Organocatalysis

DOI: 10.1002/ange.201002065

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.[1] Trifluoromethyl-substituted 2-isoxazolines are amongst an important class of heterocyclic compounds with remarkable biological activities, and they make interesting synthetic targets.[2] 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,[3a] the search for new agrochemicals and veterinary medicines has focused largely on this skeleton,[3] despite their diverse structural variants.[2] 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).[3] 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 active component.[3b] 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_3 group. As part of our ongoing research programs directed to the development of efficient methods for the asymmetric synthesis of organofluorine compounds,[4] we disclose herein the synthesis of trifluoromethyl-substituted 2-isoxazolines by a cinchona alkaloid catalyzed asymmetric hydroxylamine/enone cascade reaction consisting of a conjugate addition/cyclization/dehydration sequence (Scheme 1).

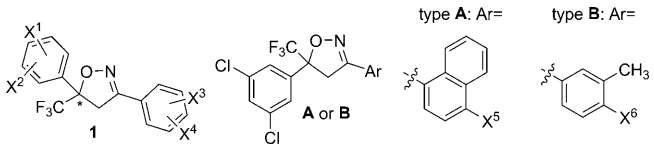
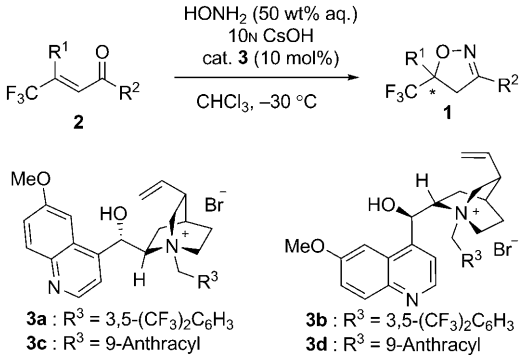


Figure 1. Structures of 3,5-diaryl-5-(trifluoromethyl)-2-isoxazolines **1** and biologically attractive derivatives of types **A** and **B**.



Scheme 1. Enantioselective synthesis of trifluoromethyl-substituted 2-isoxazolines **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,[5a–h] the asymmetric cyclization of β,γ-unsaturated oximes,[5i] stereoselective ring-closure reaction through oximes of chiral Michael adducts of thiophenol to chalcones,[5j] and proline-catalyzed conjugate addition/oxime-transfer reactions of unsaturated aldehydes.[5k] 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.[3c] 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 2-isoxazoline (*R*)-**1a** was formed in 89% *ee*, although the yield was 24% (Table 1, entry 1). Preliminary results encouraged us to change the solvent, which additionally improved

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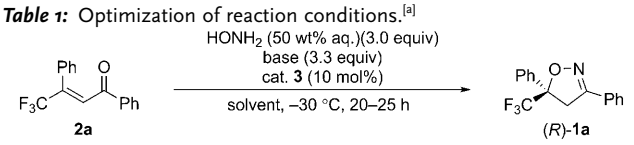
[**] Support was provided by KAKENHI (21390030, 22106515). The corresponding author thanks the JSPS for financial support of this work in part through a Joint Research Project between Japan and France.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201002065.

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, $(ClCH_2)_2$, $CHCl_3$, and $CH_2(CH_2Cl)_2$ proved to

Table 1: Optimization of reaction conditions.[a]



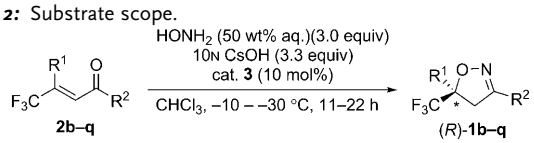
Entry	Base	Solvent	3	Yield [%][b]	*ee* [%][c]
1	10 N NaOH	toluene	**3a**	24	89(*R*)
2	10 N NaOH	THF	**3a**	16	76(*R*)
3	10 N NaOH	DME	**3a**	12	67(*R*)
4	10 N NaOH	EtOH	**3a**	36	2(*R*)
5	10 N NaOH	MeCN	**3a**	14	62(*R*)
6	10 N NaOH	CH_2Cl_2	**3a**	80	85(*R*)
7	10 N NaOH	$(ClCH_2)_2$	**3a**	99	90(*R*)
8	10 N NaOH	$CH_2(CH_2Cl)_2$	**3a**	92	89(*R*)
9	10 N NaOH	$CHCl_3$	**3a**	71	92(*R*)
10	5 N LiOH	$CHCl_3$	**3a**	34	91(*R*)
11	10 N KOH	$CHCl_3$	**3a**	38	92(*R*)
12	10 N CsOH	$CHCl_3$	**3a**	88	92(*R*)
13	10 N Na_2CO_3	$CHCl_3$	**3a**	n.r.	–
14	10 N CsOH	$CHCl_3$	**3b**	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.



Entry	2	R^1	R^2	3	1	Yield [%] [a]	*ee* [%][b]
1	**2b**	3-MeC_6H_4	Ph	**3a**	**1b**	83	92
2[c]	**2c**	4-MeC_6H_4	Ph	**3a**	**1c**	83	94
3	**2d**	4-$MeOC_6H_4$	Ph	**3a**	**1d**	99	92
4	**2e**	4-FC_6H_4	Ph	**3a**	**1e**	92	91
5	**2f**	4-ClC_6H_4	Ph	**3a**	**1f**	97	91
6	**2g**	4-BrC_6H_4	Ph	**3a**	**1g**	99	90
7	**2h**	2-naphthyl	Ph	**3a**	**1h**	94	92
8	**2i**	Ph	2-MeC_6H_4	**3a**	**1i**	92	82
9	**2j**	Ph	3-MeC_6H_4	**3a**	**1j**	96	91
10	**2k**	Ph	4-MeC_6H_4	**3a**	**1k**	99	93
11	**2l**	Ph	4-$MeOC_6H_4$	**3a**	**1l**	88	91
12	**2m**	Ph	4-FC_6H_4	**3a**	**1m**	91	88
13	**2n**	Ph	4-ClC_6H_4	**3c**	**1n**	96	90
14	**2o**	Ph	4-BrC_6H_4	**3c**	**1o**	99	91
15	**2p**	Ph	2-naphthyl	**3a**	**1p**	99	91
16	**2q**	Ph	cyclohexyl	**3a**	**1q**	80	91

[a] Yield of isolated product. [b] Determined by HPLC methods using a chiral stationary phase. [c] $(CH_2Cl)_2$ 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)

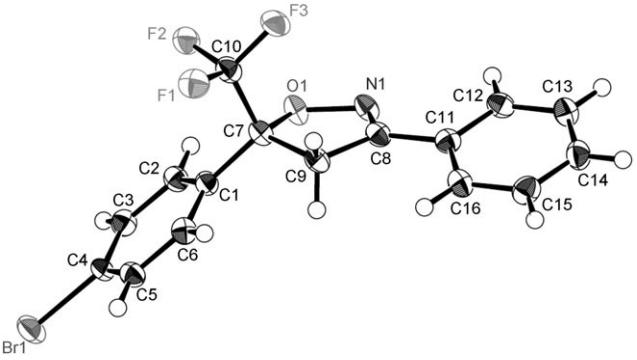
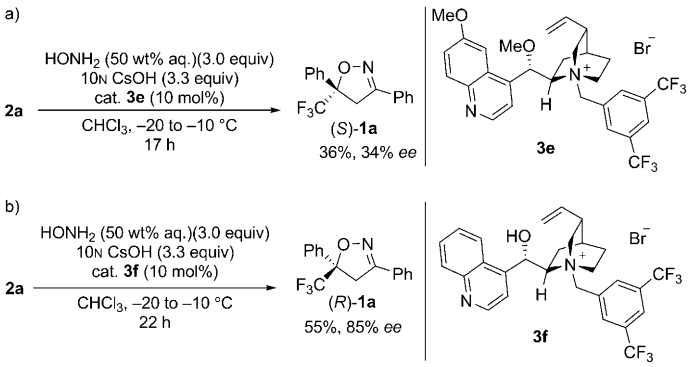


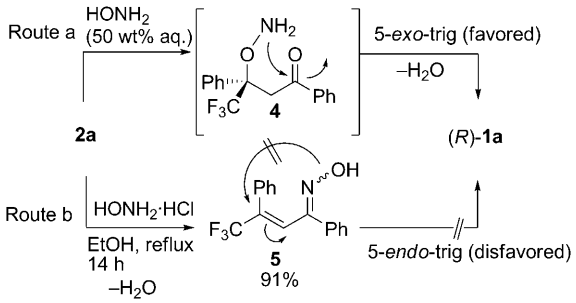
Figure 2. X-ray crystallographic analysis of (*R*)-**1g**. The thermal ellipsoids are shown at 50% probability.[10]

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.



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: 10N 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 ring-closure 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.[6] Thus, route b does not operate here. In contrast, route a consists of the ring-closure reaction in a second step through a favored 5-*exo*-trig process.[6] 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[7] (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 σ plane of **2a** are found to be nonplanar, that is, not π 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.[8] On the basis of Corey's speculation on the reaction mechanism using the charge-accelerated catalysis by a rigid quaternary ammonium salt,[8] we postulated a similar transition-state structure for the

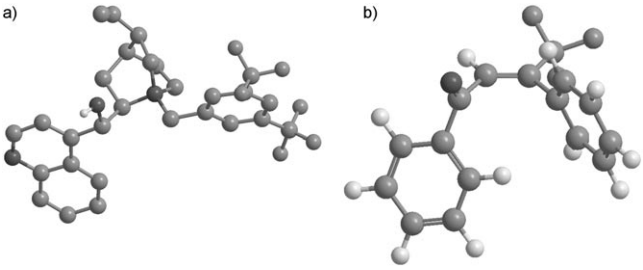


Figure 3. a) X-Ray crystallographic structure of catalyst **3f** generated from the cif file of **3f**.[11] b) Three-dimensional arrangement of **2a** optimized by using the MOPAC PM3 method.

production of (*R*)-**1a** catalyzed by **3**, that is, the specific three-dimensional 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

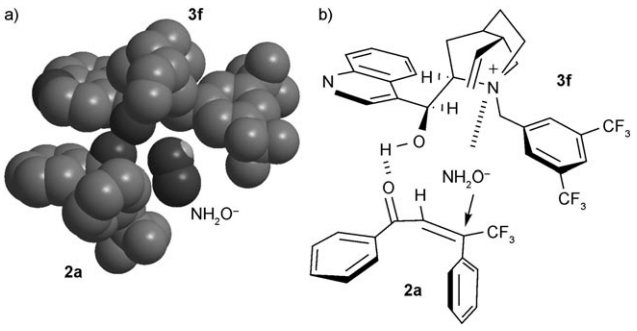
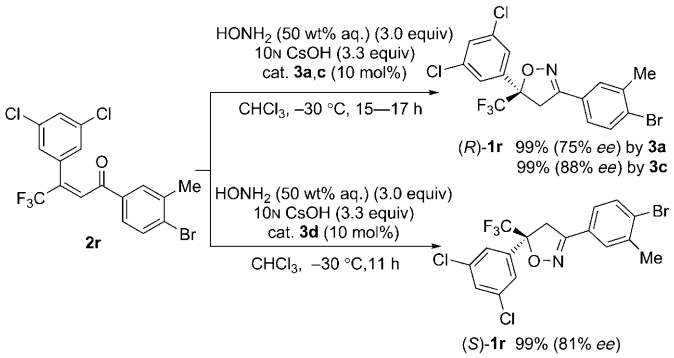


Figure 4. Proposed transition-state model from **2a** to (*R*)-**1a** catalyzed by **3f**. a) CPK model based on the X-ray crystallographic structure of **3f** and calculated structure of **2a**. b) Schematic presentation of the transition-state structure.

hydroxylamine anion should realize the highly enantioselective reaction (Figure 4b). The possibility of the aromatic π–π 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 **2r**. Under the optimized reaction conditions using catalyst **3a**, the corresponding trifluoromethyl-substituted 2-isoxazoline **1r** with an *R* configuration was obtained in 99% yield with 75% *ee*. Upon addition of catalyst **3c** instead of **3a** to the reaction, the enantioselectivity of the 2-isoxazoline was improved by as much as 13% *ee* to provide **1r** in 99% yield with 88% *ee*. As expected, (*S*)-**1r** with 81% *ee* was obtained in excellent yield from the asymmetric hydroxylamine/enone cascade reaction by using the pseudoenantiomer catalyst **3d**. The 2-isoxazoline **1r** could be a key intermediate for the synthesis of chiral type **B** compounds (Scheme 4).[3g–j]



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.[3d] Wide substrate generality, the flexibility to generate either the *S* or *R* enantiomers, and high levels of enantioselectivity have been achieved.[9]

Received: April 7, 2010
Revised: May 27, 2010
Published online: July 7, 2010

Keywords: asymmetric catalysis · fluorine · heterocycles · organocatalysis · phase-transfer catalysis

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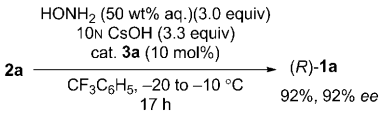
[9] Although the wisdom in using chloroform as a solvent with a strong base such as CsOH might be questionable since dichlorocarbene can be formed, an unexpected side reaction was not

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.



[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 (**3f**) 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).

