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Gold(I)-Catalyzed Asymmetric Aldol Reactions of Fluorinated Benzaldehydes with an α-Isocyanoacetamide

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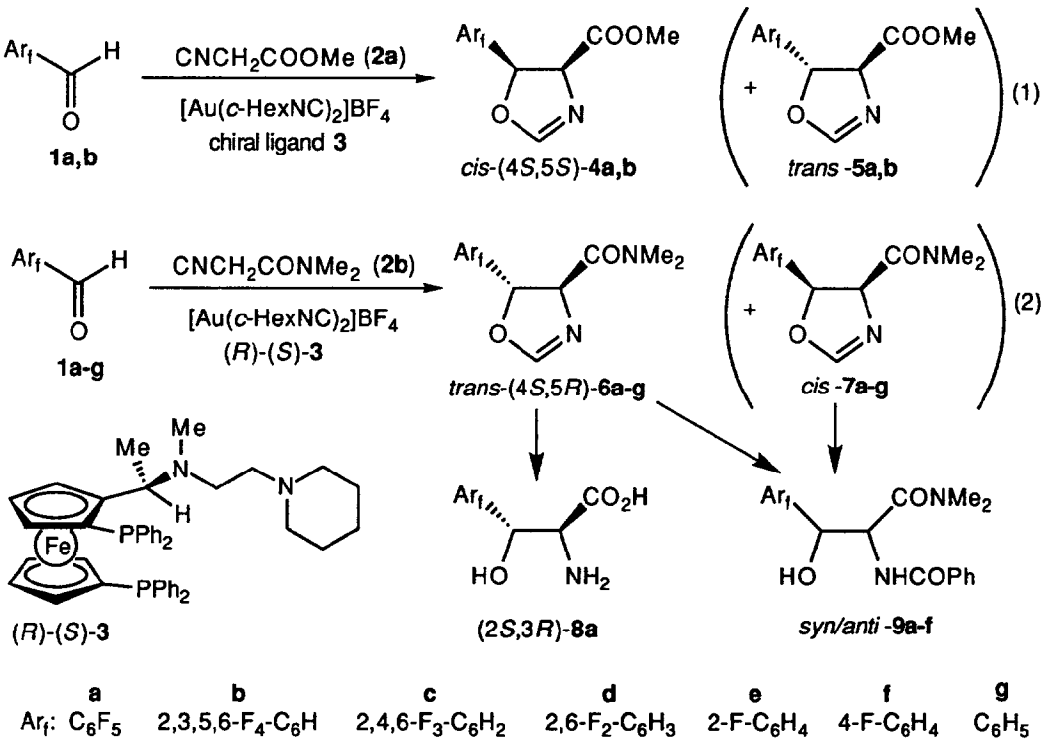
Abstract: The use of *N,N*-dimethyl-α-isocyanoacetamide instead of methyl α-isocyanoacetate in the gold(I)-catalyzed asymmetric aldol reactions with polyfluorinated benzaldehydes was found to improve both diastereo- and enantioselectivity in the formation of *trans*-oxazolines.

Recently we have reported the unusual stereochemical outcome in the gold(I)-catalyzed asymmetric aldol reaction[2] of fluorinated benzaldehydes **1** with methyl α-isocyanoacetate (**2a**).[3] Thus, the successive substitution of hydrogen atoms by fluorine in the phenyl ring of benzaldehyde brought about gradual increase of both the yield of *cis*-oxazolines **4** and their enantiomeric purity, whilst the ee's of *trans*-oxazolines **5** significantly decreased. The extremes of the trend were observed in the aldol reaction of penta- and tetrafluorobenzaldehydes **1a** and **1b** with **2a** where corresponding *cis*-oxazolines **4** were formed with higher than 60% *cis*-selectivity and with up to 90% enantioselectivity (eq 1). In this communication we report the asymmetric aldol reaction of fluorobenzaldehydes **1a-f** with *N,N*-dimethyl-α-isocyanoacetamide[4] (**2b**) which improves both *trans*-selectivity in the oxazoline ring formation and % ee of the dominant *trans*-oxazolines **6** (eq 2).



	a	b	c	d	e	f	g
Ar$_f$:	C_6F_5	2,3,5,6-F_4-C_6H	2,4,6-F_3-C_6H_2	2,6-F_2-C_6H_3	2-F-C_6H_4	4-F-C_6H_4	C_6H_5

Table 1. Gold(I)-Catalyzed Asymmetric Aldol Reactions of Fluorobenzaldehydes **1a-f** with *N,N*-Dimethyl-α-isocyanoacetamide (**2b**)

entry	Ar_f in aldehyde	conditions[a] temp (°C)	time (h)	yield[b] (%)	ratio[c] *trans*-**6**/*cis*-**7**	% ee[d] *trans*-**6**	*cis*-**7**
1	C_6F_5 (**1a**)	15[e]	48	82	77/23 (57/43)	80 (36)	20
2	C_6F_5 (**1a**)	25	24[f]	87	81/19	68	24
3	2,3,5,6-F_4-C_6H (**1b**)	20	20	88	89/11	77	28
4	2,3,5,6-F_4-C_6H (**1b**)	15[e]	50	78	84/16 (47/53)	84 (48)	26
5	2,4,6-F_3-C_6H_2 (**1c**)	10	48	83	85/15 (67/33)	91 (73)	48
6	2,6-F_2-C_6H_3 (**1d**)	20	25	84	77/23 (75/25)	93 (86)	64
7	2-F-C_6H_4 (**1e**)	22	25	87	83/13 (89/11)	93 (90)	-
8	4-F-C_6H_4 (**1f**)	20	24	89	92/8 (93/7)	94 (96)	-
9[g]	C_6H_5 (**1g**)	25	25	74[h]	94/6 (95/5)	94 (95)	-

[a] The reactions were carried out in dichloromethane under argon atmosphere. The gold catalyst was prepared *in situ* from $[Au(c\text{-}HexNC)_2]BF_4$ and chiral ligand **3**. Ratio of **1/2b**/Au(I)/**3** = 1.3/1/0.02/0.022 unless otherwise noted. [b] Isolated yield after passing reaction mixture through a short silica gel column (3 x 1.5 cm) using ethyl acetate as an eluent. [c] Determined by ^1H NMR analysis. See also ref. 8. Data previously reported on the Au(I)-catalyzed aldol reaction of corresponding fluorobenzaldehydes[3] and benzaldehyde[2] with isocyanoacetate **2a** are given in the parentheses. [d] Determined by HPLC analysis of *N,N*-dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(fluorophenyl)propanamides **9a-f**[9] with a chiral stationary phase column (SUMICHIRAL OA-2000, 2000I, 4500, or 4900), hexane/1,2-dichloroethane/ethanol = 50/15/1, 100/20/1, or 250/20/1. The absolute configuration of **6a** is (4*S*,5*R*) (see text). All other *trans*-oxazolines **6b-f** are assumed to have the same (4*S*,5*R*) configuration by similarity in the order of elution in the condition of chiral HPLC analysis. The absolute configuration of the *cis*-oxazolines **7** was not determined. The highest % ee of *trans*-(4*S*,5*R*)-oxazoline, previously reported on the Au(I)-catalyzed aldol reaction of corresponding fluorobenzaldehydes[3] and benzaldehyde[2] with isocyanoacetate **2a** are given in the parentheses. [e] Reaction was started at 0 °C and then reaction temperature was allowed to rise to the indicated temperature. [f] One mol % of the catalyst was used. [g] Previously reported data, see ref. 4. [h] Yield of *trans*-oxazoline **6h**, see ref. 4.

We started our experiments with the reaction of isocyanoacetamide **2b**[5] with pentafluorobenzaldehyde (**1a**) which was, in the light of the previous work,[3] expected to display the most significant difference in the reactivity and selectivity from fluorine-free benzaldehyde. Thus, to a stirred solution of chiral ferrocenylphosphine ligand **3** (30.6 mg, 0.044 mmol), bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate (20 mg, 0.040 mmol), and *N,N*-dimethyl-α-isocyanoacetamide (**2b**) (224 mg, 2.0 mmol) in 4 mL of freshly distilled dichloromethane at 0 °C was added under argon pentafluorobenzaldehyde (**1a**) (500 mg, 2.56 mmol). After mixing, the reaction mixture was stirred at 15 °C for 48 h. After removing the solvent under reduced pressure the crude reaction mixture was subjected to ^1H NMR analysis that has shown that the ratio of *trans*-oxazoline **6a** to *cis*-isomer **7a** is 77/23 (Table 1, entry 1). Silica gel column (3 x 1.5 cm) chromatography of the reaction mixture with ethyl acetate as eluent gave 503 mg (82%) of the oxazolines. The oxazolines **6a** and **7a** were converted into *N,N*-dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(pentafluorophenyl)propanamides **9a** by hydrolysis with conc. HCl in methanol at 50 °C (2 h) followed by benzoylation of the resulting amine with

benzoyl chloride in the presence of triethylamine in dichloromethane. Chiral HPLC analysis of *N*-benzoyl derivatives **9a** has shown that the enantiomeric purity of *syn*-isomer (derived from *trans*-oxazoline **6a**) is 80% ee and that of *anti*-isomer is 20% ee (entry 1). Hydrolysis of *trans*-**6a** with 6 N HCl gave after dehydrochlorination[6] with propylene oxide in methanol β-(pentafluorophenyl)serine **8a**. Comparison of $[\alpha]_D$ value of amino acid **8a** obtained ($[\alpha]_D^{25}$ +12.1 (*c* 0.5, 6 N HCl)) with the literature value (lit.[7] for (2*S*,3*R*)-**8a**: $[\alpha]_D^{25}$ +13.03) establishes its (2*S*,3*R*)-absolute configuration and, consequently, the (4*S*,5*R*)-absolute configuration of *trans*-oxazoline **6a**. At higher temperature (25 °C) (entry 2) the aldol reaction of isocyanoacetamide **2b** with pentafluorobenzaldehyde (**1a**) proceeded with higher *trans*-selectivity (81%) but the % ee was lower (68%). Similar reactivity and stereochemical outcome were observed in the aldol reaction of 2,3,5,6-tetrafluorobenzaldehyde (**1b**) with amide **2b** (entries 3 and 4). Thus, the highest *trans*-selectivity (89%) with 77% ee of oxazoline **6b** was observed at 20 °C, whilst low temperature reaction gave *trans*-oxazoline **6b** with 84% of diastereoselectivity and 84% ee.

In the aldol reactions of trifluoro- and difluorobenzaldehydes **1c** and **1d** with isocyanoacetamide **2b** (entries 5 and 6), the desired *trans*-oxazolines **6c** and **6d** were obtained with higher enantioselectivity (91% ee for **6c** and 93% ee for **6d**) than in the reaction with isocyanoacetate **2a**. These % ee's are in line with the highest levels of asymmetric induction which previously have been achieved in the gold(I)-catalyzed asymmetric aldol reaction.[2] Finally, the aldol reactions of isocyanoacetamide **2b** with monofluoro-substituted benzaldehydes **1e,f** gave expectedly high diastereo- and enantioselectivities (entries 7 and 8). However, the use of isocyanoacetamide **2b** for the synthesis of corresponding β-(monofluorophenyl)serines **8**, as well as fluorine free one (entry 9), through oxazolines **6e-g**, seems to have no advantages over the application of isocyanoacetate **2a**, which provides a rather better stereochemical outcome.[2,3]

The present results have revealed that the stereochemical outcome of the gold(I)-catalyzed asymmetric aldol reactions of *N,N*-dimethyl-α-isocyanoacetamide (**2b**) with polyfluorobenzaldehydes **1a** and **1b** stands in marked contrast to that of isocyanoacetate **2a**. Thus, amide **2b** provides preferential formation and high % ee of *trans*-oxazolines, while ester **2a** favors *cis*-diastereoselectivity and high % ee of *cis*-isomers. It follows that both *threo*- and *erythro*-(polyfluorophenyl)serines can be prepared selectively in high enantiomeric purity *via* gold(I)-catalyzed asymmetric aldol reaction by use of amide **2b** and ester **2a**, respectively. In the reaction of both amide **2b** and ester **2a**, the same *si*-face of enolate derived from isonitrile **2a** or **2b** is favourable for electrophilic attack of aldehyde. The rationale of the influence of the fluorine atoms on the stereochemistry of the aldol reaction requires futher investigation.

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8 Owing to an effect of aromatic ring, the methyl protons of dimethylamino group in *cis*-oxazolines **7** shifted upfield in comparison with those of the *trans*-oxazolines **6**. ^{1}H NMR (δ, $CDCl_3$) for oxazolines **6** and **7**: *trans*-**6a**, 3.02 (s, 3 H), 3.26 (s, 3 H), 4.86 (dd, *J* = 7.6 Hz, 2.1 Hz, 1 H), 6.59 (d, *J* = 7.6 Hz, 1 H), 6.89 (d, *J* = 2.1 Hz, 1 H). *cis*-**7a**, 2.77 (s, 3 H), 3.13 (s, 3 H), 5.43 (dd, *J* = 11.2 Hz, 2.1 Hz, 1 H), 5.98 (d, *J* = 11.2 Hz, 1 H), 7.08 (d, *J* = 2.1 Hz, 1 H). *trans*-**6b**, 3.01 (s, 3 H), 3.26 (s, 3 H), 4.89 (dd, *J* = 7.8 Hz, 2.1 Hz, 1 H), 6.62 (d, *J* = 7.8 Hz, 1 H), 6.88 (d, *J* = 2.1 Hz, 1 H), 7.02-7.19 (m, 1 H). *cis*-**7b**, 2.75 (s, 3 H), 3.11 (s, 3 H), 5.42 (dd, *J* = 11.1 Hz, 2.1 Hz, 1 H), 6.05 (d, *J* = 11.1 Hz, 1 H), 7.01 (d, *J* = 2.1 Hz, 1 H), 7.00-7.15 (m, 1 H). *trans*-**6c**, 2.99 (s, 3 H), 3.24 (s, 3 H), 4.84 (dd, *J* = 7.6 Hz, 2.0 Hz, 1 H), 6.54 (d, *J* = 7.6 Hz, 1 H), 6.88 (d, *J* = 2.0 Hz, 1 H), 6.60-6.75 (m, 2 H). *cis*-**7c**, 2.68 (s, 3 H), 3.15 (s, 3 H), 5.36 (dd, *J* = 11.2 Hz, 2.1 Hz, 1 H), 6.03 (d, *J* = 11.2 Hz, 1 H), 6.63-6.76 (m, 2 H), 7.10 (d, *J* = 2.1 Hz, 1 H). *trans*-**6d**, 2.94 (s, 3 H), 3.18 (s, 3 H), 4.83 (dd, *J* = 7.6 Hz, 2.3 Hz, 1 H), 6.53 (d, *J* = 7.6 Hz, 1 H), 6.85 (d, *J* = 2.3 Hz, 1 H), 7.44-7.58 (m, 3 H). *cis*-**7d**, 2.75 (s, 3 H), 2.91 (s, 3 H), 5.33 (dd, *J* = 11.3 Hz, 2.1 Hz, 1 H), 6.03 (d, *J* = 11.3 Hz, 1 H), 7.06 (d, *J* = 2.1 Hz, 1 H), 7.15-7.28 (m, 3 H). *trans*-**6e**, 3.00 (s, 3 H), 3.17 (s, 3 H), 4.71 (dd, *J* = 7.8 Hz, 2.1 Hz, 1 H), 6.22 (d, *J* = 7.8 Hz, 1 H), 6.93 (d, *J* = 2.1 Hz, 1 H), 7.05-7.30 (m, 4 H). *cis*-**7e**, 2.62 (s, 3 H), 2.88 (s, 3 H), 5.41 (dd, *J* = 10.2 Hz, 2.1 Hz, 1 H), 5.93 (d, *J* = 10.2 Hz, 1 H), 7.11-7.37 (m, 5 H). *trans*-**6f**, 2.90 (s, 3 H), 3.11 (s, 3 H), 4.53 (dd, *J* = 7.9 Hz, 2.1 Hz, 1 H), 6.06 (d, *J* = 7.9 Hz, 1 H), 6.88 (d, *J* = 2.1 Hz, ,1 H), 6.92-7.21 (m, 4 H). *cis*-**7f**, 2.63 (s, 3 H), 2.73 (s, 3 H), 5.20 (dd, *J* = 10.9 Hz, 2.0 Hz, 1 H), 5.49 (d, *J* = 10.9 Hz, 1 H), 6.91-7.20 (m, 5 H).

9 *N*-Benzoyl derivatives **9a-f** were prepared by hydrolysis of corresponding oxazolines with conc. HCl in methanol followed by benzoylation with benzoyl chloride in the presence of triethylamine. ^{1}H NMR (δ, $CDCl_3$) for *N*-benzoyl derivatives **9a-g**: *syn*-**9a**, 3.04 (s, 3 H), 3.28 (s, 3 H), 5.09 (d, *J* = 7.6 Hz, 1 H), 5.44 (dd, *J* = 7.6 Hz, 5.3 Hz, 1 H), 5.68 (dd, *J* = 7.3 Hz, 5.3 Hz, 1 H), 7.27 (d, *J* = 7.3 Hz, 1 H), 7.41-7.50 (m, 3 H), 7.71-7.75 (m, 2H). *anti*-**9a**, 3.03 (s, 3 H), 3.20 (s, 3 H), 4.61 (d, *J* = 4.4 Hz, 1 H), 5.43 (dd, *J* = 8.7 Hz, 3.3 Hz, 1 H), 5.57 (dd, *J* = 4.4 Hz, 3.3 Hz, 1 H), 7.33 (d, *J* = 8.7 Hz, 1 H), 7.44-7.56 (m, 3 H), 7.76-7.79 (m, 2H). *syn*-**9b**, 2.95 (s, 3 H), 3.20 (s, 3 H), 4.96 (d, *J* = 7.6 Hz, 1 H), 5.40 (dd, *J* = 7.6 Hz, 5.7 Hz, 1 H), 5.62 (dd, *J* = 7.3 Hz, 5.7 Hz, 1 H), 6.91 (tt, *J* = 9.6 Hz, 7.6 Hz, 1 H), 7.19 (d, *J* = 7.3 Hz, 1 H), 7.33-7.45 (m, 3 H), 7.63-7.66 (m, 2H). *anti*-**9b**, 2.92 (s, 3 H), 3.12 (s, 3 H), 4.68 (bs, 1 H); 5.40 (m, 1 H), 5.51 (dd, *J* = 5.3 Hz, 3.6 Hz, 1 H), 6.95 (tt, *J* = 9.6 Hz, 7.6 Hz, 1 H), 7.31-7.47 (m, 4 H), 7.68-7.72 (m, 2H). *syn*-**9c**, 2.99 (s, 3 H), 3.21 (s, 3 H), 4.57 (d, *J* = 7.4 Hz, 1 H), 5.36 (dd, *J* = 7.4 Hz, 6.3 Hz, 1 H), 5.66 (dd, *J* = 7.9 Hz, 6.3 Hz, 1 H), 6.59 (t, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 7.9 Hz, 1 H), 7.36-7.52 (m, 3 H), 7.67-7.70 (m, 2H). *anti*-**9c**, 2.95 (s, 3 H), 3.13 (s, 3 H), 4.41 (d, *J* = 5.0 Hz, 1 H), 5.42-5.46 (m, 2 H), 6.62 (t, *J* = 8.6 Hz, 2 H), 7.25-7.50 (m, 4 H), 7.76-7.79 (m, 2H). *syn*-**9d**, 2.96 (s, 3 H), 3.18 (s, 3 H), 4.60 (m, 1 H), 5.43 (dd, *J* = 7.6 Hz, 6.9 Hz, 1 H), 5.70 (dd, *J* = 8.3 Hz, 6.9 Hz, 1 H), 6.77-6.88 (m, 2 H), 7.14-7.48 (m, 5 H), 7.62-7.71 (m, 2H). *anti*-**9d**, 2.91 (s, 3 H), 3.09 (s, 3 H), 4.22 (bs, 1 H), 5.50 (m, 2 H), 6.80 (m, 2 H), 7.05-7.21 (m, 1 H), 7.31-7.44 (m, 4 H), 7.71-7.74 (m, 2H). *syn*-**9e**, 2.95 (s, 3 H), 3.16 (s, 3 H), 4.75 (d, *J* = 1.6 Hz, 1 H), 5.33 (dd, *J* = 8.9 Hz, 2.0 Hz, 1 H), 5.37 (m, 1 H), 6.95-7.07 (m, 3 H), 7.12-7.21 (m, 1 H), 7.28-7.52 (m, 4 H), 7.55-7.63 (m, 2 H). *syn*-**9f**, 2.86 (s, 3 H), 2.90 (s, 3 H), 4.75 (d, *J* = 2.0 Hz, 1 H), 5.04 (dd, *J* = 4.3 Hz, 2.0 Hz, 1 H), 5.18 (dd, *J* = 8.7 Hz, 4.3 Hz, 1 H), 6.90-6.96 (m, 2 H), 7.09 (d, *J* = 8.7 Hz, 1 H) 7.31-7.44 (m, 5 H), 7.63-7.67 (m, 2 H).

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