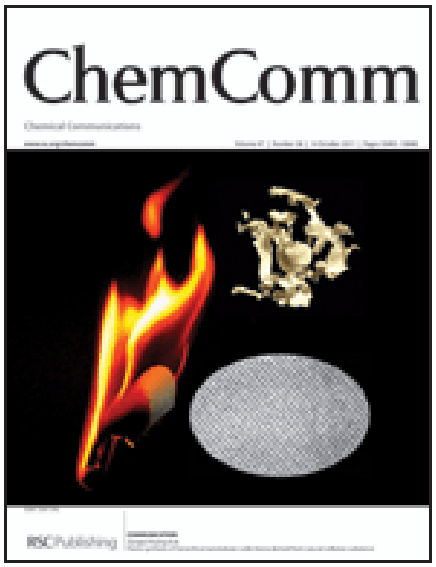

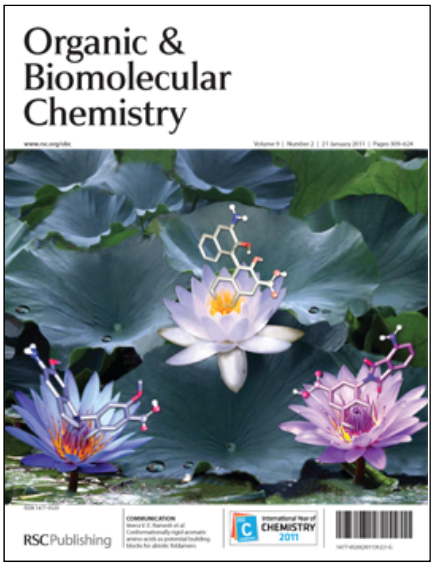

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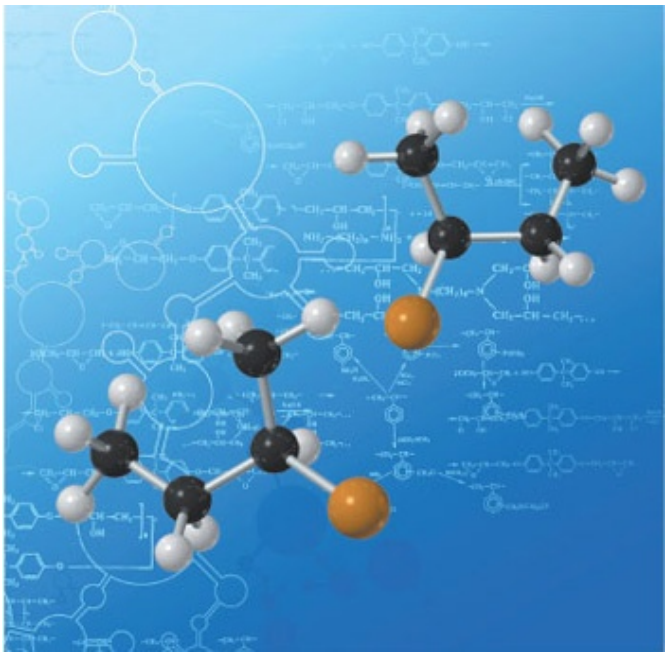

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COMMUNICATION

Partially saturated fluorinated heterocycles: diastereo- and enantioselective synthesis of β-trifluoromethyl-pyrroline carboxylates†‡

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The first asymmetric synthesis of β-trifluoromethylated pyrroline carboxylates has been achieved by organocatalytic conjugated addition of adamantyl glycine imine to β-trifluoromethylated enones, followed by a deprotection/cyclization/dehydration sequence.

Heterocycles constitute a major family of pharmaceuticals and agrochemicals with a very long history.[1] On the other hand, fluorinated organic compounds have recently emerged as the leading candidates in the future drug market, since adding fluorine or a fluorinated group to biologically active compounds can dramatically alter their metabolic stability, potency, or other properties of parent compounds.[2] In this context, heterocyclic compounds with fluorine are becoming modern attractive targets in the field of medicinal chemistry.[3] Although the aromatic heterocycles are a well-known group of heterocycles, we are interested in the partially saturated fluorinated heterocyclic compounds. Fig. 1 shows selected examples of fluorinated aromatic heterocycles **1** (X=O, isoxazole; X=NH, pyrazole; X=CH_2, 2*H*-pyrrole) and their partially saturated variants **2** (X=O, isoxazoline; X=NH, pyrazoline; X=CH_2, pyrroline).[4] The most obvious aspect that differentiates **2** from **1** is the existence of chirality in its cyclic framework. The chiral drug industry has soared in recent years as a result of leading progress in asymmetric synthesis;[5] thus the partially saturated fluorinated heterocycles containing chiral center(s) are very attractive. Indeed, a series of partially saturated five-membered fluorinated heterocycles **2** has been recognized as an important class of compounds with remarkable biological activities and thus a large number of compounds **2** have been registered in databases.[4]

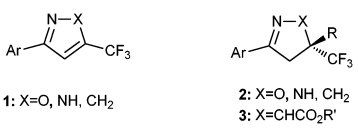
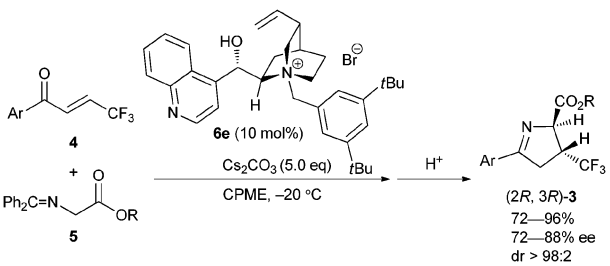


Fig. 1 While aromatic fluorinated heterocycles **1** do not have chirality, their partially saturated variants **2** and **3** have chiral center(s).

We recently reported the catalytic asymmetric synthesis of biologically important 5-trifluoromethyl-2-isoxazolines **2** (X=O) using chiral ammonium salts of *Cinchona* alkaloids.[6] An expeditious synthesis of **2** (X=O) based on the direct introduction of a trifluoromethyl group into aromatic isoxazoles was also disclosed.[7] As part of our ongoing research programs directed at the development of efficient methodologies for the construction of trifluoromethylated heterocycles,[8] we targeted β-trifluoromethyl pyrroline carboxylates **3** (X=$CHCO_2R'$) due to their potential attractiveness as drug candidates as they have two contiguous asymmetric centers. We disclose herein the first diastereo- and enantioselective synthesis of β-trifluoromethylated pyrroline carboxylates *via* organocatalytic conjugated addition of a glycinate Schiff base **5** to β-trifluoromethylated enones **4** by a phase-transfer catalyst derived from *Cinchona* alkaloids, followed by a deprotection/cyclization/dehydration sequence in excellent yields, excellent diastereoselectivities and high enantioselectivities (Scheme 1).

β-Trifluoromethylated α,β-unsaturated carbonyl compounds **4** are used as potential building blocks for construction of a stereogenic C–CF_3 center.[9] Billard and co-workers reported the racemic synthesis of β-trifluoromethylated pyrroline carboxylates **3** in good yields.[10] However, the diastereoselectivity was moderate and the asymmetric synthesis of **3** has not yet been reported. To achieve the asymmetric variant of Billard's methodology, we initiated our examination of the organocatalytic asymmetric conjugated addition of glycinate Schiff base **5** onto β-trifluoromethylated enones **4**. In recent years, enantioselective



Scheme 1 Asymmetric organocatalytic synthesis of β-trifluoromethylated pyrroline carboxylates **3**.

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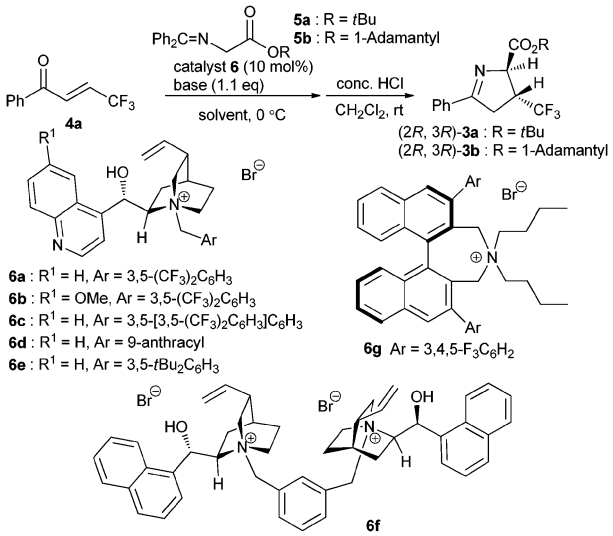
1,4-addition of glycinate Schiff base **5** to unsubstituted α,β-unsaturated carbonyl compounds to construct a single asymmetric center has been well examined.[11] However, the enantioselective 1,4-addition of **5** to β-substituted α,β-unsaturated carbonyl compounds for construction of two contiguous asymmetric centers is a challenge.[12] Kobayashi and co-workers reported the catalytic asymmetric 1,4-addition reactions of **5** to β-substituted α,β-unsaturated acrylates using Ca–Box catalysts prepared from calcium alkoxides and methylene bridged Box ligands in 22–82% de with 81–99% ee.[12a] Very recently, the catalytic asymmetric 1,4-addition reaction of **5** to chalcones catalyzed by chiral pentanidium salts to provide adducts with excellent enantioselectivities and diastereoselectivities was disclosed by Tan and co-workers.[12b] We started our investigation with the reaction of (*E*)-4,4,4-trifluoro-1-phenylbut-2-en-1-one (**4a**) with a *tert*-butyl glycinate-benzophenone Schiff base (**5a**) in the presence of 50% KOH aq., and screened a more readily available catalyst, and chiral quaternary ammonium phase transfer catalysts (Table 1). We first attempted the reaction in the presence of a catalytic amount of *N*-3,5-bis(trifluoromethylbenzyl) cinchoninium bromide (**6a**) as a chiral phase transfer catalyst in toluene at 0 °C. Although the β-trifluoromethylated pyrroline **3a** was obtained in 88% yield with a low ee (38%), excellent diastereoselectivity was observed (entry 1). The quinidine derivative **6b** gave a slightly lower ee value of 36% (entry 2). After screening several phase-transfer catalysts derived from cinchonine **6c–6f** (entries 3–6), catalyst **6e**, having a sterically demanding *t*Bu group, was found to be the most effective catalyst providing **3a** in high yield (90%) with 55% ee (entry 5). We next attempted the reaction using commercially available Maruoka catalyst **6g**; however, no improvement was observed (entry 7). We then examined the effect of bases (entries 8–15), and Cs_2CO_3 was found to be most effective in terms of enantioselectivity (71% ee, entry 10). We continued the survey of reaction conditions (entry 16–20), and a slightly better result was obtained using cyclopentyl methyl ether, CPME, as the solvent (entry 20, 96%, 72% ee). We next turned our attention to the glycinate Schiff base **5**. Steric bulkiness of **5** was necessary for achieving high enantiocontrol, and ee's up to 82% of **3b** were obtained when 1-adamantyl glycinate-benzophenone Schiff base (**5b**) was used (entry 21, 75%, 82% ee). The best result was obtained when the reaction was carried out at −20 °C in the presence of 5.0 equiv. of Cs_2CO_3 (entry 22, 95%, 86% ee). An excellent diastereoselectivity of >95/5 was observed in all cases.

With optimal conditions in hand, the scope of the conjugated addition of glycinate Schiff base **5b** to β-trifluoromethylated enones **4** catalyzed by *Cinchona* phase-transfer catalyst **6e**, followed by a deprotection/cyclization/dehydration sequence was explored with a variety of substrates selected in order to establish the generality of the process, all affording excellent yields, excellent *anti*-diastereoselectivities, and high enantioselectivities (Table 2). A series of β-trifluoromethylated enone derivatives **4c–4i** with a variety of substituents on their aromatic rings, such as methyl, methoxy, fluoro, chloro, bromo, and nitro, were nicely converted to **3c–3i** in excellent yields with excellent diastereoselectivities of >98/2 and high enantioselectivities of 77–88% ee (entries 1–8). Sterically demanding naphthyl substituted enone **4j** was also compatible, although the enantioselectivities were somewhat low, affording product **3j** in 97% yield with an ee value of 72% (entry 9). The heteroaromatic substrate **4k** bearing a furanyl group was also a suitable substrate for this transformation, providing the desired product **3k** in 96% yield with 80% ee (entry 10). *Anti*-**3** was obtained exclusively in all the cases and the absolute stereochemistry of *anti*-**3b** was determined after derivatization to its methylester (Fig. S1, ESI‡).[13] All the other products **3** were tentatively assigned by analogy.

In summary, we have developed the first asymmetric synthesis of biologically attractive β-trifluoromethyl pyrroline carboxylates **3** containing two contiguous asymmetric centers in excellent yields with excellent *anti*-diastereoselectivities and high enantioselectivities using the *Cinchona* alkaloid-catalyzed conjugated addition of a glycinate Schiff base to β-trifluoromethylated enones, followed by a deprotection/cyclization/dehydration sequence. It should be noted

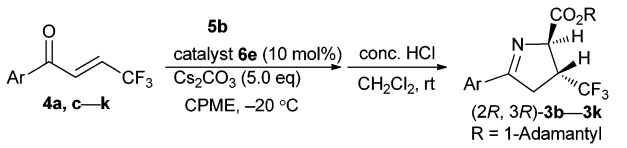
Table 1 Optimization of reaction conditions



Entry[a]	5	6	Base	Solvent	Time/h	Yield[b] (%)	ee[c] (%)
1	**5a**	**6a**	50% KOH aq.	Toluene	1	88	38
2	**5a**	**6b**	50% KOH aq.	Toluene	1	95	36
3	**5a**	**6c**	50% KOH aq.	Toluene	2	97	39
4	**5a**	**6d**	50% KOH aq.	Toluene	2	97	14
5	**5a**	**6e**	50% KOH aq.	Toluene	2	90	55
6	**5a**	**6f**	50% KOH aq.	Toluene	2	95	0
7	**5a**	**6g**	50% KOH aq.	Toluene	2	90	35
8	**5a**	**6e**	Na_2CO_3	Toluene	62	84	68
9	**5a**	**6e**	K_2CO_3	Toluene	53	76	69
10	**5a**	**6e**	Cs_2CO_3	Toluene	12	82	71
11	**5a**	**6e**	K_3PO_4	Toluene	12	70	70
12	**5a**	**6e**	*t*BuOK	Toluene	3	59	27
13	**5a**	**6e**	NaOMe	Toluene	2	86	51
14	**5a**	**6e**	Me_4NF	Toluene	2	86	39
15	**5a**	**6e**	CsF	Toluene	24	83	60
16	**5a**	**6e**	Cs_2CO_3	Mesitylene	40	95	66
17	**5a**	**6e**	Cs_2CO_3	CH_2Cl_2	12	86	25
18	**5a**	**6e**	Cs_2CO_3	THF	12	90	66
19	**5a**	**6e**	Cs_2CO_3	Et_2O	4	97	68
20	**5a**	**6e**	Cs_2CO_3	CPME	4	96	72
21	**5b**	**6e**	Cs_2CO_3	CPME	5	75	82
22[d]	**5b**	**6e**	Cs_2CO_3	CPME	9	95	86

[a] The reaction of **4a** with **5** (1.1 equiv.) was carried out in the presence of a catalyst (10 mol%) and a base in solvent at 0 °C, unless otherwise noted. [b] Isolated yield. [c] ee's were determined by chiral HPLC. [d] The reaction was carried out at −20 °C in the presence of 5.0 equiv. of Cs_2CO_3.

Table 2 Asymmetric synthesis of β-trifluoromethylated pyrroline **3**



Entry[a]	4	Ar	3	Time/h	Yield[b] (%)	dr	ee[c] (%)
1	**4a**	Ph	**3b**	9	95	98 : 2	86
2	**4c**	3-MeC_6H_4	**3c**	36	72	99 : 1	84
3	**4d**	4-MeC_6H_4	**3d**	12	95	99 : 1	87
4	**4e**	3-$MeOC_6H_4$	**3e**	36	74	98 : 2	84
5	**4f**	4-$MeOC_6H_4$	**3f**	12	94	99 : 1	88
6	**4g**	4-FC_6H_4	**3g**	15	94	99 : 1	84
7	**4h**	4-ClC_6H_4	**3h**	15	93	99 : 1	78
8	**4i**	4-BrC_6H_4	**3i**	15	96	99 : 1	77
9	**4j**	2-Naphthyl	**3j**	14	81	98 : 2	72
10	**4k**	2-Furanyl	**3k**	16	96	99 : 1	80

[a] The reaction of **4** with **5b** (1.1 equiv.) was carried out in the presence of **6e** (10 mol%) and Cs_2CO_3 (5.0 equiv.) in CPME at −20 °C. [b] Isolated yield. [c] ee's were determined by chiral HPLC.

that the combination of the new bulky adamantyl glycinate and CPME[14] solvent introduced asymmetry into the Billard chemistry,[10] with especially good diastereocontrol. The adamantyl ester would provide an attractive alternative to the analogous methyl, *tert*-butyl, or cumyl esters.[15] The use of CPME should be advantageous for industrial use due to the high stability, wide liquidity range, low heat of vaporization, resistance to peroxide formation and narrow explosion area.[14]

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