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Towards Enantioselective Electrophilic Trifluoromethylation of β-Keto Esters

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Introduction

There are a great number of new drugs and agrochemicals in the market place that contain one or more fluorine atom.[1,2] These molecules are produced either by using fluorinated building blocks early in a synthetic plan or by introduction of fluorine atoms in a late stage of the synthesis.[3,4] The approach by means of fluorinated building blocks is certainly the most common due to the availability of thousands of fluorinated molecules from fine chemicals producers. In the same way, procedures for synthesizing fluoroorganic compounds are numerous. The trifluoromethyl unit is an important structural moiety in diverse classes of organic molecules.[5] Compounds containing the trifluoromethyl group are found in a wide variety of dyes, polymers, liquid crystals, agrochemicals, and pharmaceuticals. Often, the introduction of a trifluoromethyl unit in target products induces improved properties. Synthons incorporating a CF_3 group

attached to an aromatic ring are available from many suppliers and they represent a large fraction of the commercial trifluoromethylated compounds. In contrast, other types of CF_3 synthons are less frequent; it is the case for aliphatic trifluoromethylated products. Consequently, it is highly desirable to develop the segment of small aliphatic trifluoromethylated synthons, in particular, by introducing new trifluoromethylation reactions. The electrophilic trifluoromethylation is not an easy reaction. Yagupol'skii[6] in 1984 and Umemoto[7-11] in the early 1990s prepared trifluoromethylsulfonium salts as electrophilic trifluoromethylating agents, compounds **1** and **2**, respectively (Figure 1). In 1998, Shreeve described synthetic routes to trifluoromethylsulfonium triflates **3** with different substitution patterns on the aromatics.[12] Recently, in 2006, Togni reported unprecedented 10-I-3 hypervalent iodine-based reagents for electrophilic trifluoromethylation (compounds **4**, Figure 1).[13]

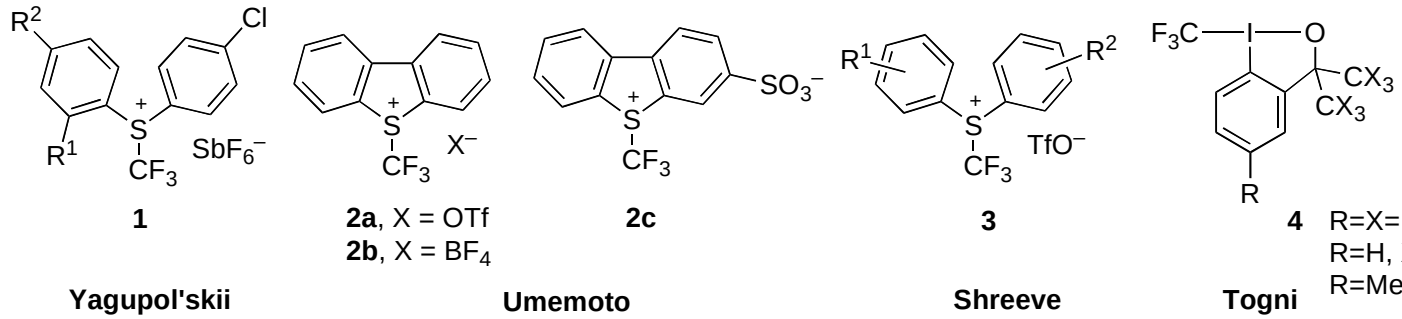
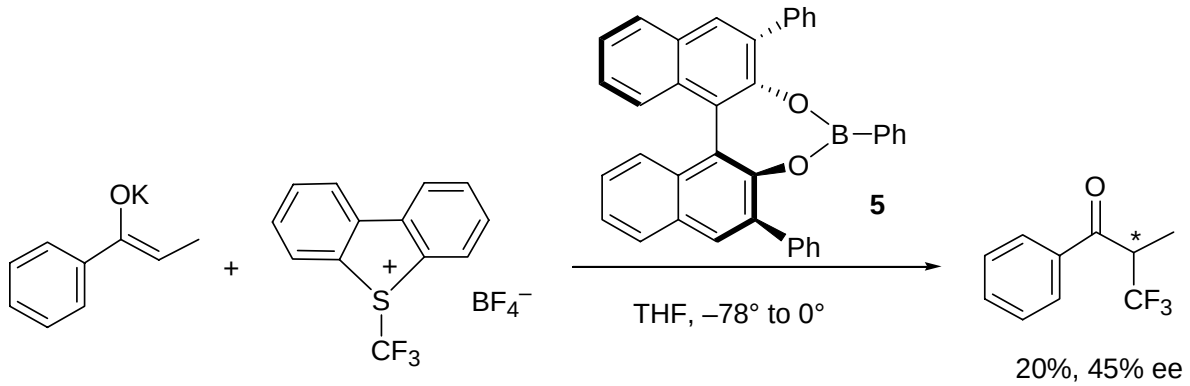


Figure 1: Electrophilic Trifluoromethylating Agents.

Although the asymmetric electrophilic trifluoromethylation reaction is very important and extremely challenging, chiral reagents are not currently known.[14] Nevertheless, Umemoto reported for the first time in 1994, an enantioselective electrophilic trifluoromethylation with reagent **2b** mediated by a chiral borepin **5** derived from a binaphthol. The best enantiomeric excess was 45% for 20% yield (Scheme 1).[9]

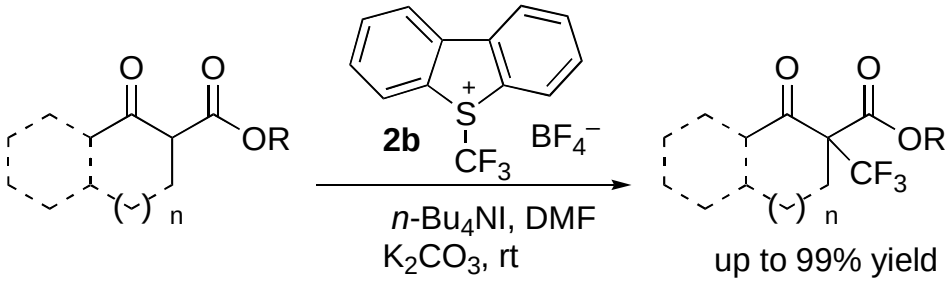


Scheme 1: First Enantioselective Electrophilic Trifluoromethylation by Umemoto in 1994.

Since this pioneering work, the enantioselective electrophilic trifluoromethylation has not been further successfully explored. On the occasion of ECSOC-10, we are presenting our preliminary results towards enantioselective electrophilic trifluoromethylation of β-keto esters, which provided enantiomeric excesses up to 71%.

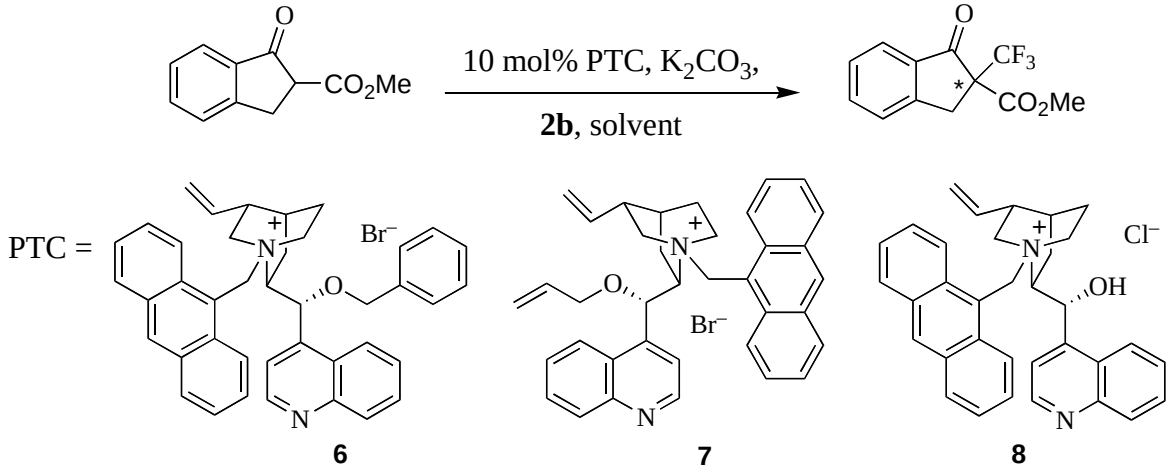
Results and discussion

In 2003, we reported the phase-transfer-catalysed electrophilic trifluoromethylation of various ammonium enolates of β-keto esters with the aid of 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate, Umemoto's reagent **2b** (Scheme 2).[15,16] The reactions were conducted in the presence of 10 mol% of tetrabutylammonium iodide in DMF at room temperature. Cyclic substrates containing an aromatic ring gave excellent yields whereas acyclic or alicyclic substrates gave moderate yields.



Scheme 2: Electrophilic Trifluoromethylation of β-Keto Esters with 5-Trifluoro methyldibenzothiophenium Salt Promoted by a Phase-Transfer Catalyst.

We next examined the use of chiral ammonium salts acting as chiral phase-transfer catalysts (PTCs) instead of the achiral tetrabutylammonium iodide. The glorious history of cinchona alkaloid-derived quaternary ammonium salts led us to consider this family of phase-transfer reagents. The bridgehead nitrogen of cinchonine and cinchonidine was quaternised by the bulky 9-methylanthracenyl group, whereas the hydroxyl group was left free (PTC **8**) or protected as a benzyl ether (PTC **6**) or an allyl ether (PTC **7**). We selected the β-keto ester 1-oxo-indan-2-carboxylic acid methyl ester as model substrate for enantioselective electrophilic trifluoromethylation. This substrate gave quantitative yield in the racemic trifluoromethylation. Potassium carbonate was used as the base. A screening approach was adopted for the identification of suitable reaction conditions for the enantioselective trifluoromethylation. Representative results are reported in Table 1.



Entry	PTC	Solvent	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	**6**	DMF	20	5	80	<2
2	**6**	MeOH	20	28	0	_
3	**6**	toluene	20	28	0	_
4	**6**	MeCN	20	28	31	<2
5	**6**	CH_2Cl_2	20	24	26	0
6	**6**	THF	20	5	68	19
7	**6**	THF	0	16	61	<2
8	**6**	THF	–20	16	73	3
9	**7**	THF	20	5	61	17
10	**8**	THF	20	3	56	<2

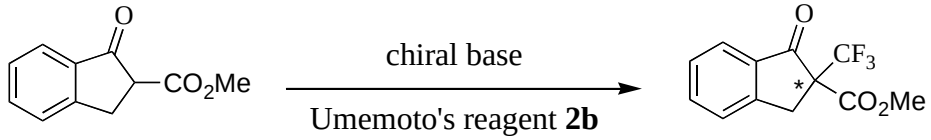
PTC 6: O-(9)-benzyl-N-methylanthracenylcinchonidinium bromide;
PTC 7: O-(9)-allyl-N-methylanthracenylcinchoninium bromide;
PTC 8: N-methylanthracenylcinchonidinium chloride

Table 1: Catalytic Enantioselective Electrophilic Trifluoromethylation.

Dimethylformamide gave a high yield of trifluoromethylated product within 5 hours at room temperature but no enantioselectivity was measured. Methanol reacts with Umemoto's reagent and does not allow the reaction to take place. Among the solvents employed, we found that THF is suitable for the reaction and for the enantioselectivity. Indeed, we observed an ee value of 19% when the reaction was run at room temperature (entry 6, Table 1). Lowering the temperature to 0° and –20°C was detrimental to the ee values. Protection of the hydroxyl group in the PTC is important to achieve an enantioselection; PTCs **6** and **7** versus PTC **8**. Of course, all combinations of PTC, solvent, base, and

temperature have not been tested; however, this approach looks promising and more experiments will be done to improve the enantioselectivity.

The poor enantioselection observed in this reaction may be attributed to the trifluoromethylation of the potassium enolate rather than the chiral quaternary ammonium enolate. The undesirable, competitive process of interfacial trifluoromethylation of the "wrong" ion-pair possessing the potassium cation should be disfavoured and the extraction of the potassium enolate into the bulk organic phase by ion exchange with the chiral quaternary ammonium would be the preferred pathway. To banish the presence of achiral enolates, we decided to use cinchona alkaloids as chiral tertiary bases for promoting the enolization of the β-keto ester and subsequent enantioselective electrophilic trifluoromethylation of the chiral ammonium enolate. Some representative results are reported in Table 2.



Entry	Solvent	Base	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	CH_2Cl_2	4-ClBzQN	–78	48	0	–
2	CH_2Cl_2	QN	–78	12	30	10
3	CH_2Cl_2	HQD	–78	12	73	13
4	CH_2Cl_2	HQN	–78	3.5	51	29
5	$CHCl_3$	HQN	20	96	42	25
6	$CHCl_3$	HQN	–60	96	55	35
7	CH_2Cl_2/toluene : 1/1	HQN	–78	72	0	–
8	CH_2Cl_2/hexane : 1/1	HQN	–78	72	45	56
9	CH_2Cl_2/hexane : 1/2	HQN	–78	96	53	71
10	CH_2Cl_2/hexane : 1/3	HQN	–78	96	34	52

4-ClBzQN: 4-chlorobenzoyl quinine; **QN**: quinine; **HQN**: dihydroquinine; **HQD**: dihydroquinidine

Table 2: Chiral Base Mediated Enantioselective Electrophilic Trifluoromethylation.

Chlorinated solvents provided the desired trifluoromethylated product with ee values in the range 10-35%. Hydroquinine gave a higher ee value than hydroquinidine whereas quinine gave a poor yield probably due to its lower solubility in the reaction solvent. The reaction is much slower in chloroform than in dichloromethane. Lowering the polarity of the solvent by using a mixture of dichloromethane and toluene didn't allow the reaction to take place. Interestingly, a mixture of dichloromethane and hexane permits the reaction with improved enantioselectivity although with longer reaction times. An appropriate ratio dichloromethane / hexane (1 / 2) gave the trifluoromethylated product in 53% yield with 71% enantiomeric excess. Such a level of enantioselectivity is attained for the first time for an enantioselective electrophilic trifluoromethylation (previous best ee value was 45% by Umemoto[9] in 1994). In addition, we demonstrated that Shreeve reagent **3** (R^1=R^2=H) is equally efficient in the trifluoromethylation reaction. Our current interest concerns the development of a catalytic version with a substoichiometric amount of chiral base in combination with an achiral base.

Conclusion

The preliminary results described in this paper show that enantioselective electrophilic trifluoromethylation is far from a trivial reaction. It remains a very challenging asymmetric reaction for which little progress has been made since the pioneering work in 1994. We are actively working to improve the enantioselectivity of the reaction. We hope that new ideas will germinate after reading our work and that it will contribute to the development of an efficient method.

Experimental section

Representative procedure of trifluoromethylation of 1-oxo-indan-2-carboxylic acid methyl ester. 1) under phase-transfer catalysis. To a stirred solution of 1-oxo-indan-2-carboxylic acid methyl ester (0.05 mmol, 9.5 mg), potassium carbonate (0.3 mmol, 41.4 mg), *O*-(9)-benzyl-*N*-methylanthracenylcinchonidinium bromide (0.005 mmol, 2.6 mg) in dry THF (1 mL) was added 5-(trifluoromethyl)dibenzothiophenium tetrafluoroborate (0.05 mmol, 17.5 mg) at room temperature. After 5 hours, the mixture was diluted with water (10 mL) and extracted with diethyl ether (2 x 8 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. A preparative TLC (cyclohexane/ethyl acetate 8/1) afforded the desired product in 68% yield and 19% ee. The ee value was determined by HPLC (Chiralpak OD-H, *n*-hexane / *i*-propanol = 99/1, 1 mL/min, 254 nm).

2) using a stoichiometric amount of chiral base. To a solution of 1-oxo-indan-2-carboxylic acid methyl ester (0.05 mmol, 9.5 mg) in dry CH_2Cl_2 (0.5 mL) was added dihydroquinine (0.05 mmol, 16.3 mg). This mixture was stirred for 10 minutes at room temperature, then hexane was added (1 mL) and the temperature cooled to –78°C. 5-(Trifluoromethyl)dibenzothiophenium tetrafluoroborate (0.05 mmol, 17.5 mg) was then added in one portion and the reaction mixture was stirred for 72-96 hours at –78°C. The solvent was evaporated and the residue purified by preparative TLC (hexane/ethyl acetate 8/1) to give the desired product in 53% yield and 71% ee. 1-oxo-2-trifluoromethyl-indan-2-carboxylic acid methyl ester : m. p. 64-65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.53 (d, J = 17.7 Hz, 1H), 3.68 (d, J = 17.7 Hz, 1H), 3.72 (s, 3H), 7.38-7.47 (m, 2H), 7.48-7.66 (m, 1H), 7.78 (d, J = 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.5, 54.0, 63.4 (q, $^{2}J_{F\text{-}C}$ = 25.9 Hz), 123.8 (q, $^{1}J_{F\text{-}C}$ = 283.0 Hz, CF_3), 126.0, 126.7, 128.9, 134.7, 136.7, 152.0, 166.0, 193.3; ^{19}F NMR

(282 MHz, $CDCl_3/CFCl_3$) δ -69.82 (s, 3F); IR (film, cm^{-1}): 2958, 2849, 1758, 1726, 1606, 1592, 1465, 1435, 1277, 1181, 1084, 1045, 890, 797; MS (EI) *m/z*: 258 (M^+); HRMS (EI) *m/z* Calcd for $C_{12}H_9F_3O_3$: 258.0504. Found: *m/z* 258.0505.

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