Highly Stereoselective Asymmetric Michael Addition Reactions Employing (*R;E*)-3,3,3-Trifluoroprop-1-enyl *p*-Tolyl Sulphoxide[1]

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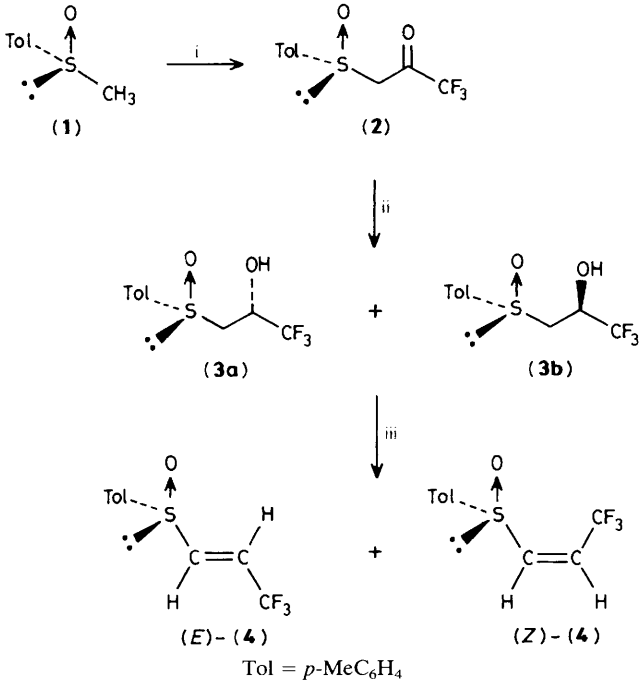
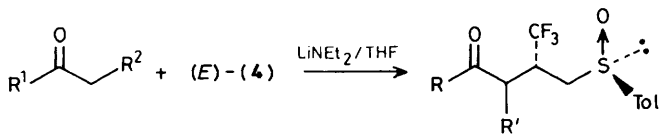
(*R;E*)-3,3,3-Trifluoroprop-1-enyl *p*-tolyl sulphoxide, prepared in three steps from ethyl trifluoroacetate, showed a high degree of diastereoselectivity in Michael addition reactions with enolates; by this means, optically active trifluoromethylated organic molecules can be obtained readily in high yield as well as in high optical purity.

General methods for preparing optically active compounds containing a trifluoromethyl (CF_3) group have not been established yet, although considerable attention has been paid to molecules containing this moiety; such compounds are of increasing importance in view of their biological activity.[2] Our strategy has been to create chiral building blocks containing this group as well as adequate functionalities for the assembly of complex molecules; stereoselective preparation is often difficult by conventional methods.[3] We have previously demonstrated the remarkable capability of racemic 3,3,3-trifluoroprop-1-enyl phenyl sulphoxide as a Michael acceptor; the adducts were found to possess a high diastereoisomeric excess (d.e. 70 to >94%).[4] In the light of these results, we considered that the introduction of an optically pure sulphoxide group[5] would afford organic molecules with high enantiomeric excess (e.e.) at the carbon atom bearing the CF_3 group. Here we report the synthesis of (*R;E*)-3,3,3-trifluoroprop-1-enyl *p*-tolyl sulphoxide (**4**) and its reaction with enolates. We also describe the determination of the absolute configuration of the Michael adducts obtained; there are very few cases in which absolute configurations of such compounds have been determined.[6]

By use of (*R*)-*p*-tolyl methyl sulphoxide (**1**),[7] prepared from methylmagnesium bromide and (−)-menthyl (*S*)-toluene-*p*-sulphinate,[8] compound (**4**) was synthesized in 70% yield in three steps, basically by the same route as for the racemic material[4] (Scheme 1). Thus, the reaction of the lithiated sulphoxide from (**1**) and ethyl trifluoroacetate at −78 °C provided the oxosulphoxide (**2**),[9] which was then reduced to yield the diastereoisomeric mixture of hydroxy derivatives (**3a** and **b**). The stereochemistry at CCF_3 for the alcohol (**3b**) was established as *R* by the transformation into (*E*)-4-phenyl-



Scheme 1. *Reagents*: i, (1) $LiNPr^i_2$ (1.1 equiv.), tetrahydrofuran (THF), 0 °C; (2) CF_3CO_2Et (1.3 equiv.), THF, −78 °C (inverse addition) (90%); (ii) $NaBH_4$ (1.3 equiv), EtOH, 0 °C (87%; 34 : 66 diastereoisomer ratio); iii (1) CH_3SO_2Cl (1.5 equiv.), Et_3NCH_2PhCl (5 mol %), aqueous 30% NaOH, 0 °C, (2) warm to room temp. (89%; 96 : 4 *E* : *Z* mixture)



Scheme 2

Table 1. Specific rotations for compounds (1)—(4).

Compound	$[\alpha]_D$ (c, solvent)
(1)	+186.6° (1.02, $CHCl_3$)[a]
(2)	+181.5° (1.02, Me_2CO)
(3a)	+257.6° (1.00, $CHCl_3$)
(3b)	+199.1° (1.00, $CHCl_3$)
(*E*)-(4)	+504.2° (1.00, $CHCl_3$)
(*Z*)-(4)	−191.1° (1.00, $CHCl_3$)

[a] 99.1% e.e. by its optical rotation.

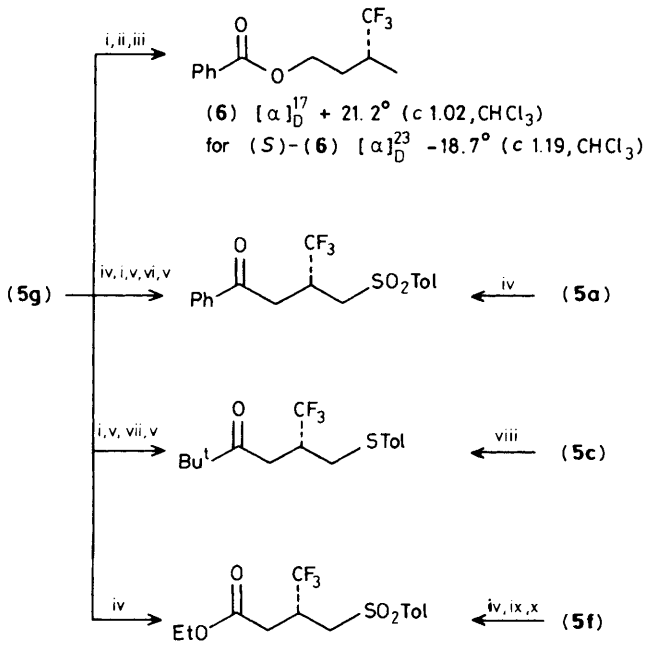
1,1,1-trifluorobut-3-en-2-ol† and comparison of its specific rotation with that of an authentic sample.[10] The dehydration[11] of (**3a**) and (**3b**) furnished (*E*)- and (*Z*)-(**4**) in the ratio 96 : 4, the former being found to possess 96.8% enantiomeric excess at the chiral sulphur atom by h.p.l.c. analysis (Chiralcel OB from Daicel Chemical Industries, Ltd.).

This optically active vinylic sulphoxide (*E*)-(**4**) was then subjected to Michael addition with enolates derived from esters or ketones. The results are summarized in Table 2. In every case, a high degree of diasteroselectivity was confirmed by h.p.l.c. and/or ^{19}F n.m.r. analysis of the adducts (**5**), and the optical antipode at CCF_3 was readily synthesized by the same route from (*Z*)-(**4**). Thus, (**5a**) and (**5b**) were oxidized to sulphones with optical rotations −67.6° and +78.1°, respectively.

To demonstrate the optical purities of the Michael adducts, although the d.e. values in Table 1 might be almost equal to the values for e.e. at CCF_3 because the sulphoxide chirality is known to be stable under these conditions, (**5a**) and (**5b**) were independently converted into the corresponding (−)-MTPA esters [MTPA = methoxy(trifluoroacetyl)phenylacetyl] by oxidation (*m*-$ClC_6H_4CO_3H$) and sodium borohydride reduction (*ca.* 1 : 1 diastereoisomer mixture), followed by acylation with (−)-MTPA–Cl.[12] ^{19}F N.m.r. measurements of each Mosher ester mixture showed two different kinds of doublet peaks, whereas the mixed sample gave four sets of doublets, one doublet attributable to each CF_3 group originally in (**5a**) or (**5b**). These results unambiguously demonstrate the high diastereoselectivity of the Michael addition. Furthermore, the optical purities of (**5a**) and (**5b**) at CCF_3 may be interpreted, by simple calculation, as 91 and >95% e.e., respectively, since the starting vinylic sulphoxide possessed 96.8% e.e.

The absolute configurations of (**5a—g**) were assigned as outlined in Scheme 3. First, (**5g**) was converted into the known

† Compound (**3b**) was treated with (i) lithium di-isopropylamide (2.2 equiv.), (ii) benzyl bromide, and (iii) Ráney nickel to afford the desired compound in 58% total yield; specific rotation +18.5°. Since the authentic sample with *R* configuration showed +36.8° (93% enantiomeric excess determined by integration of ^{19}F n.m.r. peaks for the corresponding MTPA ester), (**3b**) was considered to possess the *R* configuration at CCF_3. The partial racemization was caused presumably by Raney nickel.



Scheme 3. *Reagents*: i, $LiAlH_4/Et_2O$; ii, PhCOCl, pyridine/CH_2Cl_2; iii Raney Ni, EtOH; iv, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2; v, Swern oxidation; vi, PhMgBr, Et_2O; vii, Bu^tMgCl, Et_2O; viii, Me_3SiCl-NaI/MeCN; ix, KOH, EtOH, reflux; x, 2-chloro-1-methylpyridinium iodide, EtOH, Et_3N, CH_2Cl_2.

Table 2. Reaction of (*E*)-(**4**) with enolates.

Compound	R^1	R^2	Yield (%)	% d.e.[a]	Config.[b]
(**5a**)	Ph	H	99	94	*R*
(**5b**)[c]	Ph	H	92	>98	*S*
(**5c**)	Bu^t	H	96	>98	*R*
(**5d**)[d]	Et	Me	86[e]	>98	
(**5e**)[d]				>98	
(**5f**)	OEt	CO_2Et	95	85	*R*
(**5g**)	OEt	H	95	>98	*R*

[a] Determined by h.p.l.c. and/or ^{19}F n.m.r. [b] At CCF_3. [c] (*Z*)-(**4**) was used instead of the *E*-isomer. [d] (**5d**) and (**5e**) were diastereoisomers that resulted from $-CH(CH_3)CH(CF_3)-$ in the ratio 73 : 27. [e] Combined yield of (**5d**) and (**5e**).

benzoate[13] (**6**) by (i) reduction with an excess of lithium aluminium hydride (LAH), (ii) benzoylation, and (iii) desulphurization with Raney nickel. Comparison of specific rotations enabled us to assign the *R* figuration at CCF_3. From stereochemical correlations with (**5g**) as outlined in Scheme 2, the products (**5a, c,** and **f**) were also found to be *R* at this site. For compounds (**5d** and **e**), although the relative configurations at CCH_3 and CCF_3 remain unknown, the latter is probably *R*, by analogy with the other examples.

In summary, asymmetric Michael addition with (*E*)-(**4**) readily provides a diastereoselective synthesis of CF_3-containing sulphoxides with other functionalities such as ketone or ester, in excellent yields. To the best of our knowledge[14] this is the first example of a highly efficient asymmetric synthesis involving a CF_3 group attached to the newly formed chiral centre. Synthetic applications of these chiral bifunctional compounds (**5**) are being studied.

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