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Enantioselective additions of (trifluoromethyl)trimethylsilane to α-imino ketones derived from aryl glyoxals

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ABSTRACT

Chemoselective additions of (trifluoromethyl)trimethylsilane to α-imino ketones derived from aryl glyoxals in the presence of a catalytic amount of enantiomerically pure ammonium bromides, derived from *Cinchona* alkaloids and K_2CO_3 led to O-silylated β-imino alcohols. Subsequent reduction of these products with $NaBH_4$ gave β-(*N*-alkyl)amino-α-trifluoromethyl alcohols for which the ee values were 30–71% under optimized conditions. Enantiomeric excesses were determined for the final products on the basis of ^1H or ^{19}F NMR spectra registered in the presence of chiral solvating agents.

The synthesis of organofluorine compounds is a challenge in modern organic chemistry. Incorporation of fluorine atoms or perfluoroalkyl groups into the structure of organic molecules results in significant changes in their physical, chemical, and biological properties.[1] Among fluorinated compounds, particular interest is focused on molecules bearing a trifluoromethyl group, which have found wide applications in, for example, the synthesis of materials with specific properties as well as biologically active compounds.[1] They are also used as efficient catalysts for diverse reactions.[2] (Trifluoromethyl)trimethylsilane (the so called Ruppert–Prakash reagent, RPR) is recognized as a very convenient reagent for the introduction of a CF_3 group into electrophilic substrates.[3] Extensive research has been focused on the development of stereocontrolled RPR additions to carbonyl compounds. In a recent paper, we demonstrated that camphorquinone monoimines underwent nucleophilic trifluoromethylation in a chemo- and diastereoselective manner.[4] Effective protocols for the enantioselective trifluoromethylation of prochiral aldehydes and ketones, using RPR, have been described.[5] In these procedures, reactions were performed using methods based on phase-transfer catalysis. Typically, reactions were carried out in the presence of two catalysts: an enantiomerically pure quaternary ammonium bromide and an achiral salt being a source of fluoride, for example KF or TMAF. It turned out that the most efficient catalysts were ammonium salts derived from *Cinchona* alkaloids.

From another point of view, β-amino alcohols are considered as versatile building blocks and are widely applied in organic synthesis.[6] Many biologically active substances belong to this class of compounds, or contain in their structure the modified skeleton of a β-amino alcohol.[6] β-Amino alcohols are also employed as catalysts and chiral auxiliaries in asymmetric synthesis.[7] Their derivatives, functionalized with a CF_3 group, combine unique physical, chemical, and biological properties. Several methods for the preparation of such compounds in racemic form have already been reported.[8] Presently, the development of new and general synthetic methods for the preparation of such compounds in enantiomerically pure form, based on the application of inexpensive and easily available starting materials is a challenge in organic chemistry. Stereocontrolled methods for the preparation of the target compounds exploit the phenomenon of asymmetric induction or the use of expensive, enantiomerically pure substrates bearing a CF_3 group.[8] To the best of our knowledge, there is only one report in which an enantioselective method for the preparation of such compounds is described,[9] which involves a Henry reaction carried out in the presence of a chiral lanthanide(III) '(*S*)-binolam' complex.

In a previous report, we showed that chemoselective nucleophilic trifluoromethylation of α-imino ketones derived from aryl glyoxals, with subsequent reduction of the C=N function led to racemic β-amino-α-(trifluoromethyl) alcohols.[10] Substrates bearing an α-methylbenzyl substituent on the N-atom as a chiral auxiliary reacted with RPR with low diastereoselectivity. In the

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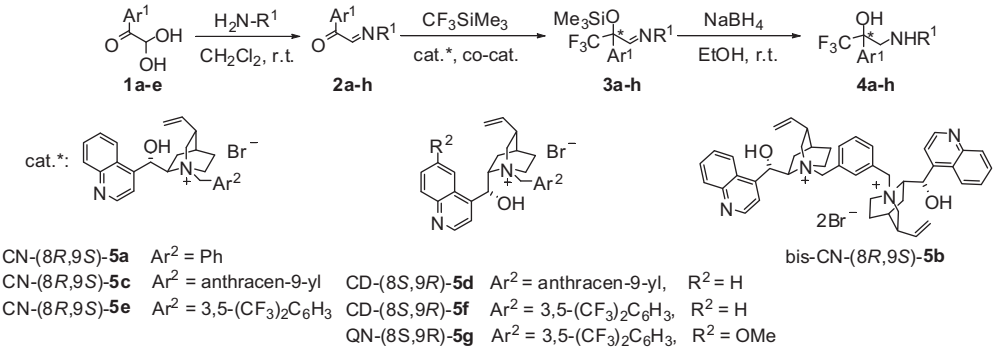

Scheme 1. Enantioselective synthesis of β-amino-α-trifluoromethyl alcohols.

Table 1

Substrate	Ar^1	R^1	Cat.*	Co-cat.	MOL %	Solvent	*T* (°C)	Yield (%) of **4**[a]	ee (%)	$[\alpha_D]$[b]
2a	Ph	*t*-Bu	CN-(8*R*,9*S*)-**5a**	KF	15	CH_2Cl_2	~20	50	0	—
2a	Ph	*t*-Bu	CN-(8*R*,9*S*)-**5a**	KF	15	Toluene	~20	88	9	—[c]
2a	Ph	*t*-Bu	Bis-CN-(8*R*,9*S*)-**5b**	KF	15	Toluene	~20	87	8	—[c]
2a	Ph	*t*-Bu	CN-(8*R*,9*S*)-**5c**	KF	15	Toluene	~20	82	18	+0.7
2a	Ph	*t*-Bu	CD-(8*S*,9*R*)-**5d**	KF	15	Toluene	~20	86	24	−0.9
2a	Ph	*t*-Bu	CN-(8*R*,9*S*)-**5e**	KF	15	Toluene	~20	79	52	+1.9
2a	Ph	*t*-Bu	CD-(8*S*,9*R*)-**5f**	KF	15	Toluene	~20	79	58	−2.0
2a	Ph	*t*-Bu	QN-(8*S*,9*R*)-**5g**	KF	15	Toluene	~20	71	35	−1.1
2a	Ph	*t*-Bu	CD-(8*S*,9*R*)-**5f**	KF	10	Toluene	~20	59	52	−1.7
2a	Ph	*t*-Bu	CD-(8*S*,9*R*)-**5f**	K_2CO_3	15	Toluene	~20	85	65	−2.7
2a	Ph	*t*-Bu	CD-(8*S*,9*R*)-**5f**	K_2CO_3	10	Toluene	~20	77	56	−1.9
2a	Ph	*t*-Bu	CD-(8*S*,9*R*)-**5f**	KOH	15	Toluene	~20	87	46	−1.5
2a	Ph	*t*-Bu	CD-(8*S*,9*R*)-**5f**	KOH	10	Toluene	~20	88	41	−1.5
2a	Ph	*t*-Bu	CD-(8*S*,9*R*)-**5f**	KF	15	Toluene	−40	82	63	−2.2
2a	Ph	*t*-Bu	CD-(8*S*,9*R*)-**5f**	K_2CO_3	15	Toluene	−40	85	67	−3.0
2a	Ph	*t*-Bu	CD-(8*S*,9*R*)-**5f**	K_2CO_3	10	Toluene	−40	78	61	−2.3
2b	*p*-$MeOC_6H_4$	*t*-Bu	CD-(8*S*,9*R*)-**5f**	K_2CO_3	15	Toluene	−40	89	71	−3.9
2c	*p*-$NO_2C_6H_4$	*t*-Bu	CD-(8*S*,9*R*)-**5f**	K_2CO_3	15	Toluene	−40	94	30	−1.5
2d	Benzofuran-2-yl	*t*-Bu	CD-(8*S*,9*R*)-**5f**	K_2CO_3	15	Toluene	−40	92	68	−3.4
2e	7-Et-benzofuran-2-yl	*t*-Bu	CD-(8*S*,9*R*)-**5f**	K_2CO_3	15	Toluene	−40	87	50	−3.2
2f	Ph	*i*-Pr	CD-(8*S*,9*R*)-**5f**	K_2CO_3	15	Toluene	−40	87	64	−2.8
2f	Ph	*i*-Pr	CD-(8*S*,9*R*)-**5f**	K_2CO_3	10	Toluene	−40	75	61	−3.0
2g	*p*-$MeOC_6H_4$	*i*-Pr	CD-(8*S*,9*R*)-**5f**	K_2CO_3	15	Toluene	−40	78	64	−2.9
2h	*p*-$NO_2C_6H_4$	*i*-Pr	CD-(8*S*,9*R*)-**5f**	K_2CO_3	15	Toluene	−40	81	32	−1.8

[a] Total yield for the two-step protocol (**2a–h** → **4a–h**).
[b] *c* = 1 mg/ml ($CHCl_3$).
[c] $[\alpha_D]$ value was not determined.

present letter, an enantioselective version of this protocol based on the use of modified *Cinchona* alkaloids is described

The preparation of 1-aryl-2,2-dihydroxyethanones **1a–e** was based on the known oxidation of aryl-methyl ketones using SeO_2 in an aqueous 1,4-dioxane solution.[11] Further condensation of **1a–e** with primary amines led to α-imino ketones **2a–h** (Scheme 1).[10,12] As chiral catalysts, quaternary ammonium bromides **5a–g**, derived from *Cinchona* alkaloids were tested. They were prepared according to the literature procedures.[5e,13]

The enantioselective synthesis of the target compounds was based on the modified protocol for obtaining racemic products (*rac*)-**4**.[10] In the key step, addition of RPR to **2** was performed in the presence of a catalytic system consisting of enantiomerically pure ammonium bromide and an achiral co-catalyst. The mixture of both salts replaced cesium fluoride as an efficient initiator of the nucleophilic trifluoromethylation reaction. The obtained silylated ethers **3a–h** were used in further transformations without purification or determination of the enantiomeric excess. Reduction of the C=N bond and desilylation of the adducts of type **3a–h** with sodium borohydride gave β-amino-α-(trifluoromethyl) alcohols **4a–h**. The initial experiments were carried out with the model substrate *N*-*tert*-butylphenyl-α-imino ketone **2a** in order to optimize the reaction conditions for the enantioselective addition of RPR (Scheme 1, Table 1).

On the basis of literature data and preliminary experiments, toluene was used as a non-polar solvent. Reactions were performed in the presence of 15 mol % of the catalysts: potassium fluoride and an appropriate chiral salt **5**. In all cases, the final products were obtained in good yields. The use of bis-cinchonium bromide bis-CN-(8*R*,9*S*)-**5b**, which gave the best results in additions to aldehydes and ketones,[5f] led to the desired product **4a** with very low enantiomeric excess. Tetramethylammonium fluoride was not tested as a co-catalyst in the present studies due to difficulties with the preparation of the catalyst in anhydrous form. Application of catalysts with an anthracenylmethyl substituent CN-(8*R*,9*S*)-**5c** and CD-(8*S*,9*R*)-**5d** did not improve the results significantly. A derivative of cinchonidine containing a 3,5-bis(trifluoromethyl)benzyl group CD-(8*S*,9*R*)-**5f** appeared to be the most effective catalyst and an ee of 60% was obtained. Application of quinidinium bromide QN-(8*S*,9*R*)-**5g** gave a worse result. In the case of pseudoenantiomeric catalysts CN-(8*R*,9*S*)-**5c**,**e** and CD-(8*S*,9*R*)-**5d**,**f**, product **4a** was obtained with an opposite configuration and comparable ee values. In