

# Organocatalytic Asymmetric Synthesis of Trifluoromethyl-substituted Diarylpyrrolines: Enantioselective Conjugate Cyanation of $\beta$ -Aryl- $\beta$ -trifluoromethyl-disubstituted Enones\*\*

Hiroyuki Kawai, Satoshi Okusu, Etsuko Tokunaga, Hiroyasu Sato, Motoo Shiro, and Norio Shibata\*

Trifluoromethylated dihydroazoles (**1**; Figure 1)<sup>[1,2]</sup> are an important class of fluorinated heterocyclic compounds<sup>[3]</sup> with remarkable biological activities, thus making their synthesis a competitive area in life science industries.<sup>[1]</sup> Ever since the first discovery of the structurally unique 3,5-diaryl-5-

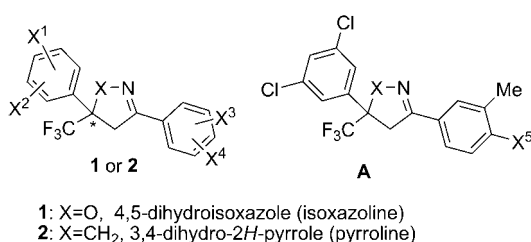


Figure 1. Trifluoromethylated 2-isoxazolines **1** and pyrrolines **2**.

(trifluoromethyl)-2-isoxazoline derivatives **1** (X = O) as pest control agents in 2004,<sup>[1a]</sup> the search for new agrochemicals and veterinary medicines has focused largely on this skeleton.<sup>[1]</sup> Thus far, more than 20000 compounds have been registered,<sup>[1]</sup> and several promising drug candidates of type **A** have been discovered (Figure 1). We recently reported the catalytic asymmetric synthesis of **1** using chiral ammonium salts of cinchona alkaloids to promote a hydroxylamine enone cascade reaction involving a conjugate addition/cyclization/dehydration sequence.<sup>[4]</sup> The expeditious synthesis of **1** based on the direct introduction of a trifluoromethyl group into aromatic isoxazoles was also disclosed.<sup>[5]</sup> As part of our ongoing research programs directed at the development of efficient methodologies for the construction of trifluoromethylated heterocyclic frameworks,<sup>[6]</sup> we became interested in the catalytic, asymmetric synthesis of the carbon variant of

**1**, that is 3,5-diaryl-5-(trifluoromethyl)-3,4-dihydro-2H-pyrrolines or  $\beta$ -trifluoromethyl 3,5-diaryl-pyrrolines (**2**; X = CH<sub>2</sub>) as a promising drug candidate such as an antiparasiticide.<sup>[2]</sup> Since the first report of **2** in 2005<sup>[2a]</sup> more than 5000 analogues of **2** in racemic form were reported within 19 patents.<sup>[2]</sup> However, no example of the asymmetric synthesis of **2** has appeared. The challenge for synthesizing **2** is the enantioselective construction of sterically demanding trifluoromethylated, all-carbon quaternary stereocenters.<sup>[7]</sup>

Construction of all-carbon quaternary chiral centers is a particularly demanding task and a challenging topic in organic chemistry.<sup>[8]</sup> The asymmetric conjugate addition of cyanide to  $\beta,\beta$ -disubstituted- $\alpha,\beta$ -unsaturated carbonyl compounds is an ideal strategy for this purpose. Several conjugate additions of cyanide to  $\beta$ -monosubstituted substrates leading to  $\beta$ -tertiary stereocenters have been reported,<sup>[9]</sup> however, there are few reports of asymmetric conjugate cyanation of  $\beta,\beta$ -disubstituted substrates resulting in high enantioselectivities.<sup>[9d,10]</sup> In 2008, the group of Jacobsen showed a single example of asymmetric conjugate cyanation of  $\beta,\beta$ -disubstituted imide substrates with trimethylsilyl cyanide using a dinuclear [(salene)Al] catalyst with high enantioselectivity but low conversion.<sup>[9d]</sup> An organocatalytic conjugate addition of cyanide to  $\beta,\beta$ -disubstituted nitroalkanes was investigated by Ricci et al. and resulted in low to moderate enantioselectivities.<sup>[10a]</sup> Shibasaki, Kanai, and co-workers dramatically improved this type of reaction for the first time using bifunctional catalysts derived from Sr(OiPr)<sub>2</sub> and D-glucose-based ligands, and trialkylsilyl cyanides.<sup>[10b]</sup> These methods, however, were not applied to the synthesis of trifluoromethylated all-carbon quaternary stereocenters.<sup>[10]</sup> We disclose herein the first enantioselective conjugate addition of cyanide to sterically demanding  $\beta$ -aryl- $\beta$ -trifluoromethyl aryl-enones (**3**) catalyzed by ammonium salts of cinchona alkaloids to provide **4**, having trifluoromethylated all-carbon quaternary stereocenters, in high yields with high to excellent enantioselectivities. Product **4** serves as a precursor for **2**, thus achieving the asymmetric synthesis of **2** for the first time (Scheme 1). Ether-type cinchona alkaloids are found to be much more efficient than conventional hydroxy-type cinchona alkaloids. The fully saturated analogue **6** was also accessed without any loss of enantiopurity of **4**. The procedure is operationally simple, and inexpensive acetone cyanohydrin and organocatalysts are used, which is an advantage for industrial purposes.

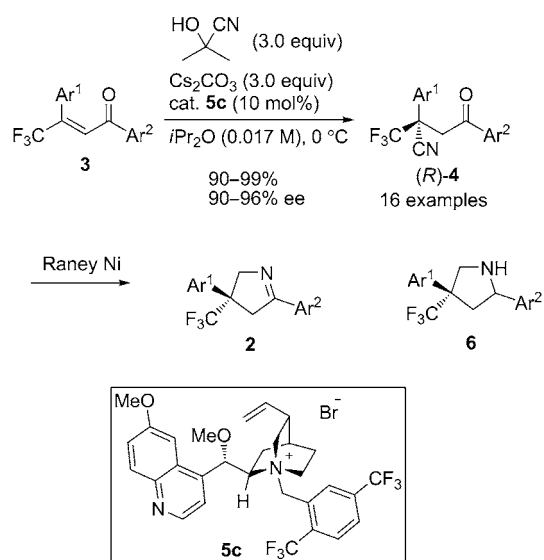
We first examined the reaction of (*E*)-4,4,4-trifluoro-1,3-diphenylbut-2-en-1-one (**3a**) with acetone cyanohydrin in the

[\*] H. Kawai, S. Okusu, E. Tokunaga, Prof. N. Shibata  
 Department of Frontier Materials, Graduate School of Engineering  
 Nagoya Institute of Technology  
 Gokiso, Showa-ku, Nagoya 466-8555 (Japan)  
 E-mail: nozshiba@nitech.ac.jp

H. Sato, Dr. M. Shiro  
 Rigaku Corporation  
 3-9-12 Mastubara-cho, Akishima, Tokyo 196-8666 (Japan)

[\*\*] Support was provided by the Grants-in-Aid for Scientific Research (21390030, 23915014, 22106515, Project No. 2105: Organic Synthesis Based on Reaction Integration). We also thank the Asahi Glass Foundation for support in part.

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201201278>.



**Scheme 1.** Enantioselective synthesis of  $\beta$ -trifluoromethyl  $\Delta^1$ -pyrrolines **2** through asymmetric conjugate cyanation.

presence of  $K_2CO_3$  and a catalytic amount of a chiral phase-transfer catalyst under conventional biphasic conditions (toluene/ $H_2O$  = 2:1) at ambient temperature (entry 1, Table 1). *N*-3,5-Bis(trifluoromethylbenzyl) quinidinium bromide (**5a**) was selected as the asymmetric catalyst as it is the best catalyst for the enantioselective asymmetric hydroxylamine enone cascade reaction of **3a** as previously reported.<sup>[4]</sup> Much to our disappointment, conjugate addition of cyanide to **3a** did not proceed as anticipated. The desired conjugate adduct **4a** was obtained only in 22% yield with 0% *ee* (entry 1). Indeed, the conjugate addition of cyanide to **3** had not been examined thus far, not even in a racemic fashion. This poor result led us to change the catalyst character entirely. It is reported that the hydroxy group of cinchona alkaloids often plays an important role both in reactivity and in asymmetric induction, probably through hydrogen bonding with substrates.<sup>[4,11]</sup> We therefore hypothesized that the hydrogen bonding could be hindering the desired conjugate addition, so a variety of OH-protected ether-type cinchona alkaloids were synthesized (see Table S1 in the Supporting Information).<sup>[12]</sup> Gratifyingly, when the reaction was carried out using the methylether catalyst **5b**, the desired **4a** was obtained in 93% with 62% *ee* (entry 2). Enantioselectivity was further improved to 72% *ee* in toluene or THF (entries 3 and 4). A screen of different bases (entries 5–8) showed that either  $K_2CO_3$  or  $Cs_2CO_3$  was the base of choice with regard to both enantioselectivity and yield (entries 4 and 6). Interestingly, when the reaction was carried out in the presence of a stoichiometric amount of KOH or NaOEt, only the 1,2-adduct was detected in low yield and moderate to good enantioselectivity (entries 7 and 8).<sup>[13]</sup> Upon screening solvents, we found that  $Et_2O$  and *iPr*<sub>2</sub>O produced good results, with *ee* values in the range of 74–76% (entries 9 and 10). Further improvement was observed under high dilution (entries 14–16), and 89% *ee* of **4a** was obtained in *iPr*<sub>2</sub>O (0.017 M, entry 16). A second catalyst screening (see Table S2 in the

**Table 1.** Optimization of the reaction conditions.<sup>[a]</sup>

| Entry               | Base       | Solvent                   | <b>5</b>  | Yield [%]         | <i>ee</i> [%] <sup>[b]</sup> |
|---------------------|------------|---------------------------|-----------|-------------------|------------------------------|
| 1                   | $K_2CO_3$  | toluene/ $H_2O$ (2:1)     | <b>5a</b> | 22                | rac                          |
| 2                   | $K_2CO_3$  | toluene/ $H_2O$ (2:1)     | <b>5b</b> | 93                | 62                           |
| 3                   | $K_2CO_3$  | toluene                   | <b>5b</b> | 85                | 72                           |
| 4                   | $K_2CO_3$  | THF                       | <b>5b</b> | 99                | 72                           |
| 5                   | $Na_2CO_3$ | THF                       | <b>5b</b> | 25                | 53                           |
| 6                   | $Cs_2CO_3$ | THF                       | <b>5b</b> | 94                | 72                           |
| 7                   | KOH        | THF                       | <b>5b</b> | 38 <sup>[f]</sup> | 52 <sup>[f]</sup>            |
| 8                   | NaOEt      | THF                       | <b>5b</b> | 31 <sup>[f]</sup> | 70 <sup>[f]</sup>            |
| 9                   | $K_2CO_3$  | $Et_2O$                   | <b>5b</b> | 98                | 76                           |
| 10                  | $K_2CO_3$  | <i>iPr</i> <sub>2</sub> O | <b>5b</b> | 81                | 74                           |
| 11                  | $K_2CO_3$  | DME                       | <b>5b</b> | 54                | 67                           |
| 12                  | $K_2CO_3$  | mesitylene                | <b>5b</b> | 24                | 72                           |
| 13                  | $K_2CO_3$  | $CH_2Cl_2$                | <b>5b</b> | 84                | 65                           |
| 14 <sup>[e]</sup>   | $K_2CO_3$  | $Et_2O$                   | <b>5b</b> | 90                | 81                           |
| 15 <sup>[d]</sup>   | $K_2CO_3$  | $Et_2O$                   | <b>5b</b> | 99                | 86                           |
| 16 <sup>[d]</sup>   | $K_2CO_3$  | <i>iPr</i> <sub>2</sub> O | <b>5b</b> | 99                | 89                           |
| 17 <sup>[d]</sup>   | $K_2CO_3$  | <i>iPr</i> <sub>2</sub> O | <b>5c</b> | 76                | 91                           |
| 18 <sup>[d]</sup>   | $Cs_2CO_3$ | <i>iPr</i> <sub>2</sub> O | <b>5c</b> | 97                | 90                           |
| 19 <sup>[d,e]</sup> | $Cs_2CO_3$ | <i>iPr</i> <sub>2</sub> O | <b>5c</b> | 90                | 92                           |

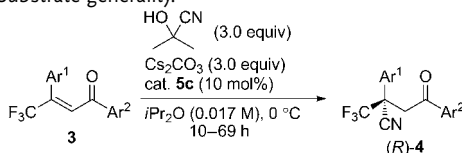
[a] The reaction of **3a** with acetone cyanohydrin (3.0 equiv) was carried out in the presence of **5** (10 mol%) and base (3.0 equiv) in solvent (0.5 mL, 0.2 M) at room temperature, unless otherwise noted.

[b] Determined by HPLC analysis using a chiral stationary phase.

[c] 3.0 mL of solvent was used (0.033 M). [d] 6.0 mL of solvent was used (0.017 M). [e] The reaction was carried out at 0 °C; [f] Corresponding 1,2-adduct was obtained instead. DME = dimethoxyethane.

Supporting Information) indicated that the use of structurally new, *N*-2,5-bis(trifluoromethylbenzyl) *O*-methyl quinidinium bromide (**5c**) displayed the highest enantioselectivity (91% *ee*, entry 17). In particular, the use of 3.0 equivalents of acetone cyanohydrin in the presence of **5c** (10 mol%) and  $Cs_2CO_3$  (3.0 equiv) in *iPr*<sub>2</sub>O at 0 °C was the most effective combination for the formation of **4a** in 90% yield with 92% *ee* (entry 19).

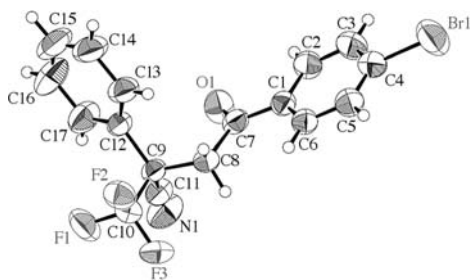
With optimal reaction conditions in hand, the scope of the enantioselective conjugate cyanation of a variety of  $\beta$ -aryl- $\beta$ -trifluoromethyl-substituted enones (**3**) in the presence of a catalytic amount of **5c** was explored to establish the generality of the process. In all cases the reactions afforded products in excellent yields and enantioselectivities (Table 2). A series of trifluoromethylated enone derivatives (**3a–f**, **3h–m**) having a variety of substituents on their aromatic rings, including methyl, methoxy, chloro, bromo, and nitro groups, were nicely converted into the corresponding products **4a–f**, **4h–m** in excellent yields with 90–96% *ee* (entries 1–6 and 8–13). The sterically demanding naphthyl-substituted enones **3g** and **3n** were also compatible with the same reaction conditions, thus affording products **4g** and **4n**, respectively, in excellent yields with 90–94% *ee* (entries 7 and 14). It should be noted that the multiply substituted substrates **3o**

**Table 2:** Substrate generality.<sup>[a]</sup>


| Entry | 3         | Ar <sup>1</sup>                                   | Ar <sup>2</sup>                                 | 4         | Yield [%] | ee [%] <sup>[b]</sup> |
|-------|-----------|---|---|-----------|-----------|-----------------------|
| 1     | <b>3a</b> | Ph  | Ph  | <b>4a</b> | 90        | 92                    |
| 2     | <b>3b</b> | 3-MeC <sub>6</sub> H <sub>4</sub>                 | Ph  | <b>4b</b> | 99        | 91                    |
| 3     | <b>3c</b> | 4-MeC <sub>6</sub> H <sub>4</sub>                 | Ph  | <b>4c</b> | 99        | 91                    |
| 4     | <b>3d</b> | 4-MeOC <sub>6</sub> H <sub>4</sub>                | Ph  | <b>4d</b> | 93        | 90                    |
| 5     | <b>3e</b> | 4-ClC <sub>6</sub> H <sub>4</sub>                 | Ph  | <b>4e</b> | 96        | 90                    |
| 6     | <b>3f</b> | 4-BrC <sub>6</sub> H <sub>4</sub>                 | Ph  | <b>4f</b> | 92        | 90                    |
| 7     | <b>3g</b> | 2-naphthyl  | Ph  | <b>4g</b> | 92        | 90                    |
| 8     | <b>3h</b> | Ph  | 4-MeC <sub>6</sub> H <sub>4</sub>               | <b>4h</b> | 92        | 92                    |
| 9     | <b>3i</b> | Ph  | 4-MeOC <sub>6</sub> H <sub>4</sub>              | <b>4i</b> | 98        | 94                    |
| 10    | <b>3j</b> | Ph  | 4-ClC <sub>6</sub> H <sub>4</sub>               | <b>4j</b> | 99        | 96                    |
| 11    | <b>3k</b> | Ph  | 3-BrC <sub>6</sub> H <sub>4</sub>               | <b>4k</b> | 99        | 90                    |
| 12    | <b>3l</b> | Ph  | 4-BrC <sub>6</sub> H <sub>4</sub>               | <b>4l</b> | 99        | 95                    |
| 13    | <b>3m</b> | Ph  | 4-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | <b>4m</b> | 99        | 91                    |
| 14    | <b>3n</b> | Ph  | 2-naphthyl                                      | <b>4n</b> | 99        | 94                    |
| 15    | <b>3o</b> | 3,5-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> | 2-Me-3-BrC <sub>6</sub> H <sub>3</sub>          | <b>4o</b> | 99        | 95                    |
| 16    | <b>3p</b> | 3,5-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> | 2-MeC <sub>6</sub> H <sub>4</sub>               | <b>4p</b> | 94        | 92                    |

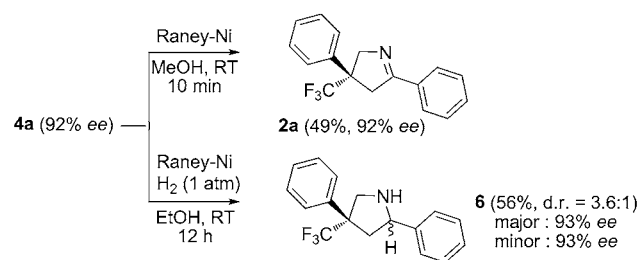
[a] The reaction of **3** with acetone cyanohydrin (3.0 equiv) was carried out in the presence of **5c** (10 mol%) and Cs<sub>2</sub>CO<sub>3</sub> (3.0 equiv) in *i*Pr<sub>2</sub>O (6.0 mL, 0.017 M) at 0 °C. [b] Determined by HPLC analysis using a chiral stationary phase.

and **3p** were also smoothly converted into the desired 1,4-adducts **4o** and **4p** with 95 and 92% *ee*, respectively (entries 15 and 16). The absolute stereochemistry of (*R*)-**4l** was clearly determined by X-ray analysis (Figure 2) and all the other products were tentatively assigned by analogy with (*R*)-**4l**.



**Figure 2.** X-ray crystallographic analysis of (*R*)-**4l**.<sup>[15]</sup> Thermal ellipsoids are shown at 50% probability.

Finally, the one-step conversion of **4** into the partially saturated target arylpyrroline **2** was carried out (Scheme 2). Treatment of **4a** with Raney nickel in MeOH at ambient temperature for 10 minutes led to **2a** in 49%, without any loss of enantiopurity in one step consisting of three sequential reactions (cyano reduction/cyclization/dehydration). The fully saturated pyrrolidine derivative **6** was also obtained from **4a** under a hydrogen atmosphere in 56% in one step consisting of four sequential reactions (cyano reduction/cyclization/dehydration/imine hydrogenation).



**Scheme 2.** Transformations of **4a** to pyrroline **2a** and pyrrolidine **6**.

In summary, we have developed an operationally simple, highly enantioselective conjugate cyanation of  $\beta$ -aryl- $\beta$ -trifluoromethyl-substituted enones (**3**) using acetone cyanohydrin and the simple cinchona alkaloid catalyst **5c** to provide conjugate addition adducts having trifluoromethylated all-carbon quaternary stereocenters.<sup>[14]</sup> Ether-type cinchona alkaloids are very effective for this transformation and excellent chemical yields with enantioselectivities, over 90% *ee*, were obtained for all cases. Complete 1,4-addition selectivity over 1,2-addition is also achieved. Transformation to the medically important trifluoromethylated arylpyrroline **2** and pyrrolidine derivative **6** were achieved from **4** for the first time. The procedure is carried out using inexpensive acetone cyanohydrin and organocatalysts, and is thus an advantage for industrial purposes.

Received: February 15, 2012

Published online: April 4, 2012

**Keywords:** asymmetric catalysis · fluorine · heterocycles · organocatalysis · synthetic methods

[1] For examples, see: a) T. Mita, Y. Kudo, T. Mizukoshi, H. Hotta, K. Maeda, S. Takii, WO2004018410, **2004**; b) T. Mita, T. Kikuchi, T. Mizukoshi, M. Yaosaka, M. Komoda, WO2005085216, **2005**; c) G. P. Lahm, W. L. Shoop, M. Xu, WO2007079162, **2007**; d) M. Yaosaka, T. Utsunomiya, Y. Moriyama, T. Matsumoto, K. Matoba, WO2009001942, **2009**; e) K. Matoba, WO2009063910, **2009**; f) J. K. Long, T. P. Selby, M. Xu, WO2009045999, **2009**; g) W. Zambach, P. Renold, WO2009049846, **2009**; h) P. Renold, W. Zambach, P. Maienfisch, M. Muehlebach, WO2009080250, **2009**; i) T. Murata, Y. Yoneta, J. Mihara, K. Domon, M. Hatazawa, K. Araki, E. Shimojo, K. Shibuya, T. Ichihara, U. Goergens, A. Voerste, A. Becker, E. Franken, K. Mueller, WO2009112275, **2009**; j) Y. Ozoe, M. Asahi, F. Ozoe, K. Nakahira, T. Mita, *Biochem. Biophys. Res. Commun.* **2010**, *391*, 744–749; k) N. P. Mulholland, E. Godineau, J. Y. Cassayre, P. Renold, M. El Qacemi, G. Revol, WO2011104089, **2011**; l) N. A. L. Chubb, T. M. Maddux, S. R. Menon, WO2011124998, **2011**.

[2] For examples, see: a) T. Mita, Y. Kudo, T. Mizukoshi, H. Hotta, K. Maeda, S. Takii, JP2005272452, **2005**; b) T. Mita, E. Ikeda, H. Takahashi, M. Komoda, WO2009072621, **2009**; c) U. Goergens, Y. Yoneta, T. Murata, J. Mihara, K. Domon, E. Shimojo, K. Shibuya, T. Ichihara, WO2009097992, **2009**; d) J. Y. Cassayre, P. Renold, T. Pitterna, V. Bobosik, M. El Qacemi, A. J. Dalencon, W. Zambach, C. R. Godfrey, P. J. Jung, J. Pabba, WO2010020522, **2010**; e) H. Ihara, K. Kumamoto, WO2010090344, **2010**; f) T. Murata, Y. Yoneta, H. Kishikawa, J. Mihara, D. Yamazaki, M. Hatazawa, N. Sasaki, K. Domon, E. Shimojo, T. Ichihara, K.

- Shibuya, M. Ataka, U. Goergens, WO2010133336, **2010**;
- g) A. W. Moradi, T. N. Mueller, T. Murata, M. Hatazawa, P. Bruechner, E. Shimojo, T. Ichihara, M. Ataka, K. Shibuya, U. Goergens, WO2011128299, **2011**; h) K. Araki, J. Mihara, N. Sasaki, P. Bruechner, K. Domon, J.-R. Jansen, N. Lui, WO2011141414, **2011**.
- [3] a) V. A. Petrov, *Fluorinated Heterocyclic Compounds: Synthesis Chemistry, and Applications*, Wiley, Hoboken, **2009**; b) P. Kirsch, *Modern Fluoroorganic Chemistry*, Wiley-VCH, Weinheim, **2004**; c) "Biomedical Frontiers of Fluorine Chemistry": I. Ojima, J. R. MacCarthy, J. T. Welch, *ACS Symp. Ser.* **1996**, 0, 0; d) R. Filler, Y. Kobayashi, L. M. Yagupolskii, *Organofluorine Compounds in Medicinal Chemistry and Bio medical Applications*, Elsevier, Amsterdam, **1993**; e) J. T. Welch, S. Eswarakrishnan, *Fluorine in Bioorganic Chemistry*, Wiley, New York, **1991**; f) R. Filler, Y. Kobayashi, *Biomedical Aspects of Fluorine Chemistry*, Elsevier Biomedical Press and Kodansya Ltd, Amsterdam, **1982**; g) V. M. Muzalevskiy, A. V. Shastin, E. S. Balenkova, G. Haufe, V. G. Nenajdenko, *Synthesis* **2009**, 3905–3929; h) A. W. Erian, *J. Heterocycl. Chem.* **2001**, 38, 793–808; i) P. Lin, J. Jiang, *Tetrahedron* **2000**, 56, 3635–3671; j) M. J. Silvester, *Adv. Heterocycl. Chem.* **1994**, 59, 1–38; k) J. T. Welch, *Tetrahedron* **1987**, 43, 3123–3197.
- [4] K. Matoba, H. Kawai, T. Furukawa, A. Kusuda, E. Tokunaga, S. Nakamura, M. Shiro, N. Shibata, *Angew. Chem.* **2010**, 122, 5898–5902; *Angew. Chem. Int. Ed.* **2010**, 49, 5762–5766.
- [5] H. Kawai, K. Tachi, E. Tokunaga, M. Shiro, N. Shibata, *Angew. Chem.* **2011**, 123, 7949–7952; *Angew. Chem. Int. Ed.* **2011**, 50, 7803–7806.
- [6] a) N. Shibata, H. Fujimoto, S. Mizuta, S. Ogawa, Y. Ishiuchi, S. Nakamura, T. Toru, *Synlett* **2006**, 3484–3488; b) S. Ogawa, N. Iida, E. Tokunaga, M. Shiro, N. Shibata, *Chem. Eur. J.* **2010**, 16, 7090–7095; c) S. Ogawa, T. Nishimine, E. Tokunaga, N. Shibata, *Synthesis* **2010**, 3274–3281; d) Y. Huang, E. Tokunaga, S. Suzuki, M. Shiro, N. Shibata, *Org. Lett.* **2010**, 12, 1136–1138.
- [7] a) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds* (Ed.: V. A. Soloshonok), Wiley, Chichester, **1999**; b) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, 108, PR1–PR43; c) N. Shibata, S. Mizuta, H. Kawai, *Tetrahedron: Asymmetry* **2008**, 19, 2633–2644; d) J. Nie, H.-C. Guo, D. Cahard, J.-A. Ma, *Chem. Rev.* **2011**, 111, 455–529.
- [8] a) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, 110, 402–415; *Angew. Chem. Int. Ed.* **1998**, 37, 388–401; b) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, 113, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, 40, 4591–4597; c) I. Denissova, L. Barriault, *Tetrahedron* **2003**, 59, 10105–10146; d) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396; e) P. G. Cozzi, R. Hilgraf, N. Zimmermann, *Eur. J. Org. Chem.* **2007**, 5969–5994.
- [9] a) G. N. Sammis, E. N. Jacobsen, *J. Am. Chem. Soc.* **2003**, 125, 4442–4443; b) G. N. Sammis, H. Danjo, E. N. Jacobsen, *J. Am. Chem. Soc.* **2004**, 126, 9928–9929; c) T. Mita, K. Sasaki, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2005**, 127, 514–515; d) C. Mazet, E. N. Jacobsen, *Angew. Chem.* **2008**, 120, 1786–1789; *Angew. Chem. Int. Ed.* **2008**, 47, 1762–1765; e) I. Fujimori, T. Mita, K. Maki, M. Shiro, A. Sato, S. Furusho, M. Kanai, M. Shibasaki, *Tetrahedron* **2007**, 63, 5820–5831; f) Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2008**, 130, 6072–6073; g) J. Wang, W. Li, Y. Liu, Y. Chu, L. Lin, X. Liu, X. Feng, *Org. Lett.* **2010**, 12, 1280–1283; h) P. Bernal, R. Fernández, J. Lassaletta, *Chem. Eur. J.* **2010**, 16, 7714–7718; i) N. Kurono, N. Nii, Y. Sakaguchi, M. Uemura, T. Ohkuma, *Angew. Chem.* **2011**, 123, 5655–5658; *Angew. Chem. Int. Ed.* **2011**, 50, 5541–5544; j) B. A. Provencher, K. J. Bartelson, Y. Liu, B. M. Foxman, L. Deng, *Angew. Chem.* **2011**, 123, 10753–10757; *Angew. Chem. Int. Ed.* **2011**, 50, 10565–10569.
- [10] a) L. Bernandi, F. Fini, M. Fochi, A. Ricci, *Synlett* **2008**, 1857–1861; b) Y. Tanaka, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2010**, 132, 8862–8863.
- [11] a) *Cinchona Alkaloids in Synthesis & Catalysis: Ligands, Immobilization and Organocatalysis*, (Ed.: C. E. Song), Wiley-VCH, Weinheim, **2009**; b) E. M. O. Yeboah, S. O. Yeboah, G. S. Singh, *Tetrahedron* **2011**, 67, 1725–1762.
- [12] Although the reason of failure of the hydroxy cinchona derivative **5a** in promoting enantioselectivity remains obscure, we propose that there is a reaction between the OH moiety and acetone cyanohydrin based on the <sup>1</sup>H NMR experiments. The <sup>1</sup>H NMR spectra of OH-protected cinchona derivative **5c** in CDCl<sub>3</sub> do not indicate any major change to the catalyst after addition of acetone cyanohydrin. In contrast, there are differences observed in the <sup>1</sup>H NMR spectrum of **5a** compared to that of **5a**/acetone cyanohydrin. These results indicate that **5a** in the presence of acetone cyanohydrin might exist as an equilibrium mixture of the OH form and an unstable cyanomethyl ether form, which interrupts the catalysis of the **5a**.
- [13] This behavior is related to the nature of the base, not to its amount. When a stoichiometric amount of Cs<sub>2</sub>CO<sub>3</sub> was used, a similarly high enantioselectivity of **4a** was observed with a slightly lower yield (*i*Pr<sub>2</sub>O, 0 °C, 18 h, 67%, 90% *ee*). In contrast, the reaction using NaCN (3.0 equiv) instead of acetone cyanohydrin furnished the 1,2-addition product in 57% with 49% *ee* (THF, RT, 24 h). These results imply that the use of a strong base such as KOH or NaOEt (entries 7 and 8, Table 1) should provide a harder CN species than acetone cyanohydrin and results 1,2-addition.
- [14] Less than one month before the submission of this manuscript, an enantioselective conjugate addition of cyanide to β-aryl-β-trifluoromethyl aryl enones using hydroxy-type cinchona alkaloids appeared in SciFinder®. However, the catalyst activity and substrate generality were not satisfactory and only three substrates were examined. See, M. El Qacemi, H. Smits, J. Y. Cassayre, N. P. Mulholland, P. Renold, E. Godineau, T. Pitterna, WO 2011154555, **2011**.
- [15] CCDC 866122 (**41**) 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.