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Gold(I)-Catalyzed Asymmetric Aldol Reaction of Methyl Isocyanoacetate with Fluorinated Benzaldehydes

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Abstract: In the title reaction, successive substitution of hydrogen atoms in the phenyl ring of benzaldehyde by fluorine atoms brought about gradual alteration of both diastereo- and enantioselectivities in the corresponding oxazolines formation. The highest values for the unusual selectivity (up to 63% *cis* with 86-90% ee) were observed in the reaction of tetrafluoro- and pentafluorobenzaldehydes.

The diverse biological activity of fluorine-containing amino acids has generated a great deal of attention to the preparative synthesis of this class of unusual man-made amino acids.[2] Taking into account the rigid requirements which have recently been established with regard to the chirality of pharmaceutical products,[3] the development of potent approaches to enantiomerically pure fluorine-containing amino acids is an area of research of critical importance in the application of these compounds to the various fields of medicinal chemistry, drug and peptide design. The most fruitful strategy in this area is an adaptation of the basic methodology of asymmetric processes which has been developed in hydrocarbon chemistry for the fluorocarbon chemistry of flustrates.[4] However, the strongly electronegative nature of fluorine can disturb or alter the course of reactions established for hydrocarbon patterns. Thus, this strategy often encounters the problems of regio- and stereoselectivity which arise from specific influence of fluorine atom(s).[5]

Recently, we have started a new research project on the stereoselective synthesis of fluorine-containing amino acids by means of homogeneous catalysis[6] which provides a sophisticated but the most direct and convenient route to optically active compounds.[7] As a first goal we chose fluorine-containing α-amino-β-hydroxycarboxylic acids which despite their attractive structural features and interesting biological activity have

Scheme 1

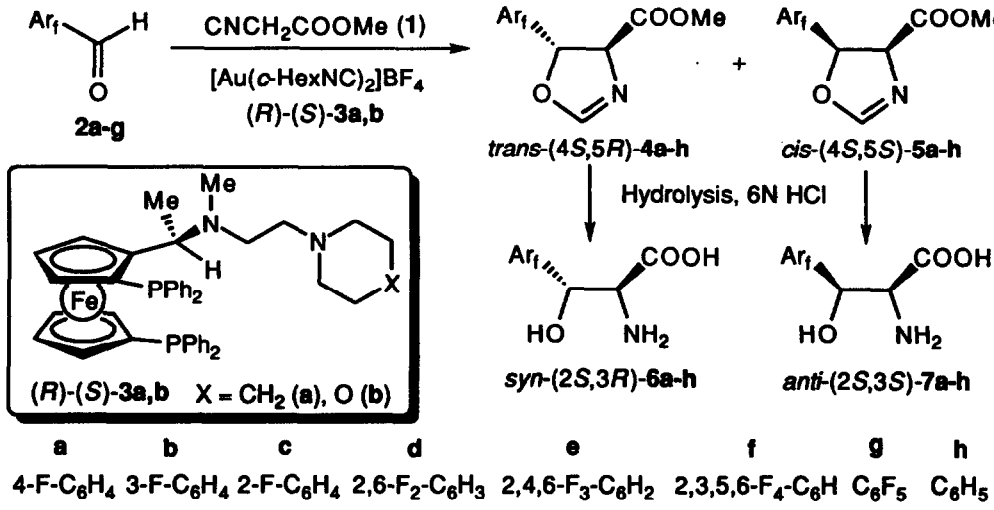

Table 1. Gold(I)-Catalyzed Asymmetric Aldol Reaction of Fluorobenzaldehydes with **1**[a]

entry	Ar_f in aldehyde (2)	conditions ligand	temp (°C)	time (h)	yield[b] (%)	ratio[c] *trans*-**4**/*cis*-**5**	% ee[d] *trans*-**4**	*cis*-**5**
1[e]	C_6H_5 (**2h**)	**3a**	25	20-40	94	94 / 6	95	49[f]
2	4-F-C_6H_4 (**2a**)	**3a**	25	10	97	93 / 7	94	20
3	3-F-C_6H_4 (**2b**)	**3a**	23	10	96	91 / 9	93	23
4	4-F-C_6H_4 (**2a**)	**3a**	0	100	96	94 / 6	96	19
5	3-F-C_6H_4 (**2b**)	**3a**	0	100	97	94 / 6	95	20
6	2-F-C_6H_4 (**2c**)	**3a**	23	10	96	84 / 14	84	38
7	2-F-C_6H_4 (**2c**)	**3a**	1	45	99	89 / 11	90	40
8	2,6-F_2-C_6H_3 (**2d**)	**3a**	0	79	98	75 / 25	86	78
9	2,4,6-F_3-C_6H_2 (**2e**)	**3a**	0	100	96	67 / 33	73	82
10	2,3,5,6-F_4-C_6H (**2f**)	**3a**	0	71	90	47 / 53	48	89
11	C_6F_5 (**2g**)	**3a**	1	21	99	57 / 43	36	78
12	C_6F_5 (**2g**)	**3b**[g]	0	100	92	37 / 63	36	86
13	2,3,5,6-F_4-C_6H (**2f**)	**3b**[g]	0	70	93	38 / 62	33	90
14	4-F-C_6H_4 (**2a**)	**3b**	0	70	92	94 / 6	94	25
15[e]	C_6H_5 (**2h**)	**3b**	25	20-40	93	95 / 5	95	12[h]

[a] The reactions were carried out in dichloromethane under argon atmosphere. The gold catalyst was prepared *in situ* from [Au(*c*-HexNC)$_2$]BF_4 and a chiral ligand. Ratio of **1**/**2**/Au(I)/ligand = 1/1.1/0.01/0.011 unless otherwise noted. [b] Isolated yield by bulb-to-bulb distillation. [c] Determined by ^1H NMR analysis. For NMR data, see ref 10. [d] Determined by chiral HPLC analysis of methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(fluorophenyl)propanoates **8**[11] with a chiral stationary phase column (SUMICHIRAL OA-2000 or 2000I), hexane/1,2-dichloroethane/ethanol = 100/20/1. The absolute configuration of all the *trans*-oxazolines **4** is assigned to be (4*S*,5*R*) by similarity in the order of elution in the HPLC analysis. See also text. [e] Previously published data.[9] [f] Absolute configuration is (4*R*,5*R*). [g] 2 Mol % of catalyst [Au(I)/Ligand] was used. [h] Absolute configuration is (4*S*,5*S*).

received a little attention so far.[2a,g,8] In this communication we report our preliminary results on the synthesis of optically active β-(fluorophenyl)serines by the gold(I)-catalyzed asymmetric aldol reaction[9] of methyl isocyanoacetate (**1**) with fluorinated benzaldehydes **2a-g** which contain from one to five fluorine atoms in the phenyl ring (Scheme 1). We started our experiments using the gold(I) complex of (*R*)-*N*-methyl-*N*-[2-(piperidino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (**3a**) which is one of the most effective ligands for the reaction of benzaldehyde providing both excellent diastereo- (88% de) and enantioselective (95% ee) formation of desirable *trans*-(4*S*,5*R*)-oxazoline **4h** (Table 1, entry 1).[9c] Under the same reaction conditions *p*-fluoro-(**2a**) and *m*-fluorobenzaldehydes (**2b**) gave the corresponding *trans*-oxazolines **4a** and **4b** (entries 2, 3) in expectedly excellent chemical yields (97% for **4a** and 96% for **4b**), diastereo- (86%, 82%) and enantioselectivities (94%, 93%). At lower temperature (0 °C) we have improved both diastereo- and enantioselectivity for *trans*-oxazolines up to 88% de and over 95% ee (entries 4, 5). The absolute configuration of the *trans*-oxazoline **4a** was determined to be (4*S*,5*R*), the same as that of **4h**, by converting it into known free amino acid (2*S*,3*R*)-**6a** ($[\alpha]_D^{25}$ –20.0 (*c* 1, H_2O), lit.[5c] for (2*R*,3*S*)-**6a**: $[\alpha]_D^{25}$ +20.5). A little lower selectivity was observed with *o*-fluorobenzaldehyde (**2c**) (entries 6, 7).

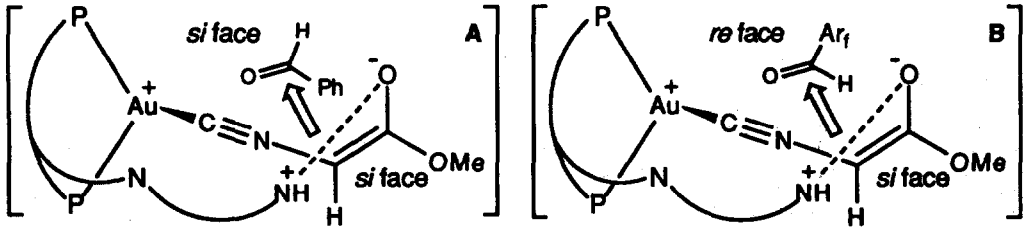

Figure 1. Proposed Transition-States Models for the Gold-Catalyzed Aldol Reaction

In the next experiments with di-, tri-, tetra- and pentafluorosubstituted benzaldehydes **2d-g**, which were done in similar conditions at 0 °C using 1 mol % of the catalyst (Au(I)/**3a**), our surprise was gradually increasing by the addition of each fluorine atom into the phenyl ring of a benzaldehyde under investigation (entries 8-11). Thus, each further addition of fluorine atom brought about gradual increase of the ratio of *cis*-oxazolines **5** and also their enantiomeric purity. On the other hand, the ee values of the corresponding *trans*-oxazolines **4** gradually dropped down. As it is shown in the Table (entries 10, 11), tetrafluoro- (**2f**) and pentafluorobenzaldehyde (**2g**), in sharp contrast to benzaldehyde (**2h**) or monofluorosubstituted ones **2a-c**, gave nearly 1 to 1 mixture of *trans*-oxazolines **4** and *cis*-oxazolines **5** with high ee (89% for **5f** and 78% for **5g**) of *cis*-**5** and quite low ee (48 and 39%) of *trans*-**4**. Such surprising differences in the stereoselectivity between benzaldehyde (**1h**) and fluorosubstituted benzaldehydes were totally unexpected. Whatever the origins of the puzzled influence of fluorine on the stereochemical outcome of the Au(I)-catalyzed aldol reaction, the gradual shift in the stereochemical results brought about by fluorine atoms is impressive. The highest *cis*-selectivity, 63% of **5g** (86% ee) and 62% of **5f** (90% ee), was achieved using morpholino derived ligand **3b**[9c] (entries 12, 13). For comparison the reaction of *p*-fluorobenzaldehyde (**2a**) with Au(I)/**3b** catalyst gave similar stereochemical outcome to that of benzaldehyde (**1h**) (entries 14, 15).

Acidic hydrolysis of **4g** and **5g** gave (2*S*,3*R*)-**6g** ($[\alpha]_D^{25}$ +3.0 (*c* 1, 6 N HCl), lit.[5c] $[\alpha]_D^{25}$ +13.03) and (2*S*,3*S*)-**7g** ($[\alpha]_D^{25}$ +35.8 (*c* 1, 6 N HCl), lit.[5c] $[\alpha]_D^{25}$ +37.4), respectively. It follows that *cis*-oxazoline **5g** has (4*S*,5*S*)-absolute configuration and *trans*-**4g** possesses (4*S*,5*R*)-one. This stereochemistry of the products suggests that favorable electrophilic attack of benzaldehyde (**2h**) and pentafluorobenzaldehyde (**2g**) occurs on the same enolate π-face (Figure 1; A, B) while the carbonyl π-face selectivities of **2h** and **2g** are different. Although rationalization of the *cis*-selectivity observed in this study is presently premature, sterically unfavorable transition-state structure B, which leads to formation of *cis*-(4*S*,5*S*)-oxazoline, could be stabilized by π-p interaction between electron deficient pentafluorophenyl ring and negatively charged enolate anion. We believe that the first case of predominant *cis*-selectivity described here will have a strong impact on a more deep understanding of the mechanism of the catalytic asymmetric aldol reaction of α-isocyanoacetic acid derivatives with aldehydes, because previous transition-state models of this reaction were designed to explain high *trans*-selectivity and high ee of *trans*-isomer.[9d]

Further works on gold(I) and silver(I)-catalyzed asymmetric aldol reaction of methyl isocyanoacetate and its derivatives with flustrates (fluorine-containing aldehydes and ketones) are now under active investigations.

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10 ^{1}H NMR (δ, $CDCl_3$) for oxazolines **4** and **5**: *trans*-**4a**, 3.84 (s, 3 H), 4.59 (dd, *J* = 7.9 Hz, 2.3 Hz, 1 H), 5.67 (d, *J* = 7.9 Hz, 1 H), 7.00-7.26 (m, 3 H), 7.28-7.33 (m, 2 H). *cis*-**5a**, 3.25 (s, 3 H), 5.08 (dd, *J* = 11.2 Hz, 2.1 Hz, 1 H), 5.73 (d, *J* = 11.2 Hz, 1 H), 7.05-7.24 (m, 3 H), 7.28-7.30 (m, 2 H). *trans*-**4b**, 3.85 (s, 3 H), 4.60 (dd, *J* = 7.9 Hz, 2.2 Hz, 1 H), 5.69 (d, *J* = 7.9 Hz, 1 H), 6.95-7.41 (m, 5 H). *cis*-**5b**, 3.27 (s, 3 H), 5.10 (dd, *J* = 11.2 Hz, 2.0 Hz, 1 H), 5.73 (d, *J* = 11.2 Hz, 1 H), 7.05-7.34 (m, 5 H). *trans*-**4c**, 3.84 (s, 3 H), 4.66 (dd, *J* = 7.6 Hz, 1.3 Hz, 1 H), 5.92 (d, *J* = 7.6 Hz, 1 H), 7.10-7.37 (m, 5 H). *cis*-**5c**, 3.25 (s, 3 H), 5.13 (dd, *J* = 10.9 Hz, 1.6 Hz, 1 H), 6.00 (d, *J* = 10.9 Hz, 1 H), 7.10-7.37 (m, 5 H). *trans*-**4d**, 3.82 (s, 3 H), 4.80 (dd, *J* = 8.5 Hz, 2.0 Hz, 1 H), 6.02 (d, *J* = 8.5 Hz, 1 H), 6.84-6.97 (m, 2 H), 7.01 (d, *J* = 2.0 Hz, 1 H), 7.23-7.36 (m, 1 H). *cis*-**5d**, 3.40 (s, 3 H), 5.18 (dd, *J* = 11.9 Hz, 2.3 Hz, 1 H), 6.10 (d, *J* = 11.9 Hz, 1 H), 6.81-6.93 (m, 2 H), 7.09 (d, *J* = 2.3 Hz, 1 H), 7.21-7.32 (m, 1 H). *trans*-**4e**, 3.83 (s, 3 H), 4.77 (dd, *J* = 8.3 Hz, 2.3 Hz, 1 H), 5.97 (d, *J* = 8.3 Hz, 1 H), 6.64-6.76 (m, 2 H), 6.99 (d, *J* = 2.3 Hz, 1 H). *cis*-**5e**, 3.48 (s, 3 H), 5.17 (dd, *J* = 11.7 Hz, 2.3 Hz, 1 H), 6.06 (d, *J* = 11.7 Hz, 1 H), 6.61-6.73 (m, 2 H), 7.09 (d, *J* = 2.3 Hz, 1 H). *trans*-**4f**, 3.84 (s, 3 H), 4.81 (dd, *J* = 8.3 Hz, 2.3 Hz, 1 H), 6.03 (d, *J* = 8.3 Hz, 1 H), 7.01 (d, *J* = 2.3 Hz, ,1 H), 7.1 (m, 1 H). *cis*-**5f**, 3.53 (s, 3 H), 5.24 (dd, *J* = 11.5 Hz, 2.3 Hz, 1 H), 6.10 (d, *J* = 11.5 Hz, 1 H), 7.1 (d, *J* = 2.3 Hz, 1 H), 7.2 (m, 1 H). *trans*-**4g**, 3.85 (s, 3 H), 4.79 (dd, *J* = 8.3 Hz, 2.3 Hz, 1 H), 5.99 (d, *J* = 8.3 Hz, 1 H), 7.00 (d, *J* = 2.3 Hz, 1 H). *cis*-**5g**, 3.57 (s, 3 H), 5.21 (dd, *J* = 11.6 Hz, 2.3 Hz, 1 H), 6.06 (d, *J* = 11.6 Hz, 1 H), 7.09 (d, *J* = 2.3 Hz, 1 H).

11 ^{1}H NMR (δ, $CDCl_3$) for *N*-benzoyl derivatives **8a-g**: *syn*-**8a**, 3.68 (s, 3 H), 4.98 (dd, *J* = 8.9 Hz, 3.3 Hz, 1 H), 5.31 (d, *J* = 3.3 Hz, 1 H), 7.16 (br d, *J* = 8.9 Hz, 1 H), 6.95-7.69 (m, 9 H). *anti*-**8a**, 3.67 (s, 3 H), 5.09 (dd, *J* = 7.6 Hz, 3.3 Hz, 1 H), 5.26 (d, *J* = 3.3 Hz, 1 H), 7.07 (br d, *J* = 7.6 Hz, 1 H), 7.00-7.68 (m, 9 H). *syn*-**8b**, 3.72 (s, 3 H), 5.03 (dd, *J* = 8.9 Hz, 3.0 Hz, 1 H), 5.36 (d, *J* = 3.0 Hz, 1 H), 6.93-7.61 (m, 9 H). *anti*-**8b**, 3.71 (s, 3 H), 5.14 (dd, *J* = 7.3 Hz, 3.3 Hz, 1 H), 5.31 (d, *J* = 3.3 Hz, 1 H), 6.90-7.72 (m, 9 H). *syn*-**8c**, 3.80 (s, 3 H), 5.17 (dd, *J* = 8.6 Hz, 3.0 Hz, 1 H), 5.69 (d, *J* = 3.0 Hz, 1 H), 6.91 (br d, *J* = 8.6 Hz, 1 H), 7.00-7.68 (m, 9 H). *anti*-**8c**, 3.82 (s, 3 H), 5.20 (dd, *J* = 6.6 Hz, 3.0 Hz, 1 H), 5.66 (d, *J* = 3.0 Hz, 1 H), 7.05-7.71 (m, 10 H). *syn*-**8d**, 3.75 (s, 3 H), 5.17 (dd, *J* = 8.3 Hz, 4.6 Hz, 1 H), 5.64 (d, *J* = 4.6 Hz, 1 H), 6.85 (m, 2 H), 7.23 (m, 2 H), 7.50 (m, 3 H), 7.78 (m, 2 H). *anti*-**8d**, 3.80 (s, 3 H), 5.27 (dd, *J* = 7.3 Hz, 4.7 Hz, 1 H), 5.58 (m, 1 H), 6.90 (m, 2 H), 7.01 (m, 1 H), 7.25 (m, 1 H), 7.53 (m, 3 H), 7.72 (m, 2 H). *syn*-**8e**, 3.77 (s, 3 H), 5.17 (m, 1 H), 5.60 (m, 1 H), 6.61 (m, 2 H), 7.00 (m, 1 H), 7.23 (m, 3 H), 7.75 (m, 2 H). *anti*-**8e**, 3.82 (s, 3 H), 5.25 (m, 1 H), 5.55 (m, 1 H), 6.62 (m, 2 H), 7.21 (m, 1 H), 7.22 (m, 3 H), 7.77 (m, 2 H). *syn*-**8f**, 3.84 (s, 3 H), 5.21 (m, 1 H), 5.63 (m, 1 H), 7.01 (m, 1 H), 7.17 (m, 1 H), 7.25 (m, 3 H), 7.75 (m, 2 H). *anti*-**8f**, 3.80 (s, 3 H), 5.31 (m, 1 H), 5.62 (m, 1 H), 7.01 (m, 1 H), 7.38 (m, 1 H), 7.22 (m, 3 H), 7.76 (m, 2 H). *syn*-**8g**, 3.80 (s, 3 H), 5.18 (dd, *J* = 8.2 Hz, 4.9 Hz, 1 H), 5.65 (d, *J* = 4.9 Hz, 1 H), 7.23 (br d, *J* = 8.2 Hz, 1 H), 7.48 (m, 3 H), 7.81 (m, 2 H). *anti*-**8g**, 3.85 (s, 3 H), 5.29 (dd, *J* = 6.6 Hz, 4.3 Hz, 1 H), 5.63 (d, *J* = 4.3 Hz, 1 H), 7.07 (br d, *J* = 6.6 Hz, 1 H), 7.50 (m, 3 H), 7.80 (m, 2 H).

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