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Facile Synthesis of Trifluoromethyl Ketones by Palladium-Catalyzed Carroll Type Reaction

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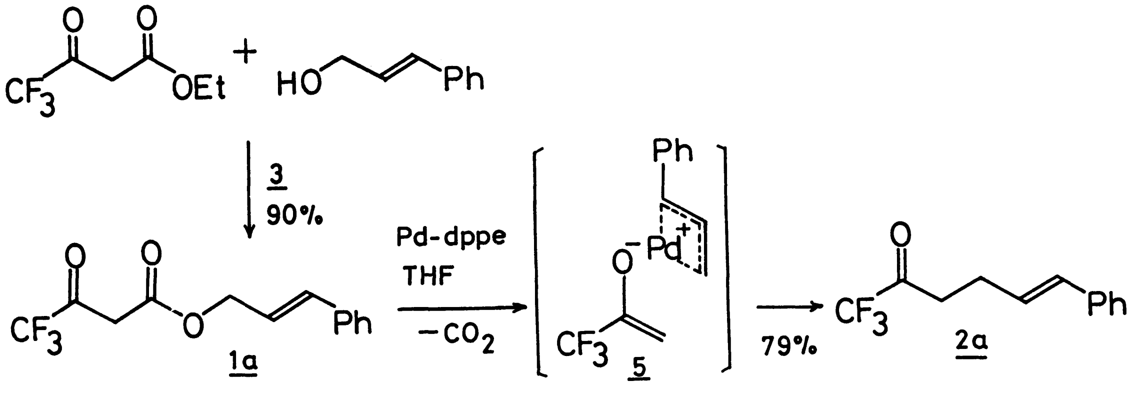
Distannoxane-catalyzed transesterification of ethyl 4,4,4-trifluoroacetoacetate with allylic alcohols gave the corresponding allylic esters, which were subjected to palladium-catalyzed decarboxylation-allylation to give trifluoromethyl ketones.

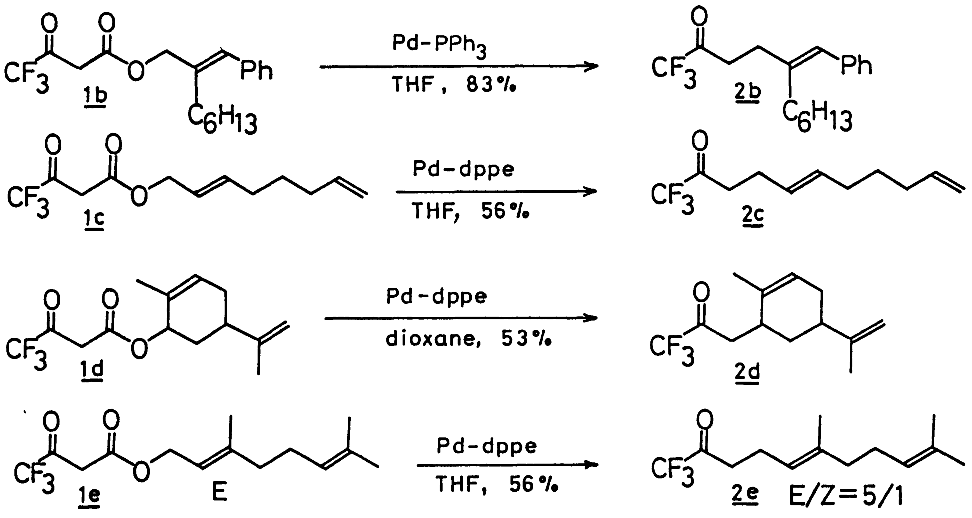
Trifluoromethyl ketones are known to have remarkable ability as enzyme inhibitors, and their preparation is of current interest.1),2) Camps reported that the thermal Carroll reaction of linalool and ethyl 4,4,4-trifluoroacetoacetate gave 1,1,1-trifluorogeranylacetone (2e) as an E and Z mixture in 84% yield.3) We have reported that decarboxylation-allylation of allylic esters of acetoacetic acid to give γ,δ-unsaturated methyl ketones is catalyzed by palladium compounds (the palladium-catalyzed Carroll type reaction), and the reaction proceeds under mild conditions.4) We wish report here a facile synthesis of the trifluoromethyl ketones by palladium-catalyzed Carroll type reaction of allylic ester of 4,4,4-trifluoroacetoacetic acid, which are prepared from ethyl 4,4,4-trifluoroacetoacetate by transesterification with distannoxane catalyst, SCN(n-Bu)$_2$Sn-O-Sn(n-Bu)$_2$OH (3) or Cl(n-Bu)$_2$Sn-O-Sn(n-Bu)$_2$OH (4).5)

Cinnamyl trifluoroacetoacetate (1a) was prepared by transesterification of ethyl 4,4,4-trifluoroacetoacetate with cinnamyl alcohol using 1 mol% of 3 in refluxing toluene in 90% yield. Other fluoro esters were also obtained in good yields (1b; 90%, 1c; 53%, 1d; 87%, 1e; 95%) by similar procedures using 3 or 4.



Scheme 1.

The palladium-catalyzed reaction of 1a was carried out in the presence of $Pd_2(dba)_3CHCl_3$ (2.5 mol%) and 1,2-bis(diphenylphosphino)ethane (dppe) (10 mol%) in refluxing THF to give the trifluoromethyl ketone 2a [IR (neat) 1757 cm^{-1}] in 79% yield after chromatographic purification on SiO_2. The reaction is considered to proceed via the π-allylpalladium enolate of trifluoroacetone 5. In a similar manner other esters 1b-e were also converted to the correponding trifluoromethyl ketones 2b-e (Scheme 2). In the reaction of 1c-e, the trifluoromethyl ketones 2c-e were obtained in moderate yields, and small amounts of 1,2,7-octatriene, 1,5,8-mentatriene, and a mixture of myrcene and ocimene were formed respectively by β-elimination of Pd-H from the π-allylpalladium intermediates.[6)]



Scheme 2.

The reaction presented here provides a useful method for the trifluoromethyl substituted compounds. This work was supported by the Foundation, Hattori Hokokai.

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