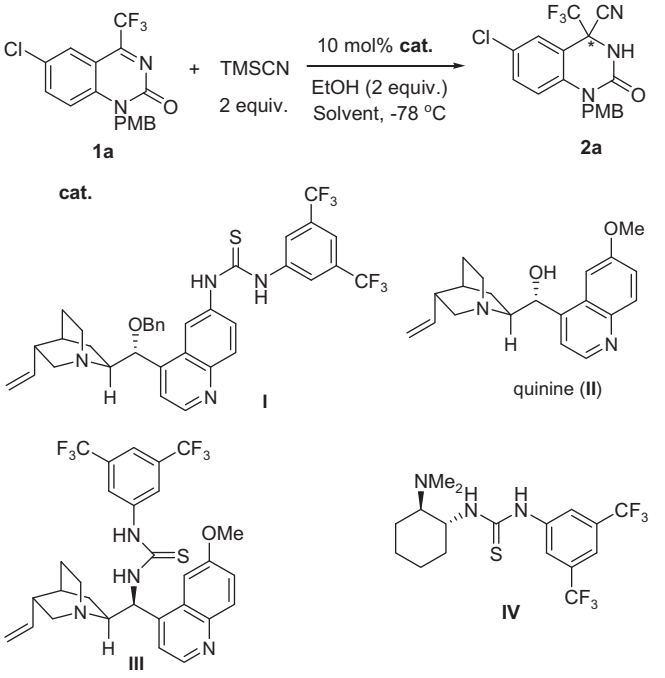
Table 1
Exploration of organocatalytic enantioselective Strecker reaction with 2(1*H*)-quinazolinone (**1a**)[a]



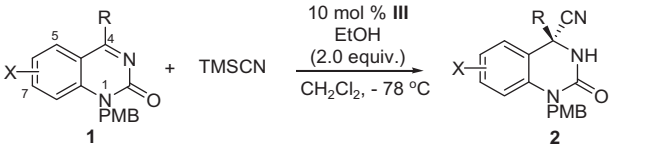
Entry	Cat	Solvent	*t* (h)	Yield[b] (%)	Ee[c] (%)
1[d]	**I**	CH_2Cl_2	36	87	30 (*R*)
2	**I**	CH_2Cl_2	36	95	53 (*R*)
3	**II**	CH_2Cl_2	36	83	42 (*S*)
4	**III**	CH_2Cl_2	36	92	97 (*R*)
5	**III**	Toluene	36	91	95 (*R*)
6	**IV**	CH_2Cl_2	36	91	96 (*S*)

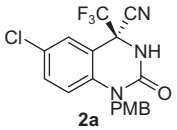
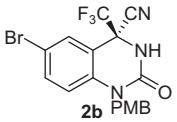
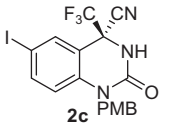
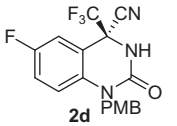
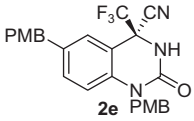
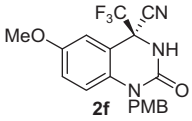
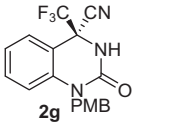
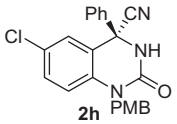
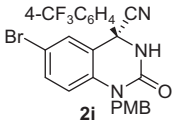
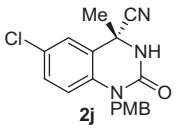
[a] Unless otherwise specified, a mixture of quinazolin-2(*1H*)-one **1** (0.07 mmol), EtOH (0.14 mmol) and catalyst (0.007 mmol) in CH_2Cl_2 or toluene (1 mL) in dry ice–acetone bath (−78 °C) was added TMSCN (0.14 mmol) slowly (the CH_2Cl_2 solution needs to be sufficiently cooled before TMSCN is added, otherwise, lower ee might be observed). The resulting mixture was then stirred in dry ice–acetone bath for a specific amount of time, then the reaction was allowed to raise to room temperature slowly. The pure product was obtained after purification by column chromatography on silica gel.
[b] Isolated yields.
[c] Enantiomeric excess (ee) determined by chiral HPLC analysis (Chiralcel OD-H).
[d] Without MeOH.

was carried out (Table 1, entry 1). Disappointingly, despite high yield, poor enantioselectivity (30% ee) was obtained. We envisioned that the use of HCN might deliver the product with improving enantioselectivity since the amine functionality in the catalysts affords stronger interaction with HCN instead with TMSCN. Accordingly, 2.0 equiv of EtOH was used in situ to generate HCN from TMSCN. Indeed, an enhanced enantioselectivity was observed (53% ee, entry 2). Screening of other organocatalysts[11–13] revealed that quinine gave rise to an unsatisfactory outcome (entry 3). Nevertheless, Soós's catalyst **III**[11] and Takemoto's **IV**[12] afforded product **2a** in high yields (92% and 91% respectively, entries 4 and 6) and with high enantioselectivities (97% and 96%, respectively). Change of CH_2Cl_2 to toluene, a medium used in our early aza-Henry process,[7] did not give a more encouraging result. Therefore, we decided to use Soós's catalyst **III** to probe the scope of the process in CH_2Cl_2.

With the optimal conditions in hand, the generality of the Strecker reaction was investigated accordingly. Notably, as shown in Table 2, the **III**-promoted Strecker process exhibits a relatively

Table 2
Scope of **III**-catalyzed Strecker reactions of 2(1*H*)-quinazolinone (**1**) with TMSCN[a]



Entry	X, R, **2**	*t* (d)	Yield[b] (%)	Ee[c] (%)
1	 **2a**	1.5	92	97
2	 **2b**	2	88	96
3	 **2c**	2	96	97
4	 **2d**	2	95	94
5	 **2e**	2	98	95
6	 **2f**	2	95	95
7	 **2g**	2	70	92
8[d]	 **2h**	6	69	59
9[d]	 **2i**	3	77	52
10	 **2j**	3	No reaction	—

[a] See footnote in Table 1 and Supplementary data.
[b] Isolated yield after chromatographic purification.
[c] Determined by chiral HPLC analysis (Chiralpak AS-H, or Chiralcel OD-H).
[d] At room temperature.

broad substrate tolerance and a quaternary stereogenic center is generated highly enantioselectively in all cases (entries 1–7). A full range of cyclic ketoimine 1, including electron-withdrawing (entries 1–4), -donating (entries 5 and 6), and -neutral substituents

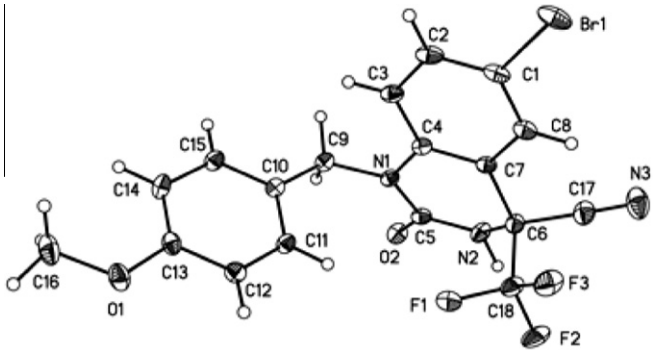


Figure 1. Single X-ray crystallographic structure of **2b**.

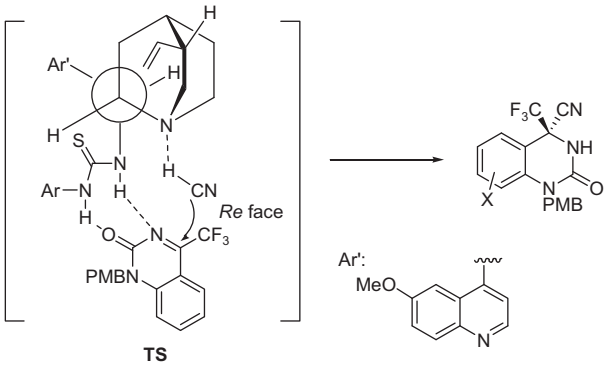


Figure 2. Proposed transition state (TS) model.

(entry 7) can engage in the reactions in good to excellent yields (70–98%) and with excellent enantioselectivities (92–97%). A similar trend observed in the aza-Henry reactions is also obeyed in the Strecker reactions that the CF_3 moiety in the cyclic ketoimines **1** is important for reactivity and enantioselectivity. As shown, moderate ee values but good yields are obtained when Ph and 4-CF_3Ph instead of CF_3 group are employed (Table 2, entries 8 and 9), while no reaction occurs in the aza-Henry reaction. No reaction is also seen with less reactive methyl group (entry 10). The absolute configuration of **2b** was determined by X-ray crystallographic analysis (Fig. 1).[14]

A transition state (TS) model is proposed to rationalize the outcome of high enantioselectivity and absolute (*R*) configuration of the asymmetric Strecker reaction (Fig. 2). The amine and thiourea moieties in the rigid catalyst **III** gauche each other as well so that they can simultaneously activate nucleophile HCN through base-acid interaction and electrophile carbonyl imine through two stronger H-bond interactions of the thiourea moiety. More importantly, the resulting rigid TS can provide products in high levels of enantioselectivity, as observed from the investigation. Furthermore, the TS model also explains the stereochemistry outcome of the addition adduct with *R* configuration. The base–acid interaction directs the nucleophile CN^- to attack substrates **1** from the *Re* face.

In conclusion, we have developed a highly enantioselective Strecker reaction of cyclic ketoimines using a simple bifunctional thiourea as catalyst under mild reaction conditions. The process expands the scope of organocatalyzed asymmetric reactions of synthetically challenging cyclic ketoimines for the construction of quaternary carbon stereocenters from the Henry[7] to the Strecker reactions. The process affords an alternative access to structurally diverse, biologically interesting optically active 4-trifluoromethyl-dihydroquinazolinones. The investigation on the biological properties of these products and their application in diversity-oriented synthesis is currently being pursued.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.119.

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