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Highly Diastereoselective Aldol Reaction of Fluoroalkyl Aryl Ketones with Methyl Isocyanoacetate Catalyzed by Silver(I)/Triethylamine

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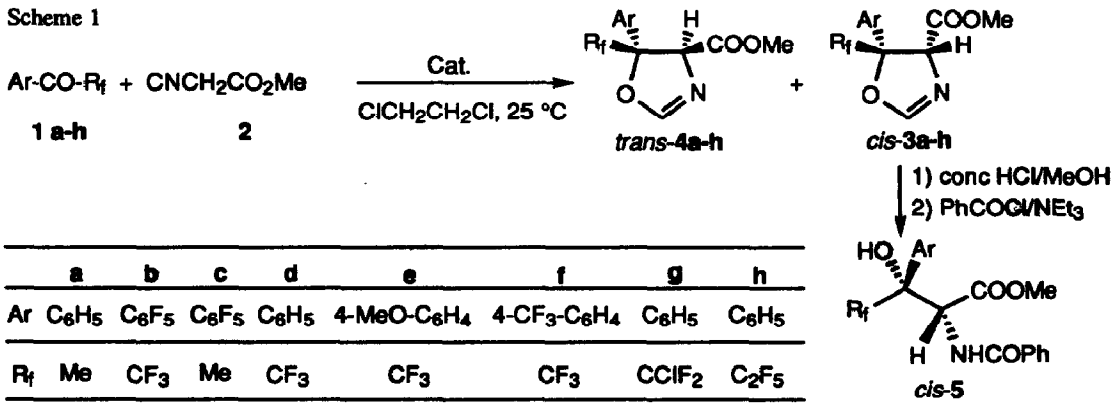
Abstract: Transition metal-catalyzed aldol reaction of aryl fluoroalkyl ketones with methyl isocyanoacetate was found to proceed with high diastereoselectivity that is in sharp contrast to the very poor diastereoselectivity in the similar reaction of nonfluorinated ketones. The superiority of $AgClO_4/NEt_3$ as a homogeneous catalyst (1 mol %) for these reactions was disclosed.

During last two decades, a growing number of papers dealing with fluorine-containing amino acids have demonstrated the usefulness of these amino acids in the design of novel biologically active compounds as well as in the study of the biological chemistry.[2] A large number of fluoroamino acids have been synthesized and some of them are nowadays used as chemotherapeutic agents.[3] In recent years the design of new typies of fluorine-containing amino acids has attracted particular attention. The rapidly increasing interest in new fluoroamino acids is caused not only by curiosity in their potential biological activity but also by their apparent importance as conformational modifiers in the design of physiologically active peptides.[4] Having started new research project on stereoselective synthesis of fluorine-containing amino acids by means of homogeneous catalysis we report herein our preliminary results toward synthesis of fluorinated analogs of β-hydroxy-α-amino acids, which are of considerable current interest.[5]

Aldol reaction between carbonyl compounds and derivatives of isocyanoacetic acid has been continuously demonstrated to be of fundamental importance in the construction of β-hydroxy-α-amino acids' framework.[6] While the old-fashioned version of this reaction, with alkaline metal derived base as a catalyst, has found wide application, relatively little attention has been paid until recently to the more sophisticated variant using homogeneous catalysis by transition metals. Studies primarily by Y. Ito have defined many of the key parameters of the copper-catalyzed reaction[7] and several elegant synthetic applications have appeared.[8]

Scheme 1



	a	b	c	d	e	f	g	h
Ar	C_6H_5	C_6F_5	C_6F_5	C_6H_5	4-MeO-C_6H_4	4-CF_3-C_6H_4	C_6H_5	C_6H_5
R_f	Me	CF_3	Me	CF_3	CF_3	CF_3	$CClF_2$	C_2F_5

Table I. Catalytic Aldol Reaction of Octafluoroacetophenone (**1b**) with Methyl Isocyanoacetate (**2**)

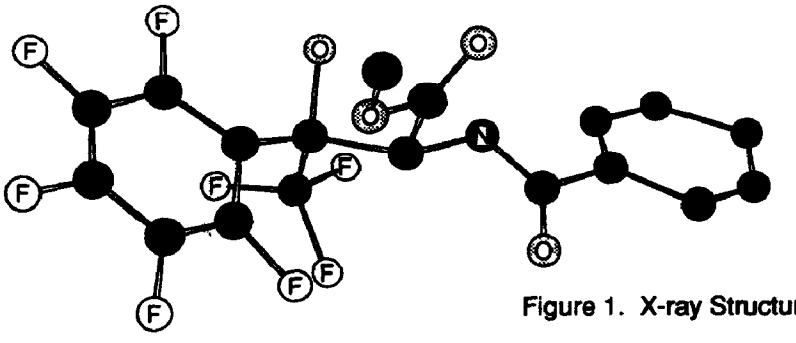
Entry	Ketone	Catalyst	Conditions[a]	Yield[b], %	Ratio[c]	
					cis-**3**	*trans*-**4**
1	PhCOMe	10% Cu(I)[d]	24 h, 50 °C	80	54	46
2	$C_6F_5COCF_3$	10% Cu(I)[d]	10 min, 23 °C	93	91	9
3	$C_6F_5COCF_3$	1% Cu(I)[d]	10 h, 23 °C	91	90	10
4	$C_6F_5COCF_3$	1% Au(I)[e]	4 h, 23 °C	95	92	8
5	$C_6F_5COCF_3$	1% Ag(I)[f]	3.5 h, 23 °C	92	94	6

[a] All reactions were run in 1,2-dichloroethane. [b] Isolated yield. [c] Determined by GLC and ^{1}H NMR analysis. [d] CuCl/NEt_3. [e] [Au(*c*-HexNC)$_2$]BF_4/NEt_3. [f] $AgClO_4$/NEt_3.

However, nearly entirely this reaction was studied in aldehydes series and examples with involvement of ketones are notably rare. Nevertheless, it was shown, that Cu_2O-catalyzed (20 mol %) reaction of ethyl isocyanoacetate with acetophenone provides a 1:1 mixture of the diastereoisomeric oxazolines.[8b]

We began with the reaction of acetophenone (**1a**) with methyl isocyanoacetate (**2**) using 10 mol % of CuCl/NEt_3 as a catalyst. As it is shown in Table 1 (entry 1), in our hands, the sluggish reaction (for 24 h at 50 °C) afforded 80% yield of a 1.2:1 mixture of oxazolines **3a** and **4a**. In sharp contrast the exothermic reaction of octafluoroacetophenone (**1b**), in the presence of the same CuCl/NEt_3 catalyst (10 mol %) resulted in excellent isolated yield (93%) of corresponding oxazolines **3b** and **4b** with unexpectedly high diastereomeric excess (9:1 ratio) of one of them (entry 2). To determine the relative configuration of dominant diastereoisomer we performed X-ray analysis of the crystalline *N*-benzoyl derivative **5b**, which was obtained from the dominant isomer **3b**.[9] Figure 1 shows the molecular structure of compound **5b**.[10] Thus, the relative configuration of dominant diastereoisomer **3b** is unambiguously determined to be ***2R*,3R**** (or ***cis*** in respect of relationship between pentafluorophenyl and methoxycarbonyl groups). In agreement with the X-ray crystallographic analysis, ^{1}H NMR spectra of **3b** and **4b** show the methyl protons of methoxycarbonyl group of *cis*-**3b**, owing to an effect of aromatic ring, are shifted upfield (3.71 ppm) in comparison with those of the *trans*-**4b** (3.86 ppm).

Having this interesting result, we decided to explore a possibility to affect diastereoselectivity in the catalytic aldol reaction. First of all we investigated the catalytic ability of gold(I) and silver(I) derivatives whicl previously were used along with chiral ferrocenylphosphine ligands in asymmetric version of the aldol reaction of isocyanoacetate **2** with aldehydes.[11] The results (Table I, entries 3-5) revealed that 1 mol % of homogeneous Au(I)/NEt_3 and Ag(I)/NEt_3 is sufficient to obtain oxazolines **3b** and **4b** in excellent isolated yield within a



cis-**5b**

Figure 1. X-ray Structure of *cis*-**5b**

Table II. Silver(I)/Triethylamine-Catalyzed Aldol Reaction of Fluorinated Ketones[a]

Entry	Ketone (1)	Conditions[b]	Yield[c],%	Ratio[d]	
				cis (3)	*trans* (4)
1	(b) $C_6F_5COCF_3$	5 h	92	94	6
2	(c) $C_6F_5COCH_3$	48 h	85	40	60
3	(d) $C_6H_5COCF_3$	5 h	92	86	14
4	(e) 4-CF_3-$C_6H_4COCF_3$	5 h	94	88	12
5	(f) 4-CH_3O-$C_6H_4COCF_3$	6 h	89	87	13
6	(g) $C_6H_5COCClF_2$	5 h	96	93	7
7	(h) $C_6H_5COC_2F_5$	6 h	93	95	5

[a] For the representative example see ref 12 and for ^{1}H NMR data see ref 13. [b] All reactions were run in 1,2-dichloroethane (1 mmol scale); ketone 1b-h/isocyanoacetate 2/$AgClO_4$/NEt_3 = 100/100/1/2. [c] Isolated yield. [d] Determined by GLC and ^{1}H NMR analysis; upfielded signals of methyl protons (COOMe) were attributed to *cis*-3b-h and downfielded ones to *trans*-4b-h, see also text.

convenient time span. The latter proved to be superior, affording 92% yield of the oxazolines with 94% *cis*-(2*R**,3*R**)-selectivity and was therefore used in the rest of this study.

We turned next to the reactions of pentafluorophenyl methyl ketone (1c) and phenyl trifluoromethyl keton (1d) with isocyanoacetate 2, which would enable us to address whether a pentafluorophenyl or trifluoromethyl group alone is sufficient to achieve the high diastereoselectivity. The reactions, conducted under the same conditions, resulted in quite opposite stereochemical outcome to each other (Table II, entries 2,3). The aldol reaction of 1c favored the formation of *trans*-oxazoline 4c, while 1d gave *cis*-oxazoline 3d as a main product. These findings clearly demonstrate that the presence of trifluoromethyl group in the starting ketone is crucial to the high *cis*-diastereoselectivity.

The high *cis*-selectivity (in respect of relationship between aromatic ring and methoxycarbonyl groups) was also observed in the series of silver-catalyzed (1 mol %) reactions of various fluoroalkyl aryl ketones, which possess electron-withdrawing (CF_3) and electron-releasing (OCH_3) groups in aromatic site and other substituents than a trifluoromethyl group in the alkyl site. Thus, in the aldol reaction of *p*-trifluoromethyl- and *p*-methoxy-substituted trifluoromethyl ketones 1e (Table II, entry 4) and 1f (entry 5) much the same *cis*-selectivity (88% for 1e and 89% for 1f) like in the case of unsubstituted trifluoroacetophenone 1d (86%) was achieved. A modification of the alkyl side chain of starting ketone with more bulky chlorodifluoromethyl 1g (entry 6) and pentafluoroethyl groups 1h (entry 7) sizably increases *cis*-selectivity up to 93% for 1g and 95% for 1h. These results demonstrate a generality of the present reaction and its potential for diastereoselective synthesis of hitherto unknown type of β-(fluoro)aryl-β-fluoroalkyl-β-hydroxy-α-amino acids.

We are continuing to study the reasons for the remarkable differences in the diastereoselectivity of an oxazoline ring formation in the aldol reaction of fluoroalkyl-containing ketones and acetophenone by examining on substituent effects as well as the design of new homogeneuos catalytic systems to further enhance diastereoselectivity and applying this reaction to the synthesis of interesting and important previously unknown fluorine-containing amino acids.

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9 To a solution of **3b** and **4b** (diastereoisomeric ratio 9:1) (240 mg) in MeOH (4 ml) was added conc HCl (0.7 ml) . The mixture was stirred for 2 h at 50 °C and then evaporated *in vacuo* to yield white solid.To the crystalline residue, CH_2Cl_2 (6 ml), NEt_3 (0.4 ml) and PhCOCl (0.16 ml) were added and it was stirred for 2 h at ambient temperature. After usual work up, the crude product was purified by preparative TLC on silica gel using mixture hexane/ethyl acetate (3:1) as an eluent. Compound **5b**, ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3 H), 4.77 (t, J = 4.1 Hz, 1 H), 6.13 (d, J = 10.1 Hz, 1 H), 7.02 (br d, J = 10.1 Hz, 1 H), 7.43-7.60 (m, 3 H), 7.76-7.83 (m, 2 H).

10 Crystals of compound **5** were grown from diethyl ether and pentane. Crystal data for **5**: $C_{18}H_{11}F_8NO_4$, monoclinic, space group $C2/c$. Radiation: graphite monochromatized Cu Kα radiation. Crystal size: 0.8 x 0.2 x 0.1 mm^3. Unit cell: a = 29.111(6), b = 6.995(1), c = 19.583(4) Å, β = 110.01(2)°, V = 3747 Å^3, Z = 8, D_X = 1.621 Mg cm^{-3}, μ for Cu Kα = 14.7 cm^{-1}. Diffraction data were measured on an Rigaku AFC-5S diffractometer. 1386 Unique reflexions were considered and used in the analysis. The structure was solved by TEXSAN method. The R and R_W factors were of 0.056 and 0.052. A number of heavy atoms refined 31 (C, N, O, F). A number of H atoms refined 0, a number of H atoms not refined 11.

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12 A typical experimental procedure is described for the reaction of methyl isocyanoacetate **2** with octafluoroacetophenone **1b**; to a solution of **1b** (1 mmol) in 1,2-dichloroethane (2 ml), $AgClO_4$ (0.01 mmol), NEt_3 (0.02 mmol) and isocyanoacetate **2** (1 mmol) were added under argon atmosphere. After the completion of the reaction (monitored by GLC), the solution was evaporated *in vacuo* and a residue was subjected to bulb-to-bulb distillation (0.2 mm Hg, 100-110 °C).

13 ^{1}H NMR (δ, $CDCl_3$) for oxazolines **3a-h** and **4a-h**. **3a**: 1.86 (br s, 3 H), 3.16 (s, 3 H), 4.65 (d, J = 1.8 Hz, 1 H), 7.21 (d, J = 1.8 Hz, 1 H), 7.26-7.57 (m, 5 H). **4a**: 1.61 (br s, 3 H), 3.86 (s, 3 H), 4.84 (d, J = 2.0 Hz, 1 H), 7.11 (d, J = 2.0 Hz, 1 H), 7.26-7.57 (m, 5 H). **3b**: 3,71 (s, 3 H), 5.32 (m, 1 H), 7.15 (d, J = 1.6 Hz, 1 H). **4b**: 3.86 (s, 3 H), 5.31 (m, 1 H), 7.14 (d, J = 1.8 Hz, 1 H). **3c**: 1.83 (t, J = 1.8 Hz, 3 H), 3.54 (s, 3 H), 4.81 (d, J = 1.6 Hz, 1 H), 7.09 (d, J = 1.6 Hz, 1 H). **4c**: 1.78 (t, J = 2.5 Hz, 3 H), 3.82 (s, 3 H), 4.91 (d, J = 2.0 Hz, 1 H), 7.04 (d, J = 2.0 Hz, 1 H). **3d**: 3.27 (s, 3 H), 5,24 (d, J = 2.0 Hz, 1 H), 7.24 (d, J = 2.0 Hz, 1 H), 7.33-7.41 (m, 3 H), 7.42-7.48 (m, 2 H). **4d**: 3.91 (s, 3 H), 5.14 (d, J = 2.2 Hz, 1 H), 7.16 (d, J = 2.2 Hz, 1 H), 7.33-7.41 (m, 3 H), 7.42-7.48 (m, 2 H). **3e**: 3.33 (s, 3 H), 3.81 (s, 3 H), 5.21 (d, J = 2.0 Hz, 1 H), 6.86 (d, J = 2.0 Hz, 1 H), 7.20-7.42 (m, 4 H). **4e**: 3.91 (s, 3 H), 3.82 (s, 3 H), 5.16 (d, J = 2.0 Hz, 1 H), 6.84 (d, J = 2.0 Hz, 1 H), 7.20 - 7.42 (m, 4 H). **3f**: 3.27 (s, 3 H), 5.26 (d, J = 2.0 Hz, 1 H), 7.26 (d, J = 2.0 Hz, 1 H), 7.55-7.66 (m, 4 H). **4f**: 3.93 (s, 3 H), 5.10 (d, J = 2.2 Hz, 1 H), 7.19 (d, J = 2.2 Hz, 1 H), 7.70-7.90 (m, 4 H). **3g**: 3.28 (s, 3 H), 5.28 (d, J = 2.0 Hz, 1 H), 7.24 (d, J = 2.0 Hz, 1 H), 7,34-7.41 (m, 3 H), 7.42-7.48 (m, 2 H). **4g**: 3.93 (s, 3 H), 5.16 (d, J = 2.3 Hz, 1 H), 7.16 (d, J = 2.3 Hz, 1 H), 7,34-7.41 (m, 3 H), 7.42-7.48 (m, 2 H). **3h**: 3.27 (s, 3 H), 5.41 (d, J = 2.0 Hz, 1 H), 7.21 (d, J = 2.0 Hz, 1 H), 7.36-7.41 (m, 3 H), 7.43-7.46 (m, 2 H). **4h**: 3.91 (s, 3 H), 5.07 (d, J = 2.2 Hz, 1 H), 7.18 (d, J = 2.2 Hz, 1 H), 7.36-7.41 (m, 3 H), 7.43-7.46 (m, 2 H).

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