## Organocatalysis

## **Enantioselective Synthesis of Trifluoromethyl-Substituted 2-Isoxazolines: Asymmetric Hydroxylamine/Enone Cascade Reaction**\*\*

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Heterocycles containing a trifluoromethyl group are representatives of a major structure type in agricultural and medicinal chemistry, and thus the development of a simple and flexible method to generate a novel trifluoromethylated heterocyclic system has received much attention.<sup>[1]</sup> Trifluoromethyl-substituted 2-isoxazolines are amongst an important class of heterocyclic compounds with remarkable biological activities, and they make interesting synthetic targets.<sup>[2]</sup> Since the first discovery of the structurally unique 3,5-diaryl-5-(trifluoromethyl)-2-isoxazoline derivatives **1** (Figure 1) as pest control agents in 2004,<sup>[3a]</sup> the search for new agro-



*Figure 1.* Structures of 3,5-diaryl-5-(trifluoromethyl)-2-isoxazolines **1** and biologically attractive derivatives of types **A** and **B**.

chemicals and veterinary medicines has focused largely on this skeleton,<sup>[3]</sup> despite their diverse structural variants,<sup>[2]</sup> Thus far, more than 20000 compounds have been synthesized and patented in the past 5 years (the results of substructure searching using **1** with Scifinder), and many promising drug candidates have been disclosed including an antiparasiticide compound of either type **A** or **B** (Figure 1).<sup>[3]</sup> More interestingly, recent biological evaluation of the optically active type **B** compound ( $X^6 = CONHCH_2COCH_2CF_3$ ), obtained by HPLC methods using a chiral stationary phase, revealed that the *R* enantiomer of **B** is inactive and the *S* enantiomer is the

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active component.<sup>[3b]</sup> Once the importance of the optical

purity of these compounds was verified, the next challenge

was to control the stereochemistry at a quaternary carbon

center bearing a CF<sub>3</sub> group. As part of our ongoing research

programs directed to the development of efficient methods for the asymmetric synthesis of organofluorine compounds,<sup>[4]</sup>

we disclose herein the synthesis of trifluoromethyl-substituted

2-isoxazolines by a cinchona alkaloid catalyzed asymmetric

hydroxylamine/enone cascade reaction consisting of a con-

jugate addition/cyclization/dehydration sequence (Scheme 1).

**Scheme 1.** Enantioselective synthesis of trifluoromethyl-substituted 2isoxazolines **1** by an asymmetric hydroxylamine/enone cascade reaction.

Optically active 2-isoxazolines are mostly constructed by the asymmetric 1,3-dipolar cycloaddition of nitrile oxides to olefins,<sup>[5a-h]</sup> the asymmetric cyclization of  $\beta$ , $\gamma$ -unsaturated oximes,<sup>[5i]</sup> stereoselective ring-closure reaction through oximes of chiral Michael adducts of thiophenol to chalcones,[5] and proline-catalyzed conjugate addition/oxime-transfer reactions of unsaturated aldehydes.<sup>[5k]</sup> These methods, however, were not applicable to the synthesis of 1 because of the limitations in substrate specificity, and indeed, the catalytic enantioselective synthesis of trifluoromethyl-substituted 2-isoxazolines 1 has not been reported. We therefore started to investigate the asymmetric version of the nonchiral 2-isoxazoline-formation reaction.<sup>[3c]</sup> We first examined the reaction of (E)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-one (2a) with hydroxylamine in the presence of NaOH and a catalytic amount of N-3,5-bis(trifluoromethylbenzyl) quinidinium bromide (3a) as a chiral phase-transfer catalyst in toluene at -30°C (Table 1). The trifluoromethylated 2isoxazoline (R)-1a was formed in 89% ee, although the vield was 24% (Table 1, entry 1). Preliminary results encouraged us to change the solvent, which additionally improved



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the yields under the same catalyst conditions. Whereas THF, DME, MeCN, and EtOH did not effectively improve both the yield and *ee* value (Table 1, entries 2–5), chlorinated solvents such as  $CH_2Cl_2$ , (ClCH<sub>2</sub>)<sub>2</sub>, CHCl<sub>3</sub>, and  $CH_2(CH_2Cl)_2$  proved to

Table 1:	Optimization	of reaction	conditions. <sup>[a]</sup>
	•	HONH <sub>2</sub> (50 y	wt% aq.)(3.0 equiv)

Ph O ↓、 II		base (3.3 equiv) cat. <b>3</b> (10 mol%)		Ph, O-N	
F <sub>3</sub> C	Ph	solvent, -30 °C, 20	)–25 h	F <sub>3</sub> C	∕Ph
2a				( <i>R</i> )-1a	
Entry	Base	Solvent	3	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	10 N NaOH	toluene	3 a	24	89(R)
2	10 N NaOH	THF	3 a	16	76(R)
3	10 N NaOH	DME	3 a	12	67(R)
4	10 N NaOH	EtOH	3 a	36	2(R)
5	10 N NaOH	MeCN	3 a	14	62(R)
6	10 N NaOH	$CH_2Cl_2$	3 a	80	85(R)
7	10 N NaOH	(CICH <sub>2</sub> ) <sub>2</sub>	3 a	99	90(R)
8	10 N NaOH	$CH_2(CH_2CI)_2$	3 a	92	89(R)
9	10 N NaOH	CHCl₃	3 a	71	92(R)
10	5 n LiOH	CHCl <sub>3</sub>	3 a	34	91 (R)
11	10 n KOH	CHCl <sub>3</sub>	3 a	38	92(R)
12	10 n CsOH	CHCl₃	3 a	88	92(R)
13	10 N Na <sub>2</sub> CO <sub>3</sub>	CHCl <sub>3</sub>	3 a	n.r.	-
14	10 n CsOH	CHCl₃	3 b	89	88(S)

[a] All reactions performed at 0.10 mmol substrate in 1.1 mL of solvent. [b] Yield of isolated product. [c] Determined by HPLC methods using a chiral stationary phase. DME=1,2-dimethoxyethane, n.r. = no reaction, THF=tetrahydrofuran.

be better solvents, providing 1a with up to 92% *ee* (Table 1, entries 6–9). A subsequent survey of bases (Table 1, entries 10–13) revealed that CsOH was the base of choice with regards to both enantioselectivity and yield (Table 1, entry 12). We also discovered that the analogous ammonium bromide, **3b**, derived from quinine showed excellent enantioselectivity for giving 1a with the opposite (S) stereochemistry (Table 1, entry 14). Screening of the cinchona alkaloids ascertained that the use of 3a displayed the highest enantioselectivity in the formation of 1a (see Table S1 in the Supporting Information).

With optimal reaction conditions in hand, the scope of the asymmetric hydroxylamine/enone cascade reaction was explored using a variety of substrates selected to establish the generality of the process. By using a catalytic amount of **3a**, all substrates afforded good to excellent yield and high to excellent enantioselectivity (Table 2). A series of trifluoromethylated enone derivatives, 2b-m, having a variety of substituents such as bromo, chloro, fluoro, methyl, and methoxy, on their aromatic rings were nicely converted into the corresponding products 1b-m in good yields with 82%-94% ee (Table 2, entries 1-12). Catalyst 3c was a better catalyst for a couple of substrates such as 2n and 2o, furnishing 1n and 1o, respectively, in excellent yields with high enantioselectivity (Table 2, entries 13 and 14). Sterically demanding naphthyl-substituted enones 2h and 2p, and enolizable aliphatic aryl enone 2q were also compatible with the reaction conditions, affording the respective products

Table 2: Substrate scope.         HONH <sub>2</sub> (50 wt% aq.)(3.0 equiv)         10N CsOH (3.3 equiv)         cat. 3 (10 mol%) $F_3C$ 2b-q         R <sup>1</sup> O         (R)-1030 °C, 11-22 h         (R)-1b-q							R <sup>2</sup>
Entry	2	R <sup>1</sup>	R <sup>2</sup>	3	1	Yield [%] $[a]$	ee [%] <sup>[b]</sup>
1	2 b	3-MeC <sub>6</sub> H₄	Ph	3 a	1 b	83	92
2 <sup>[c]</sup>	2 c	$4-MeC_6H_4$	Ph	3 a	1c	83	94
3	2 d	$4-MeOC_6H_4$	Ph	3 a	1 d	99	92
4	2e	$4-FC_6H_4$	Ph	3 a	1e	92	91
5	2 f	4-CIC <sub>6</sub> H <sub>4</sub>	Ph	3 a	1 f	97	91
6	2 g	$4-BrC_6H_4$	Ph	3 a	1g	99	90
7	2h	2-naphthyl	Ph	3 a	1h	94	92
8	2 i	Ph	$2 - MeC_6H_4$	3 a	1i	92	82
9	2j	Ph	3-MeC <sub>6</sub> H₄	3 a	1j	96	91
10	2k	Ph	4-MeC <sub>6</sub> H₄	3 a	1 k	99	93
11	21	Ph	$4-MeOC_6H_4$	3 a	11	88	91
12	2 m	Ph	$4-FC_6H_4$	3 a	1m	91	88
13	2 n	Ph	$4-C C_6H_4$	3 c	1n	96	90
14	2 o	Ph	$4-BrC_6H_4$	3 c	10	99	91
15	2p	Ph	2-naphthyl	3a	1p	99	91
16	2q	Ph	cyclohexyl	3 a	1q	80	91

[a] Yield of isolated product. [b] Determined by HPLC methods using a
chiral stationary phase. [c] (CH <sub>2</sub> Cl) <sub>2</sub> was used as a solvent.

**1h**, **1p**, and **1q** in high yields with *ee* values of 91%-92% (Table 2, entries 7, 15, and 16). The absolute stereochemistry of (*R*)-**1g** was clearly determined by X-ray analysis (Figure 2)



Figure 2. X-ray crystallographic analysis of (R)-1 g. The thermal ellipsoids are shown at 50% probability.  $^{[10]}$ 

and all the other products were tentatively assigned by analogy with 1g. Notably, the enantioselectivity was dramatically changed when the cascade reaction of 2a with hydroxylamine was performed using the methylether catalyst 3e to give (S)-1a with 34% ee (Scheme 2a). This result indicates the hydrogen bond of the OH group is crucial for asymmetric induction. Furthermore, a similarly high enantioselectivity of (R)-1a with 85% ee was observed in the presence of the cinchonine-type catalyst 3f instead of the quinidinium catalyst 3a (Scheme 2b). Consequently, the methoxy group on the quinoline ring of 3a does not effect on the enantiomeric excess of the products.

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Scheme 2. Effects of the hydroxy group and methoxy group on 3 for asymmetric induction.

This isoxazoline-formation reaction consists of two distinct steps, Michael addition and imine formation reactions. The possible reaction routes, a and b, are shown in Scheme 3.



Scheme 3. The possible reaction routes, a or b, for 1a. Reaction conditions:  $10 \times CsOH$  (3.3 equiv), 3a (10 mol%),  $CHCl_3$ , -30 to -10°C, 10-20 h.

The first hypothesis (route a) is that the oxygen anion of hydroxylamine adds in Michael fashion to the unsaturated ketone 2a to furnish 4, with a subsequent intramolecular ringclosure cascade from the nitrogen atom onto ketone moiety. Then the elimination of water generates the isoxazoline 1a. An alternative (route b) is that the reaction proceeds through an imine formation first to produce the intermediate oxime 5; this then ring closes in a second step by intramolecular conjugated addition. To identify the mechanism, the oxime 5 was isolated individually and then we attempted to cyclize it under the same reaction conditions in a separate experiment. However, no isoxazoline 1a was detected. This result can also be supported by Baldwin's rules of guidelines for ring-closing reactions that the 5-endo-trig is disfavored.<sup>[6]</sup> Thus, route b does not operate here. In contrast, route a consists of the ringclosure reaction in a second step through a favored 5-exo-trig process.<sup>[6]</sup> Accordingly, intermediate 4 is difficult to isolate because of the rapid cyclization of **4** into **1a**.

To understand the high enantioselectivity observed for the present reaction catalyzed by the ammonium salts of cinchona alkaloids, the three-dimensional arrangement of the starting enones **2** and either the catalyst **3a** or **3f** is required. Although the X-ray crystallographic structure of catalyst **3f** has been disclosed by us<sup>[7]</sup> (Figure 3a), the conformational information

of **2** is difficult to obtained because of the viscous character of **2**. The three-dimensional conformation of **2a** was therefore generated through calculations with MOPAC PM3 method (Figure 3b). It is of great interest that the two phenyl substituents and the carbonyl  $\sigma$  plane of **2a** are found to be nonplanar, that is, not  $\pi$  conjugated. This phenomena is surprisingly similar to the case of the highly enantioselective epoxidation of enones using the ammonium salt of a cinchona alkaloid reported by Corey and co-workers.<sup>[8]</sup> On the basis of Corey's speculation on the reaction mechanism using the charge-accelerated catalysis by a rigid quaternary ammonium salt,<sup>[8]</sup> we postulated a similar transition-state structure for the



**Figure 3.** a) X-Ray crystallographic structure of catalyst **3 f** generated from the cif file of **3 f**. <sup>[11]</sup> b) Three-dimensional arrangement of **2 a** optimized by using the MOPAC PM3 method.

production of (R)-1a catalyzed by 3, that is, the specific threedimensional arrangement of cation 3, 2a, and the hydroxylamine anion (Figure 4). The free hydroxy group in 3 captures substrate 2a, presumably by intermolecular hydrogen-bond formation to the oxygen atom in 2a. Only the arrangement as shown in the Figure 4a should be acceptable because of the very limited space available by the sterically demanding and rigid structure of 3. The hydroxylamine anion generated by the base is sandwiched between 3f and 2a, and associates strongly with the nitrogen cation of the catalyst 3, as a nearest neighbor, through ion pairing. The hydroxylamine approaches from the *Re* face of 2a. Both the hydrogen bonding between the prochiral substrate 2 and catalyst 3, and the ionic interaction between the ammonium cation 3 and



Figure 4. Proposed transition-state model from 2a to (*R*)-1a catalyzed by 3f. a) CPK model based on the X-ray crystallographic structure of 3f and calculated structure of 2a. b) Schematic presentation of the transition-state structure.

hydroxylamine anion should realize the highly enantioselective reaction (Figure 4b). The possibility of the aromatic  $\pi$ - $\pi$ interactions between **2a** and **3** might be ruled out because the nonaromatic substrate **2p** was also converted into product **1p** with high enantiomeric excess.

We next focused on the asymmetric hydroxylamine/enone cascade reaction of multiply substituted substrate  $2\mathbf{r}$ . Under the optimized reaction conditions using catalyst  $3\mathbf{a}$ , the corresponding trifluoromethyl-substituted 2-isoxazoline  $1\mathbf{r}$  with an *R* configuration was obtained in 99% yield with 75% *ee*. Upon addition of catalyst  $3\mathbf{c}$  instead of  $3\mathbf{a}$  to the reaction, the enantioselectivity of the 2-isoxazoline was improved by as much as 13% *ee* to provide  $1\mathbf{r}$  in 99% yield with 88% *ee*. As expected, (*S*)- $1\mathbf{r}$  with 81% *ee* was obtained in excellent yield from the asymmetric hydroxylamine/enone cascade reaction by using the pseudoenantiomer catalyst  $3\mathbf{d}$ . The 2-isoxazoline  $1\mathbf{r}$  could be a key intermediate for the synthesis of chiral type **B** compounds (Scheme 4).<sup>[3g-j]</sup>



Scheme 4. Synthesis of key type B compounds (see Figure 1).

In summary, we have developed the first catalytic enantioselective synthesis of trifluoromethyl-substituted 2-isoxazolines by a cinchona alkaloid-catalyzed asymmetric hydroxylamine/enone cascade reaction consisting of conjugate addition/cyclization/dehydration reactions to provide the medicinally important trifluoromethylated compounds.<sup>[3d]</sup> Wide substrate generality, the flexibility to generate either the *S* or *R* enantiomers, and high levels of enantioselectivity have been achieved.<sup>[9]</sup>

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detected at all. Importantly, we have ascertained that environmentally benign trifluorotoluene can be used as a solvent in this transformation without any loss of the yields and enantioselectivity.

> HONH<sub>2</sub> (50 wt% aq.)(3.0 equiv) 10 N CsOH (3.3 equiv) cat. 3a (10 mol%) CF<sub>3</sub>C<sub>6</sub>H<sub>5</sub>, -20 to -10 °C 17 h
> 92%, 92% ee

- [10] CCDC 763815 ((*R*)-1g) 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).
- [11] CCDC 738896 (3 f) 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).