

β-Trifluoromethyl-α,β-unsaturated Ketones

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Amparo Sanz-Marco was born in Valencia, Spain, in 1986. She obtained her B.Sc. and M.Sc. degrees in chemistry from the University of Valencia, where she is currently pursuing her Ph.D. under the supervision of Prof. José Ramón Pedro and Prof. Gonzalo Blay. She has carried out a pre-doctoral stay at Boston College, Massachusetts, USA, with Prof. James P. Morken. Her Ph.D. research is focused on asymmetric conjugate alkylation.

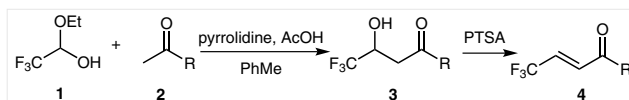


Introduction

β-Trifluoromethyl enones are important synthetic precursors of molecules containing chiral centers with a trifluoromethyl substituent, a structural motif which is present in biologically active compounds, chiral reagents and in materials for optoelectronic devices.¹ The presence of the strong electron-withdrawing β-trifluoromethyl group increases the electrophilicity of the double bond expediting the conjugate nucleophilic additions.

Preparation

β-Trifluoromethyl-α,β-unsaturated ketones can be prepared by different methods.² Among them, one of the most general applications is the aldol reaction of trifluoroacetaldehyde ethyl hemiacetal with a ketone followed by dehydration.

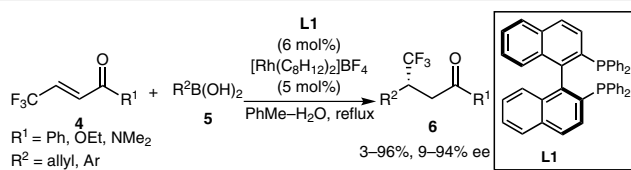


Scheme 1 Synthesis of β-Trifluoromethyl-α,β-unsaturated ketones

Table 1 Use of β-Trifluoromethyl-α,β-unsaturated Ketones

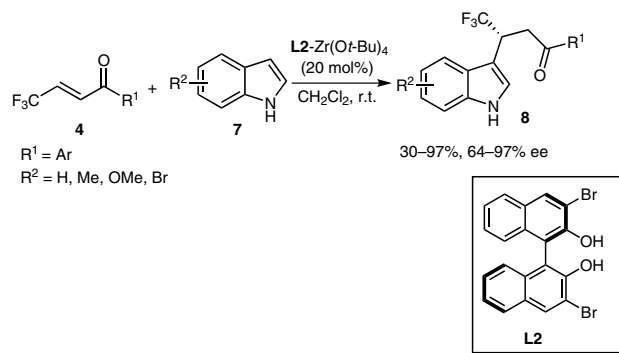
(A) Arylation

The enantioselective conjugate arylation of β-trifluoromethyl-α,β-unsaturated ketones was carried out by treatment with arylboronic acids **5** under catalysis with the Rh(I)-BINAP (**L1**) complex. The products **6** were obtained in high yields and enantioselectivities with a variety of arylboronic acids.³



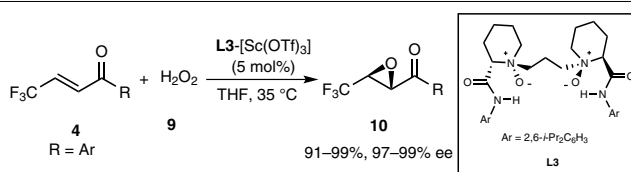
(B) Friedel–Crafts Alkylation

Pedro and co-workers reported the first example of enantioselective Friedel–Crafts alkylation of indoles **7** with β-trifluoromethyl-α,β-unsaturated ketones, using a chiral Zr(IV)-BINOL (**L2**) complex as catalyst. Functionalized indoles **8** bearing a stereogenic tertiary center attached to a trifluoromethyl group were afforded with good yields and high enantiomeric excesses.^{4a} A similar reaction was described later by Feng and co-workers using an yttrium(III) complex.^{4b}



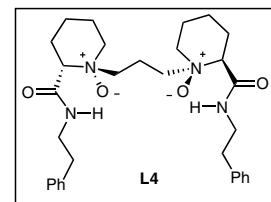
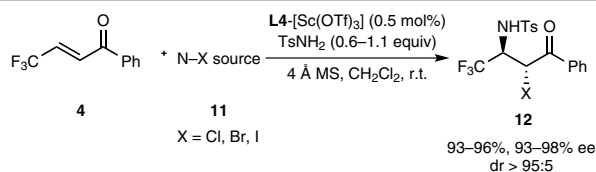
(C) Epoxidation

The asymmetric epoxidation of α,β-unsaturated carbonyl compounds using a chiral Sc(III)-N,N'-dioxide (**L3**) complex was achieved by Feng and co-workers. The authors describe several examples with β-trifluoromethyl-α,β-unsaturated ketones giving the corresponding epoxides **10** in excellent yields and enantioselectivities under mild conditions.⁵

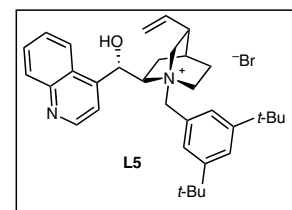
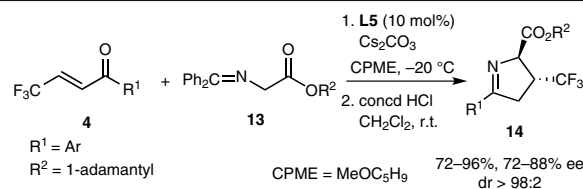


(D) Haloamination

The enantioselective haloamination of β -trifluoromethyl enones **4** was achieved upon treatment with TsNH₂ and the electrophilic halogen source **11** in the presence of a catalytic amount of a complex of Sc(OTf)₃ with the *N,N'*-dioxide ligand **L4**. NIS, NBS and TsNCl₂ were used as halogen sources to provide the desired haloaminated products **12** in excellent yields, diastereo- and enantioselectivities.⁶

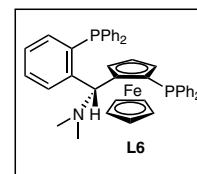
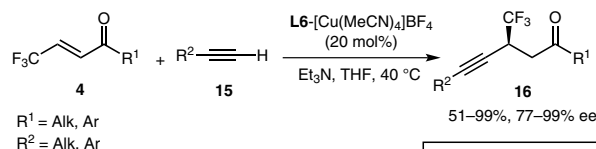
(E) Michael Addition: Synthesis of β -Trifluoromethyl-pyrroline Carboxylates

Shibata and co-workers carried out the conjugate addition of glycinyl imine **13** to **4** under PTC conditions with a cinchona alkaloid derived catalyst **L5**. Pyrroline carboxylates **14** were obtained with excellent yields, diastereo- and enantioselectivities after a deprotection–cyclization–dehydration sequence.^{7a} Enantioenriched β -trifluoromethyl pyrrolines were also obtained via organocatalytic conjugate addition of nitromethane to enones **4** followed by a nitroreduction–cyclization–dehydration sequence.^{7b}



(F) Alkynylation

The enantioselective conjugate addition of terminal alkynes **15** to β -trifluoromethyl- α,β -unsaturated ketones **4** catalyzed by a chiral Cu(I)–taniaphos (**L6**) complex afforded ketones bearing a trifluoromethylated propargylic chiral center in β -position. The alkynylation products **16** were obtained with good yields and high enantiomeric excesses. Iodocyclisation of **16** furnished access to 4-trifluoromethyl-4*H*-pyrans without any loss of optical purity.⁸



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