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Practical synthesis of 4,4,4-trifluorocrotonaldehyde: a versatile precursor for the enantioselective formation of trifluoromethylated stereogenic centers *via* organocatalytic 1,4-additions†

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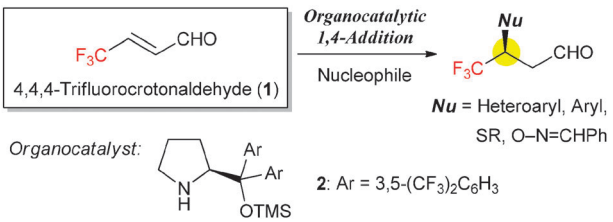
The practical synthesis of 4,4,4-trifluorocrotonaldehyde (1) and its application to enantioselective 1,4-additions are described. The organocatalytic 1,4-addition of 1 with several nucleophiles such as heteroaromatics, alkylthiols and aldoximes afforded the corresponding products, each bearing a trifluoromethylated stereogenic center with high optical purity. A resulting product was converted into an MAO-A inhibitor, befloxatone.

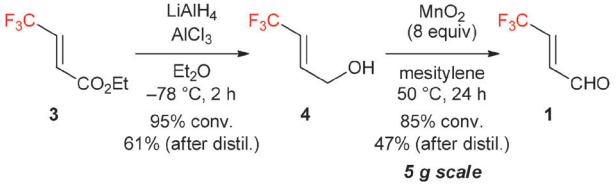
Incorporation of perfluoroalkyl substituents into organic molecules is a highly valuable process in pharmaceutical, agrochemical and material sciences. In particular, introduction of a trifluoromethyl (CF_3) group into biologically active compounds often modifies their physical and/or biological properties such as lipophilicity, metabolic stability, and bioavailability.[1] Although a large number of pharmaceuticals contain the CF_3 group(s), developing flexible methods for the highly enantioselective construction of trifluoromethylated stereogenic centers remains a challenging task. Trifluoromethylated chiral carbon centers are mostly constructed by either of these approaches: (i) asymmetric direct trifluoromethylation of a prochiral carbon; (ii) asymmetric functionalization of a trifluoromethylated prochiral carbon. Although the former approach is simpler and straightforward, only a few catalytic methods that provide high enantioselectivity are known.[2] Therefore, the latter approach, the so-called building block approach, has often been adopted to obtain a chiral center bearing a CF_3 moiety, mainly by using trifluoromethyl ketones, trifluoroacetaldehyde, trifluoropyruvates or their derivatives as precursors.[3] Intrigued by the fact that 4,4,4-trifluorocrotonates are simple building blocks of various trifluoromethyl compounds, some research groups, including our group, have applied them to asymmetric transformations.[4] During the course of our continuous research in this direction, we envisaged that 4,4,4-trifluorocrotonaldehyde (**1**) would be a versatile precursor for the construction of trifluoromethylated stereogenic centers (Scheme 1). However, to the best of our knowledge,



Scheme 1 Synthetic strategy.

there are only four reports on the synthesis of **1**,[5] but no report on the isolation of this compound or its use in enantioselective transformations, although α,β-enals have been widely used as precursors in numerous organocatalytic asymmetric transformations.[6] One possible reason for this is the high volatility of **1** and the consequent difficulty in its purification. In the present research, we successfully isolated **1** for the first time and applied it to enantioselective 1,4-addition with several nucleophiles in the presence of the Jørgensen–Hayashi-type prolinol ether catalyst **2**.[7]

We first focused on the development of an efficient method for the synthesis of **1**. Since **1** is highly volatile, we decided to avoid the use of liquid–liquid extraction and column chromatography for the isolation and purification of this compound. Thus, we planned to synthesize **1** by the oxidation of 4,4,4-trifluoro-2-butenol (**4**) with manganese dioxide, which can be removed from the reaction system by a simple filtration process. First, **4** was synthesized in 61% yield by the reduction of ethyl 4,4,4-trifluorocrotonate (**3**) with lithium aluminum hydride and aluminum trichloride.[8] Fortunately, the manganese dioxide oxidation of **4** proceeded smoothly to afford the desired product with high conversion (85%, determined by ^{1}H NMR analysis using an internal standard). After the removal of manganese dioxide by filtration, the filtrate was distilled to afford nearly pure **1** (98% purity) in 47% yield on a 5 g scale (Scheme 2).



Scheme 2 Synthesis of 4,4,4-trifluorocrotonaldehyde.

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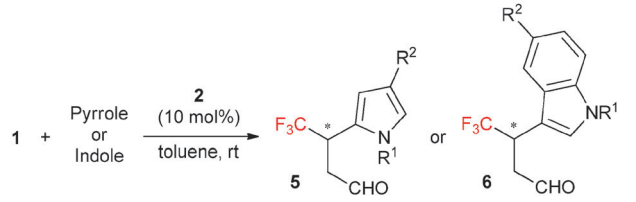
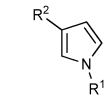
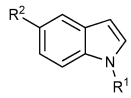
† Electronic supplementary information (ESI) available: Experimental procedures and characterization of all new compounds. See DOI: 10.1039/c2cc32757k

Table 1 Enantioselective Friedel–Crafts arylation of **1**[a]

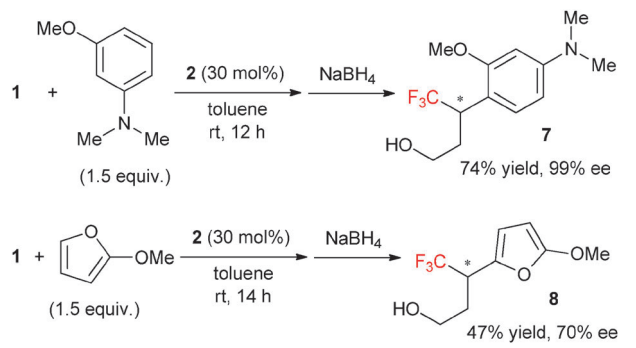


Entry	Pyrrole or indole	R^1	R^2	Product	Time/h	Yield[b] (%)	ee[c] (%)
1		H	H	**5a**	10	92	96
2[d]					4	92	93
3		Me	H	**5b**	12	96	97
4		Bn	H	**5c**	16	85	99
5[e]		H	Me	**5d**	11	61	80
6		H	H	**6a**	12	98	90
7		Me	H	**6b**	14	83	97
8		H	OMe	**6c**	13	71	93

[a] All reactions were carried out using 1.5 equiv. pyrrole or indole in the presence of 10 mol% of **2**. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether was used instead of **2**. [e] The product was obtained as a mixture of 2,4- and 2,3-disubstituted forms.

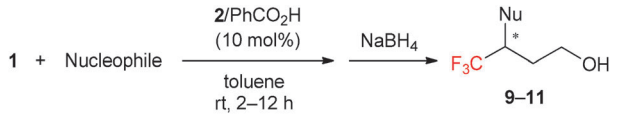
With the method for the practical synthesis of **1** in hand, we attempted the enantioselective transformation of **1**. First, organocatalytic Friedel–Crafts arylation of **1** was carried out with pyrroles and indoles as the nucleophiles.[9] The reaction of an unprotected pyrrole with **1** in the presence of 10 mol% **2** afforded the corresponding 2-substituted pyrrole **5a** in 96% ee (Table 1, entry 1).[10] High enantioselectivity was also observed when *N*-substituted pyrroles were used (97% and 99% ee, entries 3 and 4). The reaction of 3-methylpyrrole with **1** afforded the corresponding 2,4-disubstituted product **5d** in 61% yield with good enantioselectivity, along with a 2,3-disubstituted product in 25% yield (entry 5). When indoles were employed, the corresponding 3-substituted indoles **6** were obtained with high enantioselectivities, irrespective of the substituent on the indole ring (entries 6–8). We also examined the use of other electron-rich aromatic compounds. The reaction with 3-methoxy-*N*,*N*-dimethylaniline[11] afforded the desired compound **7** with 99% ee. On the other hand, the reaction with 2-methoxyfuran afforded the corresponding product **8** with 70% ee (Scheme 3).

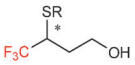
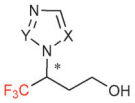
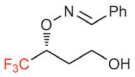
We next attempted the enantioselective Michael addition of **1** with heteroatom nucleophiles. As per the reported procedure,[12]



Scheme 3 Enantioselective Friedel–Crafts arylation of **1** with electron-rich aromatic compounds.

Table 2 Enantioselective Michael addition of heteroatom nucleophiles[a]



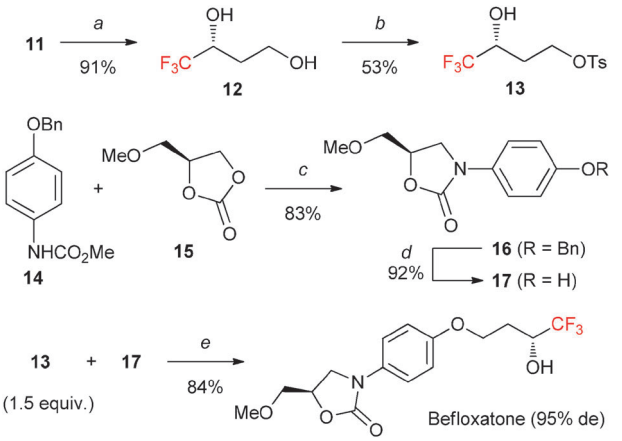
Entry	Nucleophile	Product		Yield[b] (%)	ee[c] (%)
1	RSH		**9a**: R = Ph	97	94
2[d]			**9a**	92	90
3			**9b**: R = CH_2Ph	98	95
4			**9c**: R = *c*-Hex	99	96
5			**9d**: R = *n*-Bu	93	93
6			**9e**: R = CH_2CO_2Et	87	92
7[e]	1,2,4-Triazole		**10a**: X = N Y = CH	77	86
8[e]	1,2,3-Triazole		**10b**: X = CH Y = N	74	83
9[f,g]	PhCH=N–OH		**11**	73	95

[a] All reactions were carried out using 1.5 equiv. of **1** (based on the nucleophile) in the presence of 10 mol% **2** and benzoic acid, unless otherwise noted. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] α,α-Diphenyl-2-pyrrolidinemethanol trimethylsilyl ether was used instead of **2**. [e] Reaction was carried out at −20 °C for 40 h with 20 mol% of **2** and benzoic acid. [f] *ent*-**2** was used instead of **2**. [g] Reaction was carried out using 3 equiv. of aldoxime (based on **1**).

1 was allowed to react with several nucleophiles in the presence of 10–20 mol% **2** and benzoic acid (Table 2). The reaction of **1** with alkylthiols proceeded smoothly to yield the corresponding adducts, which were subsequently reduced to the primary alcohols **9** in good yields. The optical purity of **9** was found to be 92–96% ee (entries 1, 3–6). The reactions of **1** with triazoles also afforded the corresponding adducts with good enantioselectivities (entries 7 and 8). Unfortunately, the reactions with succinimide and *N*-methoxycarbamates were not productive. Furthermore, the oxa-Michael reaction of **1** was carried out using benzaldehyde oxime as the nucleophile (entry 9). The reaction yielded the corresponding β-oxime ether with good conversion, which was isolated after reduction to **11** (73% yield, 95% ee).

Finally, we demonstrated the asymmetric synthesis of a reversible monoamine oxidase A (MAO-A) inhibitor, befloxatone,[13] using a literature procedure (Scheme 4).[13e] First, 4,4,4-trifluorobutane-1,3-diol **12** was synthesized by palladium-catalyzed hydrogenolysis of **11**.[14,15] Selective tosylation of the primary alcohol in **12** afforded tosylate **13** in 53% yield. Next, oxazolidinone **17** was synthesized. Carbamate **14** was prepared by the treatment of 4-benzyloxyaniline with methyl chloroformate. Subsequent condensation with commercially available (*S*)-4-methoxymethyl-1,3-dioxolane-2-one (**15**) in the presence of K_2CO_3 afforded **16** in 83% yield.[16] Then, deprotection of **16** by palladium-catalyzed hydrogenolysis yielded oxazolidinone **17**. Finally, etherification of **17** with **13** yielded befloxatone in 84% yield with 95% de, as shown in Scheme 4.

In conclusion, we developed a practical synthetic route to 4,4,4-trifluorocrotonaldehyde (**1**), which is a versatile precursor for organocatalytic enantioselective 1,4-additions. Reactions with



Scheme 4 Asymmetric synthesis of befloxatone. Reaction conditions: (a) $Pd(OH)_2$ (20 mol% Pd), MeOH, H_2, rt, 3 h; (b) TsCl (1.5 equiv.), pyridine, rt, 24 h; (c) K_2CO_3 (3 equiv.), DMF, reflux, 3 h; (d) Pd/C (10 mol% Pd), MeOH, H_2 (1 atm), rt, 3 h; (e) K_2CO_3 (2 equiv.), DMF, 85 °C, 6 h.

various nucleophiles such as alkylthiols, pyrroles, indoles, triazoles, and aldoximes afforded a variety of trifluoromethylated chiral stereogenic centers in a highly enantioselective manner. We also demonstrated the application of this method to the asymmetric synthesis of an MAO-A inhibitor, befloxatone.

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