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FLUORIDE-CATALYZED MICHAEL ADDITION OF NITROTOLUENES TO ACTIVATED α, β-UNSATURATED ESTERS

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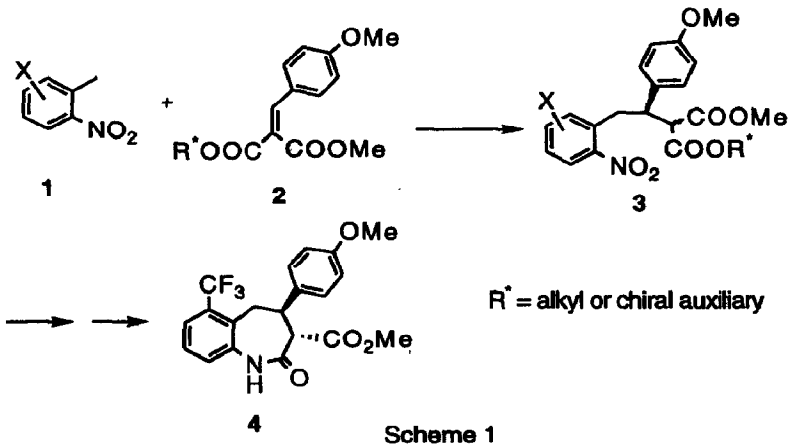
Abstract: We have found that in the presence of fluoride ion, nitrotoluenes of type **1** undergo Michael addition to activated α, β-unsaturated esters of type **2** in good to excellent yield (Scheme 1). The generality and limitation of this reaction and its application to the chiral synthesis of benzazepine **4** are described.

As part of a program directed toward the chiral synthesis of benzazepine **4**, an intermediate in the synthesis of calcium channel blocking agents such as SQ 33,351,[1] we needed a mild method for the stereoselective Michael addition of nitrotoluenes such as **1** to α,β-unsaturated esters such as **2** to give adducts such as **3** (Scheme 1).

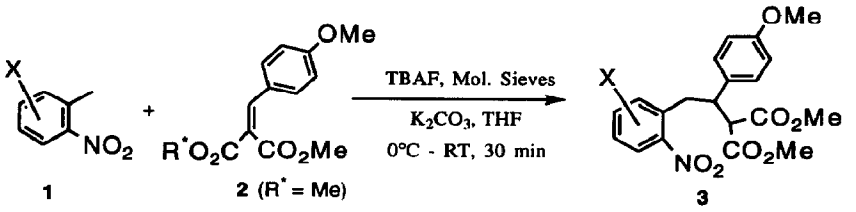


Scheme 1

Since dimerization[2] of the anion of nitrotoluene **1** to the corresponding bisbenzyl derivative is a common side reaction associated with the use of bases such as LDA, KHMDS, NaHMDS, *etc.*, we carefully examined other bases for the deprotonation of **1**. The use of tetrabutylammonium fluoride to effect Michael addition of nitroalkanes to α,β-unsaturated

esters and other transformations is known in the literature.[3] Moreover, Bartoli and coworkers[4] reported the generation of nitrotoluene anion by the desilylation of (trimethylsilyl methyl)nitroarenes in the presence of tetrabutylammonium fluoride.

Thus, dropwise addition of nitrotoluene **1** (when X = 6-CF_3) to a slurry of anhydrous K_2CO_3, powdered 4Å molecular sieves,[5] tetrabutylammonium fluoride, and α,β-unsaturated ester **2** (when R* = Me) in dry THF at 0°C followed by warming to room temperature for 30 minutes gave adduct **3e** in 90% isolated yield (Table 1). The presence of molecular sieves and potassium carbonate were crucial to drive the reaction to completion. In the absence of these reagents, the reaction proceeded only to 60% completion in 30 minutes; longer reaction times (~16 hr) produced a mixture of unknown products. Examples of this methodology using a variety of nitrotoluenes are shown in Table 1. Electron-withdrawing substituents on the nitrotoluene derivatives usually give higher yields of the Michael adducts.



1 **2** (R* = Me) **3**

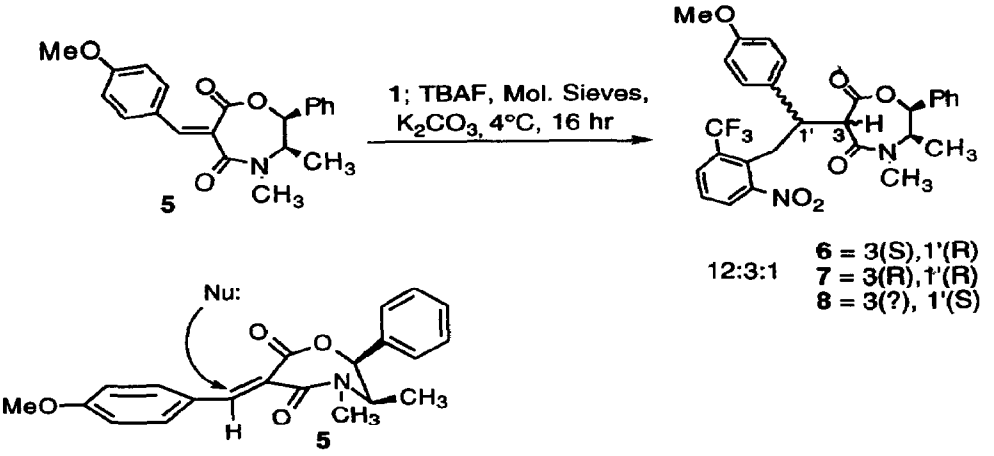
Table 1

X	Yields	X	Yields
6-Cl, 1a	70%, 3a	6-CF_3, 1e	90%, 3e
5-Cl, 1b	62%, 3b	5-CF_3, 1f	75%, 3f
6-F, 1c	82%, 3c	H, 1g	70%, 3g
5-F, 1d	70%, 3d	6-CH_3, 1h	0%, 3h

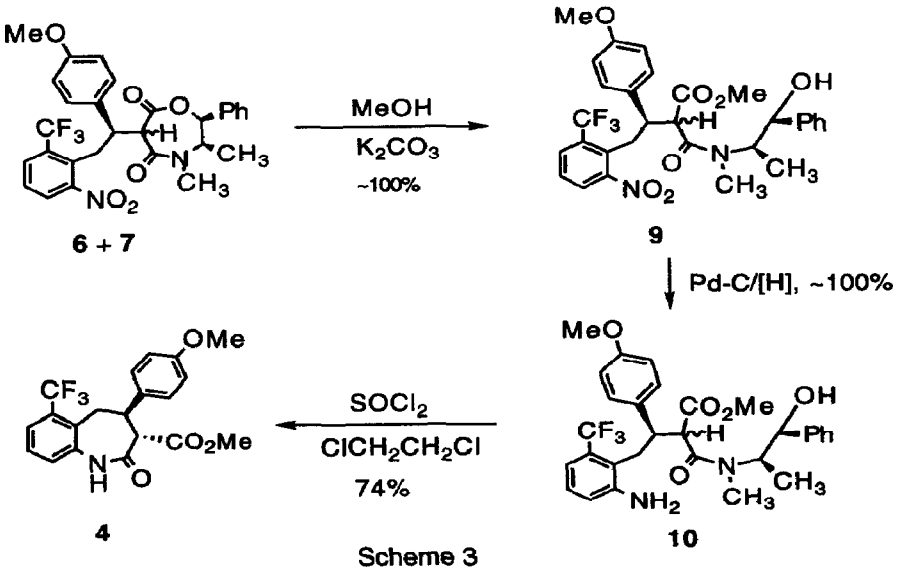
Since we were interested in the direct synthesis of optically active benzazepine **4**, Michael addition of **1** (when X = 6-CF_3) to optically active α,β-unsaturated ester **5**[6] was attempted. Under the reaction conditions described above (except the reaction was kept at 4°C for 16 hr), a 12:3:1 mixture of Michael adducts[7] **6**, **7**, and **8** were obtained in a yield of 88% (Scheme 2). The absolute stereochemistry of Michael adduct **6** was established by single crystal X-ray analysis.[8] The stereo outcome of the major isomers were derived from nucleophilic attack from the convex side of the boat conformation (picture shown in Scheme 2).

Subsequent treatment of the resulting Michael adducts **6** and **7** with MeOH in the presence of catalytic K_2CO_3 followed by hydrogenation over Pd-C gave **10**. Amino alcohol

10, without any further purification, was subjected to $SOCl_2$ in $ClCH_2CH_2Cl$ at room temperature to give the desired optically active key intermediate **4** in 74% yield (Scheme 3). Compound **4** of known absolute stereochemistry had been prepared previously.[1]

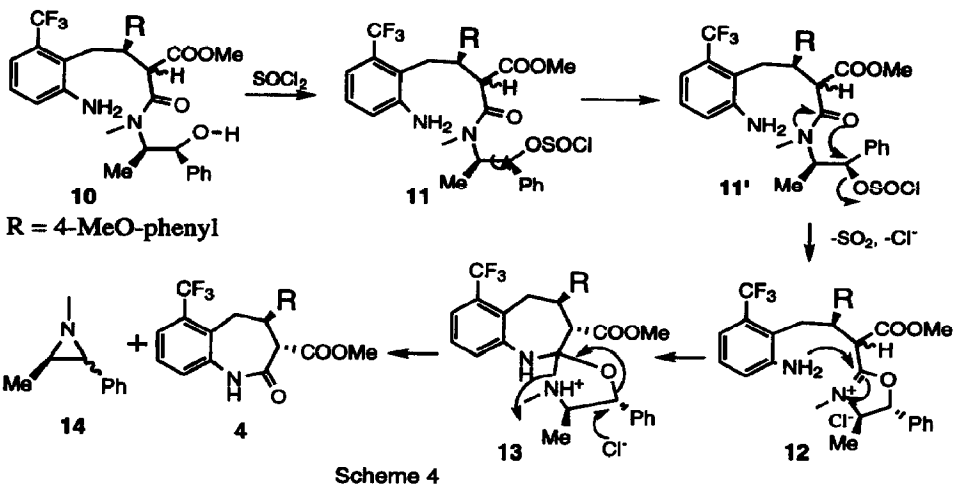


Scheme 2



Scheme 3

Removal of the chiral auxiliary involves a reiterative neighboring-group participation reaction[9] (Scheme 4). It can be speculated that thiony chloride reacts with alcohol followed by amide replacement of the sulfinyl chloride **11** to give an oxazolidinium salt **12**. Then, the aniline moiety attacks the oxazolidinium salt to generate a benzazepine **13**. Subsequent transformations furnish **4** and aziridine **14** (the stereoconfiguration was not confirmed).



Scheme 4

In conclusion, we have developed a new strategy for the asymmetric construction of the two contiguous stereogenic centers of benzazepine **4** through an enantioselective Michael reaction.

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7. The ratio was determined by isolation of each product by chromatography. **7** can be transformed in part to **6** by treatment with DBU in MeOH.
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