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Gold(I)-Catalyzed Asymmetric Aldol Reactions of Isocyanoacetic Acid Derivatives with Fluoroaryl Aldehydes

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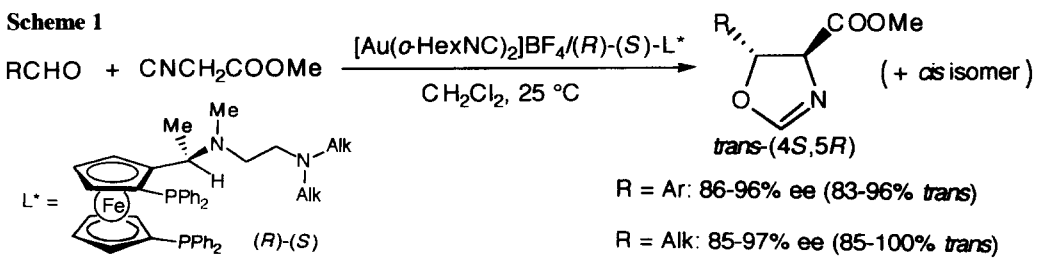
Abstract: The catalytic asymmetric synthesis of stereochemically defined fluoro-phenylserines is reported. In the title reaction, when methyl isocyanoacetate is employed, the number of fluorine atoms in the phenyl ring of benzaldehyde controls stereochemical outcome of the reaction giving rise in the case of monofluorobenzaldehydes corresponding *trans*-oxazolines with more than 90% of both *trans*-selectivity and % ee, while in the case of polyfluorobenzaldehydes corresponding *cis*-oxazolines are formed as dominant isomers with high enantiomeric excess (up to 63% of *cis* with 86-90% ee). In contrast to this, aldol reactions of isocyanoacetamide with fluoro-benzaldehydes provide dominant formation of *trans*-oxazolines (77-92% of *trans* with 80-94% ee) in all cases studied. The observed unusual stereodifferentiation in the reaction of methyl isocyanoacetate with polyfluorobenzaldehydes is rationalized on the basis of an electron donor—acceptor type attractive interaction between the polyfluorophenyl ring and the enolate oxygen.

INTRODUCTION

Owing to the general awareness of the effects that stereochemistry may have on a chiral compound biological activity, metabolism, and disposition,[2] the development of EPC synthesis[3] is today a topic of fundamental importance.[4] The efficient asymmetric approaches, allowing to achieve levels of stereoselectivity that rival enzymatic systems, have been developed for many classes of organic compounds. By contrast, fluoro-organic compounds turned out to be difficult targets for EPC synthesis. Now it is commonly recognized, that fluorine can dramatically alter both the course and stereochemical outcome of the reactions established for hydrocarbon patterns thus providing a challenge to the asymmetric synthesis of fluorinated compounds.[5] With the growing importance of enantiomerically pure fluoro-organic compounds in the pharmaceutical, agrochemical and optoelectronic industries, stereocontrolled preparation of fluorine-containing compounds has received much attention recently.[6] Methods to achieve this aim, wherein truly catalytic amount of an asymmetric agent is required, represent the most desirable solutions.[7] In the recent communications[1] we have demonstrated that the gold(I)-catalyzed asymmetric aldol reaction[8] (Scheme 1) provides an effective, synthetically useful approach to the series of fluoro-phenylserines of high diastereo- and enantiomeric purity. In this paper we report full details of our investigations which, apart from synthetic results, have revealed surprising dependence of stereochemical outcome of the asymmetric aldol reactions upon the number of fluorine atoms in the phenyl ring of starting benzaldehyde and the nature of isocyanoacetic acid derivative used as well.

Scheme 1



RESULTS AND DISCUSSION

Gold(I)-catalyzed asymmetric aldol reaction consists in the interaction between an aldehyde and methyl isocyanoacetate,[9] catalyzed by 1-2 mol % of gold(I) complex co-ordinated with chiral *N,N,N',N'*-tetra-alkylethylenediamino-substituted bis(diphenylphosphino)ferrocene ligand, leading to the optically active *trans*-5-substituted-2-oxazoline-4-carboxylates[10] with high enantio- and diastereoselectivity (Scheme 1).[8] Desirable *syn*-(2*S*)-β-(substituted)serines can be easily released from the corresponding diastereo- and enantiomerically pure *trans*-oxazolines under the standard conditions of acidic hydrolysis. External chiral ferrocenylphosphine ligands used in this reaction, differing for *N,N*-dialkylamino group at the terminal position of the pendent side chain, are commercially available or can be readily prepared with high overall yield and even in the ten-grams scale by well established 7-steps procedure starting with commercial ferrocene.[8b,h,11] Previous extensive studies on the gold(I)-catalyzed asymmetric aldol reaction have demonstrated its generality for the asymmetric synthesis of various β-(substituted)serines and other natural products[12] as well as its preparative advantage over stoichiometric versions of asymmetric aldol reaction.[13] However, despite the general applicability of this reaction to the wide range of alkyl, alkenyl, and aryl aldehydes its stereochemical outcome is not always unambiguous, varying from the excellent (100% de, 97% ee, R = *tert*-Bu)[8a,h] to poor (50% de, 6% ee, R = 2-C_5H_4N)[8i] depending on the nature of aldehyde used. Behavior of fluoroaryl aldehydes under the conditions of the gold(I)-catalyzed asymmetric aldol reaction was not previously studied. Therefore, the lure of a general asymmetric synthesis of biologically important fluorine-containing phenylserines and related compounds,[14] prompted us to undertake the present investigation.

As it was shown earlier, for the particular case of benzaldehyde (**1a**) aldol reaction with methyl α-isocyanoacetate (**2a**), complex of bis(*c*-hexyl isocyanide)gold(I) tetrafluoroborate (**3**) with (*R*)-*N*-methyl-*N*-[2-(piperidino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (**4a**) proved to be a superior catalyst for this condensation, providing formation of *trans*-oxazoline **5a** in 88% diastereomeric and 95% enantiomeric excess (de and ee respectively), (Scheme 2, Table 1, entry 1).[8b,c,h] Under the same reaction conditions *p*-fluoro-(**1b**) and *m*-fluorobenzaldehydes (**1c**) gave corresponding *trans*-oxazolines **5b** and **5c** (entries 2, 3) in the excellent chemical yields (97% for **5b** and 96% for **5c**), diastereo- (86%, 82%) and enantioselectivities (94%, 93%). At the lower temperature (0 °C) we have improved both diastereo- and enantioselectivity for *trans*-oxazolines **5b** and **5c** up to 88% de and over 95% ee (entries 4, 5). A little lower selectivity was observed for *o*-fluorobenzaldehyde (**1d**) reaction with **2a** (entries 6, 7). The absolute

Scheme 2

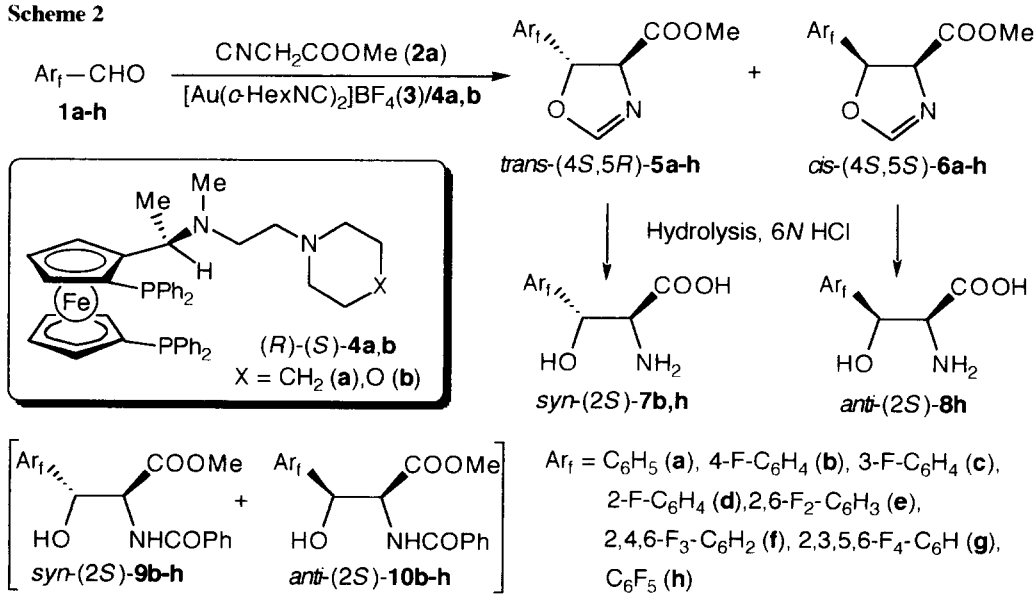


Table 1. Gold(I)-Catalyzed Asymmetric Aldol Reaction of Fluorobenzaldehydes **1b-h** with **2a**[a]

entry	Ar_f in aldehyde (**1**)	conditions ligand	temp(°C)	time (h)	yield[b] (%)	ratio[c] *trans*-**5**/*cis*-**6**	% ee[d] *trans*-**5**	*cis*-**6**
1[e]	C_6H_5 (**a**)	**4a**	25	20-40	94	94 / 6	95	49[f]
2	4-F-C_6H_4 (**b**)	**4a**	25	10	97	93 / 7	94	20
3	3-F-C_6H_4 (**c**)	**4a**	23	10	96	91 / 9	93	23
4	4-F-C_6H_4 (**b**)	**4a**	0	100	96	94 / 6	96	19
5	3-F-C_6H_4 (**c**)	**4a**	0	100	97	94 / 6	95	20
6	2-F-C_6H_4 (**d**)	**4a**	23	10	96	84 / 14	84	38
7	2-F-C_6H_4 (**d**)	**4a**	1	45	99	89 / 11	90	40
8	2,6-F_2-C_6H_3 (**e**)	**4a**	0	79	98	75 / 25	86	78
9	2,4,6-F_3-C_6H_2 (**f**)	**4a**	0	100	96	67 / 33	73	82
10	2,3,5,6-F_4-C_6H (**g**)	**4a**	0	71	90	47 / 53	48	89
11	C_6F_5 (**h**)	**4a**	1	21	94	47 / 53	28	79
12	C_6F_5 (**h**)	**4a**	23	1	91	67 / 33	23	67
13[e]	C_6H_5 (**a**)	**4b**	25	20-40	93	95 / 5	95	12[g]
14	C_6F_5 (**h**)	**4b**[h]	0	100	96	37 / 63	36	86
15	2,3,5,6-F_4-C_6H (**g**)	**4b**[h]	0	70	93	38 / 62	33	90
16	4-F-C_6H_4 (**b**)	**4b**	0	70	92	94 / 6	94	25

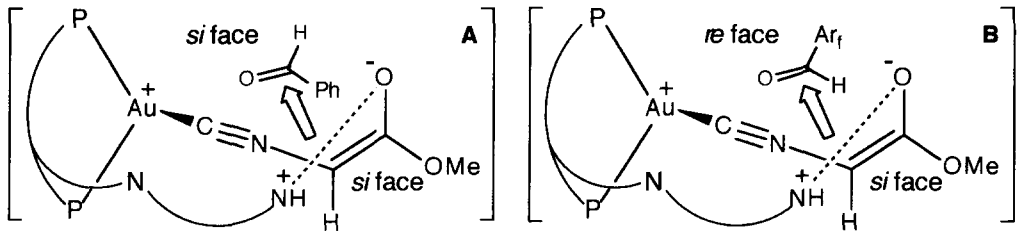
[a] The reactions were carried out in dichloromethane under argon atmosphere. The gold catalyst was prepared *in situ* from [Au(*c*-HexNC)$_2$]BF_4 **3** and corresponding chiral ligand **4a** or **4b**. Ratio of **1b-h/2a/3/4a,b** = 1/1.1/0.01/0.011 unless otherwise noted. [b] Isolated yield by bulb-to-bulb distillation. [c] Determined by ^{1}H NMR analysis. [d] Determined by chiral HPLC analysis of methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(fluorophenyl)propionates **9,10** 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 **5** is assigned to be (4*S*,5*R*), and of *cis*-**6** to be (4*S*,5*S*) by similarity in the order of elution of derivatives **9, 10** under the conditions of chiral HPLC analysis. See also text. [e] Previously published data, see text. [f] Absolute configuration is (4*R*,5*R*). [g] Absolute configuration is (4*S*,5*S*). [h] 2 Mol % of catalyst (**3/4b**) was used.

configuration of the *trans*-oxazoline **5b** was determined to be (4*S*,5*R*), the same as that of **5a**, by converting it into the known free *syn*-(2*S*)-β-(*p*-fluorophenyl)serine **7b** [(2*S*,3*R*)-**7b**].

The next experiments with di-, tri-, tetra- and pentafluorosubstituted benzaldehydes **1e-h**, which were done under the same reaction conditions at 0-1 °C using 1 mol % of the catalyst (**3/4a**), have revealed a surprising influence of the number of fluorine atoms in the phenyl ring of starting benzaldehyde on the stereochemical outcome of aldol reactions (entries 8-11 vs 2-7). Thus, the increase of fluorine substitution for hydrogen in the series of fluorobenzaldehydes **1e-h** was accompanied by gradual increase of the ratio of *cis*-oxazolines **6e-h** and their enantiomeric purity as well. On the other hand, the ee values of the corresponding *trans*-oxazolines **5e-h**, formed in the reactions of **1e-h** with **2a**, were gradually decreasing. The extremes of this trend, 57% of cis-diastereoselectivity, were observed in the tetrafluoro-**1g** and pentafluorobenzaldehyde (**1h**) reaction with isocyanoacetate **2a** (entries 10, 11). Enantiomeric purity of *cis*-oxazolines **6g,h** was shown to be 89 and 79% ee, respectively. At room temperature (entry 12), ratio of *trans*-oxazoline **5h** in the reaction of **1h** with **2a** was markedly increased, however ee of both *trans*- and *cis*-oxazolines **5h** and **6h** was low.

For determination of oxazolines **5h** and **6h** absolute configuration, they were separated and then, each of them was hydrolyzed to give corresponding β-(pentafluorophenyl)serines **7h** and **8h** of known configuration. Comparison of $[\alpha]_D$ values of amino acids **7h** and **8h** obtained with that reported in literature (see experimental) has revealed their *syn*-(2*S*) and *anti*-(2*S*) configuration respectively, and consequently (4*S*,5*R*) configuration for

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



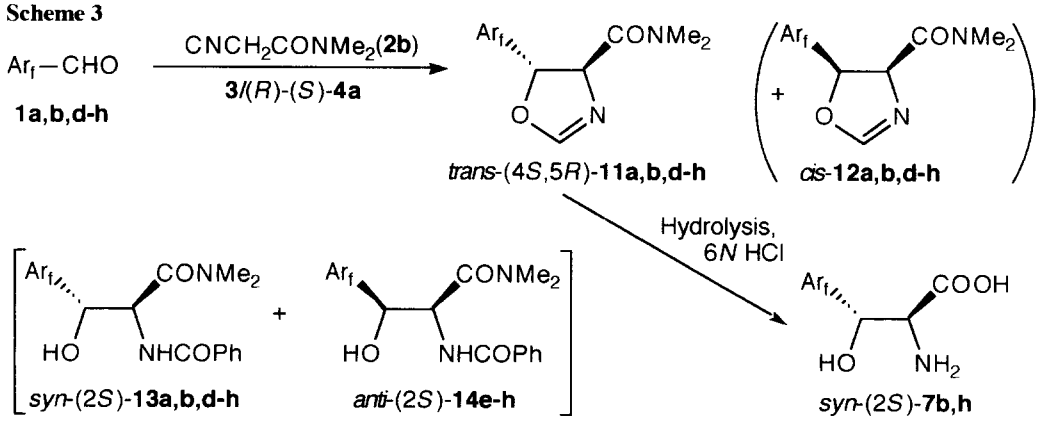
trans-**5h** and (4*S*,5*S*) for *cis*-oxazoline **6h**. With these results in hands we suggested that chiral ferrocenylphosphine ligand **4b**, bearing a morpholino residue on the terminal position of the pendant side chain, which in contrary to **4a** provides (4*S*,5*S*) absolute configuration of corresponding *cis*-oxazoline in the reaction of **1a** with **2a** (entry 13), might increase stereoselectivity of polyfluorobenzaldehydes reactions with isocyanoacetate **2a**. Indeed, application of morpholino derived ligand **4b** in the complex with gold(I) **3** for catalysis of aldol reactions of aldehydes **1g** and **1h** with **2a** has improved both the ratio of *cis*-oxazolines **6g** (62%) and **6h** (63%) and their enantiomeric purity (90% and 86% ee, respectively), (entries 14, 15). Reaction of *p*-fluorobenzaldehyde (**1b**) with isocyanoacetate **2a**, catalyzed by the complex **3**/**4b**, gave a stereochemical outcome similar to that of benzaldehyde (**1a**) reaction (entries 13 vs 16).

As it follows from the results obtained, gold(I) **3**/chiral ferrocenylphosphine ligand **4a**,**b**-catalyzed aldol reactions of methyl α-isocyanoacetate (**2a**) with tetrafluoro- **1g** and pentafluorobenzaldehydes (**1h**), in sharp contrast to that of benzaldehyde (**1a**) or monofluorosubstituted benzaldehyde reactions **1b-d**, gave corresponding *cis*-oxazolines **6g**,**h** as the main reaction products with high % ee. The gradual inversion of the stereochemical result of aldol reactions under investigation, brought about by fluorine atoms, was totally unexpected. The reasons behind the phenomenon could be reasonably ascribed to the increasing electrophilicity (electron-deficiency) of a phenyl ring in the series from mono- to pentafluorosubstituted benzaldehydes **1b-h**. The working model for the transition-state of the stereoselective step of the gold(I)-catalyzed aldol reaction postulates the following features (Figure 1, transition-state **A**): a) the gold(I) cation is co-ordinated to the two phosphorus atoms of ferrocenylphosphine ligand, and the carbon of the isocyanoacetate ester; b) the enolate anion of the isocyanoacetate is formed by the abstraction of one of the active protons by the terminal dialkylamino group of the ligand pendant side chain. The chiral environment of the enolate formed determines electrophilic attack by the *si*-face of an aldehyde on the si-face of the enolate. This mode of interactions (transition-state **A**) provides *trans*-oxazoline formation. The stereochemistry of the products **5h**, **6h** suggests that favorable electrophilic attack of pentafluorobenzaldehyde (**1h**) occurs on the same enolate π-face while the carbonyl π-face selectivity is different than that of the benzaldehyde (**1a**) reaction. Sterically unfavorable transition-state **B**, which leads to the formation of *cis*-(4*S*,5*S*)-oxazoline **6h**, could be stabilized by π-p attractive interaction between the electron-deficient pentafluorophenyl ring and the negatively charged enolate anion. The assumption that the electron-deficient nature of the polyfluorophenyl ring is responsible for an enhanced *cis*-diastereoselectivity, observed in the reactions of fluorinated benzaldehydes with isocyanoacetate **2a**, is supported by the other examples of the gold(I)-catalyzed aldol condensations of **2a** with benzaldehydes bearing strongly electron-withdrawing substituents. Thus, for instance, reaction of *p*-nitrobenzaldehyde with **2a**, catalyzed by 1 mol % of **3**/**4b**, gave 83/17 (vs 95/5 for benzaldehyde) ratio of *trans*-(2*R*,3*S*)/*cis*-(2*S*,3*S*)-oxazolines with lowered ee (86% ee) of *trans*-isomer and quite high ee (75% ee) of *cis*-oxazoline,[8h] as compared with the corresponding values of benzaldehyde reaction with **2a** (Table 1, entry 13). There is also a very close analogy between our observations and the results reported by Ojima and Kwon on the unique stereodifferentiation disclosed for pentafluorophenyl-containing chiral iron acyl complex (PFCHIRAC).[15] They had proven that this very case of electron donor-acceptor type attractive interaction between the enolate oxygen and pentafluorophenyl moiety caused the opposite stereochemical outcome in the addition reactions of PFCHIRAC and fluorine-free CHIRAC.[16]

Based on this reasoning, we envisioned that the application of *N*,*N*-dimethyl-α-isocyanoacetamide (**2b**) instead of methyl isocyanoacetate (**2a**), due to the both electronic and steric factors, might disturb transition-state **B** (Figure 1) and thus enhance the *trans*-diastereoselectivity of the polyfluorobenzaldehydes aldol reactions. Previously, *N*,*N*-dialkyl-α-isocyanoacetamides were used to increase both enantio- and *trans*-selectivity in the gold(I)-catalyzed aldol reactions of less sterically demanded primary alkyl aldehydes.[8d] Stereoselectivity of benzaldehyde (**1a**) reaction with **2b** (Scheme 3), catalyzed by 1 mol % of **3/4a**, was shown to be similar to that of **1a** condensation with isocyanoacetate **2a** (Table 1, entry 1 vs Table 2, entry 1).[8d] Firstly, we investigated reaction of isocyanoacetamide **2b** with pentafluorobenzaldehyde (**1h**) which was, in the light of the results discussed above, expected to display the most significant difference in the reactivity and selectivity from fluorine-free benzaldehyde (**1a**) (Scheme 3). In accordance with our expectation, the reaction of pentafluorobenzaldehyde (**1h**) with isocyanoacetamide **2b**, performed at 25 °C in the presence of 1 mol % of **3/4a**, gave a mixture of *trans*/*cis*-oxazolines **11h** and **12h** with remarkable domination of *trans*-**11h**, albeit formed with moderate ee (Table 1, entry 2). Lowering of the reaction temperature and application of 2 mol % of the catalyst (**3/4a**) allowed marked increase of enantioselectivity for *trans*-oxazoline **11h** formation, however, with a bit lower diastereoselectivity (entry 3). For determination of the absolute configuration of the amino acid moiety in the oxazoline **11h**, it was hydrolyzed to give known β-(pentafluorophenyl)serine **7h**. Comparison of $[\alpha]_D$ value of amino acid **7h** obtained with the literature value established its *syn*-(2*S*) absolute configuration and, consequently, the (4*S*,5*R*) absolute configuration of *trans*-oxazoline **11h**. Similar reactivity and stereochemical outcome were observed in the aldol reaction of 2,3,5,6-tetrafluorobenzaldehyde (**1g**) with isocyanoacetamide **2b** (entries 4, 5). Thus, the highest *trans*-selectivity (89%) with 77% ee of oxazoline **11g** was observed at 20 °C, whilst low temperature reaction gave *trans*-oxazoline **11g** with 84% of diastereoselectivity and 84% ee.

In the aldol reactions of trifluoro- and difluorobenzaldehydes **1f** and **1e** with isocyanoacetamide **2b** (entries 6 and 7, respectively), the desirable *trans*-oxazolines **11f** and **11e** were obtained with both higher diastereo and enantioselectivity (91% ee for **11f** and 93% ee for **11e**) than the corresponding *trans*-oxazolines **5f** and **5e** (Scheme 2, Table 1, entries 9, 8) in the reaction of **1f**,**e** with isocyanoacetate **2a**. Finally, the aldol reactions of isocyanoacetamide **2b** with monofluorosubstituted benzaldehydes **1b**,**d** gave *trans*-oxazolines **11b** and **11d** with the expected high diastereo- and enantioselectivities (entries 9 and 8, respectively). However, the use of isocyanoacetamide **2b** for the synthesis of corresponding *syn*-(2*S*)-β-(monofluorophenyl)serines **7**, through oxazolines **11b**,**d**, seemed to have no advantages over the application of isocyanoacetate **2a**, which provided a better stereochemical outcome of corresponding oxazolines **5b**,**d**.

Scheme 3



Ar$_f$ = C_6H_5 (**a**), 4-F-C_6H_4 (**b**), 2-F-C_6H_4 (**d**), 2,6-F_2-C_6H_3 (**e**), 2,4,6-F_3-C_6H_2 (**f**), 2,3,5,6-F_4-C_6H (**g**), C_6F_5 (**h**)

Table 2. Gold(I)-Catalyzed Asymmetric Aldol Reactions of Fluorobenzaldehydes **1b,d-h** with **2b**[a]

entry	Ar_f in aldehyde **1**	conditions temp(°C)	time (h)	yield[b] (%)	ratio[c] *trans*-**11**/*cis*-**12**	% ee[d] *trans*-**11**	*cis*-**12**
1[e]	C_6H_5 (**a**)	25	25	74[f]	94/6	94	-
2	C_6F_5 (**h**)	25	24[g]	87	81/19	68	24
3	C_6F_5 (**h**)	15[h]	48	82	77/23	80	20
4	2,3,5,6-F_4-C_6H (**g**)	20	20	88	89/11	77	28
5	2,3,5,6-F_4-C_6H (**g**)	15[h]	50	78	84/16	84	26
6	2,4,6-F_3-C_6H_2 (**f**)	10	48	83	85/15	91	48
7	2,6-F_2-C_6H_3 (**e**)	20	25	84	77/23	93	64
8	2-F-C_6H_4 (**d**)	22	25	87	83/13	93	-
9	4-F-C_6H_4 (**b**)	20	24	89	92/8	94	-

[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 (**3**) and chiral ligand **4a**. Ratio of **1/2b/3/4a** = 1.3/1/0.02/0.022 unless otherwise noted. [b] Isolated yield after passing reaction mixture through a short silica gel column (3×1.5 cm) using ethyl acetate as an eluent. [c] Determined by ^1H NMR analysis. [d] Determined by HPLC analysis of *N,N*-dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(fluorophenyl)propionamides **13, 14** 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 **11h** was determined to be (4*S*,5*R*) (see text). All other *trans*-oxazolines **11b,d-g** are assumed to have the same (4*S*,5*R*) configuration by similarity in the order of elution under the condition of chiral HPLC analysis. The absolute configuration of the *cis*-oxazolines **12** was not determined. [e] Previously reported data, see ref. 8d. [f] Yield of *trans*-oxazoline **6h**, see ref. 8d. [g] One mol % of the catalyst was used. [h] Reaction was started at 0 °C and then reaction temperature was allowed to rise to 15 °C.

CONCLUSIONS

The present results have revealed that the stereochemical outcome of the gold(I)-catalyzed asymmetric aldol reactions studied dramatically depends on the nature of both fluorobenzaldehyde and isocyanoacetic acid derivative being used. The result of methyl α-isocyanoacetate (**2a**) reactions with fluorinated benzaldehydes was shown to be controlled by the number of fluorine atoms in the aryl moiety of fluorobenzaldehyde used. Thus, aldol condensations of **2a** with monofluorobenzaldehydes furnished *trans*-oxazolines with more than 90% of *trans*-diastereoselectivity and % ee, while in the case of the reactions with polyfluorobenzaldehydes corresponding *cis*-oxazolines were formed as dominant isomers with high ee (up to 90% ee). In marked contrast to this, reactions of *N,N*-dimethyl-α-isocyanoacetamide (**2b**) with fluorobenzaldehydes provided preferential formation and high % ee of *trans*-oxazolines regardless of the fluorosubstituted benzaldehyde used. It follows that both *syn*-and *anti*-β-(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. Lastly, the reactive π-face of the enolate formed from amide **2b** or ester **2a**, being controlled by chiral ferrocenylphosphine ligand, was shown to be the same for the reactions of hydrocarbon and fluorocarbon aryl aldehydes.

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EXPERIMENTAL PART

General. ^{1}H NMR spectra were recorded with a JEOL (300 MHz) spectrometer. Chemical shifts are reported in δ ppm relative to TMS [$(CH3)_4Si$] in $CDCl_3$. Optical rotations were measured on a Perkin-Elmer 243 polarimeter. Preparative medium-pressure liquid chromatography (MPLC) was performed with a silica gel 60 pre-packed Lobar (Merck) column. Chiral HPLC analyses of methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(fluorophenyl)propionates **9**,**10** and *N*,*N*-dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(fluorophenyl)propionamides **13**, **14** were performed on a Jasco HPLC system using chiral stationary phase columns SUMICHIRAL OA-2000, 2000I, 4500, or 4900, hexane/1,2-dichloroethane/ethanol = 50/15/1, 100/20/1, or 250/20/1 for determination of enantiomeric composition of **13**, **14**, and SUMICHIRAL OA-2000 or 2000I (hexane/1,2-dichloroethane/ethanol = 100/20/1) for **9**,**10**. Fluoro-aldehydes **1b-h** and methyl α-isocyanoacetate (**2a**) are commercially available. *N*,*N*-Dimethyl-α-isocyanoacetamide (**2b**) was prepared by the reaction of isocyanoacetate **2a** with dry dimethylamine in methanol,[17] and prior to use was crystallized from hexane/benzene to give colorless needle shape crystals. Bis(cyclohexyl isocyanide)gold(I) tetrafluoroborate (**3**) was prepared as described in the literature.[18] Chiral ligands (*R*)-*N*-methyl-*N*-[2-(piperidino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (**4a**), (*R*)-*N*-methyl-*N*-[2-(morpholino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (**4b**) were prepared by the reaction of (*R*)-1-[(*S*)-1'2-bis(diphenylphosphino)ferrocenyl]ethyl acetate with an appropriate amine according to the reported procedure.[8h,11]

Aldol Reactions of Isocyanoacetic Acid Derivatives 2a,b with Fluoro-Benzaldehydes 1b-h. General Procedure. To a stirred solution of gold(I) tetrafluoroborate **3** (0.010 mmol), chiral ferrocenylphosphine ligand **4a,b** (0.010-0.011 mmol) and methyl α-isocyanoacetate (**2a**) or *N*,*N*-dimethyl-α-isocyanoacetamide (**2b**) (1.0 mmol) in 2 mL of freshly distilled dichloromethane, appropriate fluorobenzaldehyde **1b-h** (1.0-1.1 mmol) was added under nitrogen. The resulted mixture was stirred until all of the **2a** or **2b** had been consumed (monitored by GC and TLC). Reaction temperature and time are indicated in the Tables 1 and 2. After completion of the reaction solvent was evaporated under reduced pressure and the residual material was either bulb-to-bulb distilled or passed through a short silica gel column (3×1.5 cm, ethyl acetate as an eluent) to provide the oxazolines **5,6b-h**, starting from **2a**, and **11,12b,d-h**, starting from **2b**, as a colorless sticky oil. Racemic syntheses of corresponding oxazolines were accomplished in the same manner with the difference that CuCl/NEt_3 (0.1 mmol) was used instead of **3**/**4**. The ratio of *trans*/*cis* was determined by ^{1}H NMR spectra of the mixtures **5,6b-h** and **11,12b,d-h** obtained. Owing to an effect of aromatic ring, the methyl protons of methoxy or dimethylamino group in *cis*-oxazolines **6b-h** and **12b,d-h** respectively, shifted up-field in comparison with those of the *trans*-oxazolines **5b-h**, **11b,d-h**. Diastereomeric ratio (*trans*/*cis*) are given in the Tables 1 and 2. ^{1}H NMR spectra and micro-analytical data for oxazolines **5,6b-h** and **11,12b,d-h** are listed below.

4-(Methoxycarbonyl)-5-(4-fluorophenyl)-2-oxazolines **5,6b**: *trans*-**5b**, 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*-**6b**, 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). Anal. Calcd for $C_{11}H_{10}FNO_3$: C, 59.19; H, 4.52; N, 6.27. Found: C, 59.29; H, 4.31; N, 6.44.

4-(Methoxycarbonyl)-5-(3-fluorophenyl)-2-oxazolines **5,6c**: *trans*-**5c**, 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*-**6c**, 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). Anal. Calcd for $C_{11}H_{10}FNO_3$: C, 59.19; H, 4.52; N, 6.27. Found: C, 59.35; H, 4.66; N, 6.21.

4-(Methoxycarbonyl)-5-(2-fluorophenyl)-2-oxazolines **5,6d**: *trans*-**5d**, 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*-**6d**, 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). Anal. Calcd for $C_{11}H_{10}FNO_3$: C, 59.19; H, 4.52; N, 6.27. Found: C, 59.22; H, 4.49; N, 6.38.

4-(Methoxycarbonyl)-5-(2,6-difluorophenyl)-2-oxazolines **5,6e**: *trans*-**5e**, 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*-**6e**, 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). Anal. Calcd for $C_{11}H_9F_2NO_3$: C, 54.77; H, 3.76; N, 5.81. Found: C, 55.01; H, 3.78; N, 5.94.

4-(Methoxycarbonyl)-5-(2,4,6-trifluorophenyl)-2-oxazolines **5,6f**: *trans*-**5f**, 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*-**6f**, 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). Anal. Calcd for $C_{11}H_8F_3NO_3$: C, 50.97; H, 3.11; N, 5.40. Found: C, 51.12; H, 3.21; N, 5.51.

4-(Methoxycarbonyl)-5-(2,3,5,6-tetrafluorophenyl)-2-oxazolines **5,6g**: *trans*-**5g**, 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*-**6g**, 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). Anal. Calcd for $C_{11}H_7F_4NO_3$: C, 47.66; H, 2.55; N, 5.05. Found: C, 47.74; H, 2.57; N, 5.19.

4-(Methoxycarbonyl)-5-pentafluorophenyl-2-oxazolines **5,6h**: *trans*-**5h**, 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*-**6h**, 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). Anal. Calcd for $C_{11}H_6F_5NO_3$: C, 44.76; H, 2.05; N, 4.75; F, 32.19. Found: C, 44.91; H, 2.01; N, 4.55; F, 32.23.

5-(4-Fluorophenyl)-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12b**: *trans*-**11b**, 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*-**12b**, 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). Anal. Calcd for $C_{12}H_{13}FN_2O_2$: C, 61.01; H, 5.54; N, 11.86. Found: C, 60.93; H, 5.55; N, 11.93.

5-(2-Fluorophenyl)-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12d**: *trans*-**11d**, 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*-**12d**, 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). Anal. Calcd for $C_{12}H_{13}FN_2O_2$: C, 61.01; H, 5.54; N, 11.86. Found: C, 61.13; H, 5.62; N, 11.76.

5-(2,6-Difluorophenyl)-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12e**: *trans*-**11e**, 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*-**12e**, 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). Anal. Calcd for $C_{12}H_{12}F_2N_2O_2$: C, 56.69; H, 4.76; N, 11.02. Found: C, 56.74; H, 4.89; N, 11.23.

5-(2,4,6-Trifluorophenyl)-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12f**: *trans*-**11f**, 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*-**12f**, 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). Anal. Calcd for $C_{12}H_{11}F_3N_2O_2$: C, 52.94; H, 4.07; N, 10.29. Found: C, 53.04; H, 4.13; N, 10.31.

5-(2,3,5,6-Tetrafluorophenyl)-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12g**: *trans*-**11g**, 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*-**12g**, 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). Anal. Calcd for $C_{12}H_{10}F_4N_2O_2$: C, 49.66; H, 3.47; N, 9.65. Found: C, 49.81; H, 3.56; N, 9.71.

5-Pentafluorophenyl-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12h**: *trans*-**11h**, 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*-**12h**, 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). Anal. Calcd for $C_{12}H_9F_5N_2O_2$: C, 46.76; H, 2.94; N, 9.09. Found: C, 46.92; H, 2.83; N, 9.17.

Transformation of Oxazolines 5,6b-h and 11,12b,d-h into the *N*-Benzoyl Derivatives 9,10b-h and 13b,d-h, 14e-h. General Procedure. To a stirred solution of oxazolines **5,6** or **11,12** (1.0 mmol) 10 mL of methanol 1.5 mL of conc. HCl was added. The resulted mixture was stirred at 50 °C for 2 hrs.. and evaporated under reduced pressure to dryness. The residual material was dissolved or suspended in 5 mL of dichloromethane and treated with triethylamine (3.0 mmol) and then with benzoyl chloride (1.1 mmol). The resulted mixture was stirred at r.t. for 2 hrs. and evaporated under reduced pressure. Desired *N*-benzoyl derivatives were isolated with preparative TLC plates (hexane/ethyl acetate 2-1/1) and after confirmation of their structure by ^{1}H NMR spectra, they were subjected to chiral HPLC analysis. Racemic *N*-benzoyl derivatives, for being used as standards for HPLC analysis of optically active **9,10,13,14**, were prepared according to the same procedure starting from corresponding racemic oxazolines. ^{1}H NMR spectra of *N*-benzoyl derivatives **9,10b-h** and **13b,d-h**, **14e-h** are listed below.

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(4-fluorophenyl)propionates **9,10b**: *syn*-**9b**, 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*-**10b**, 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).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(3-fluorophenyl)propionates **9,10c**: *syn*-**9c**, 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*-**10c**, 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).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(2-fluorophenyl)propionates **9,10d**: *syn*-**9d**, 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*-**10d**, 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).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(2,6-difluorophenyl)propionates **9**,**10e**: *syn*-**9e**, 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*-**10e**, 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).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(2,4,6-trifluorophenyl)propionates **9**,**10f**: *syn*-**9f**, 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*-**10f**, 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).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(2,3,5,6-tetrafluorophenyl)propionates **9**,**10g**: *syn*-**9g**, 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*-**10g**, 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).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(pentafluorophenyl)propionates **9**,**10h**: *syn*-**9h**, 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*-**10h**, 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).

syn-*N*,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(4-fluorophenyl)propionamide **13b**, 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).

syn-*N*,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(2-fluorophenyl)propionamides **13d**, 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).

N,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(2,6-difluorophenyl)propionamides **13**,**14e**:*syn*-**13e**, 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*-**14e**, 2.91 (s, 3 H), 3.09 (s, 3 H), 4.22 (br.s, 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).

N,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(2,4,6-trifluorophenyl)propionamides **13**,**14f**: *syn*-**13f**, 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*-**14f**, 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).

N,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(2,3,5,6-tetrafluorophenyl)propionamides **13**,**14g**:*syn*-**13g**, 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*-**14g**, 2.92 (s, 3 H), 3.12 (s, 3 H), 4.68 (br.s, 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).

N,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(pentafluorophenyl)propionamides **13**,**14h**: *syn*-**13h**, 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*-**14h**, 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).

Preparative Synthesis of *syn*-(2*S*)-3-(4-Fluorophenyl)serine 7b, *syn*-(2*S*)-3-(Pentafluorophenyl)serine 7h, and *anti*-(2*S*)-3-(Pentafluorophenyl)serine 8h. General Procedure. Synthesis of oxazolines **5b**, **6h**, and **11b**,**h** was accomplished according to the general procedure given above. Yields of **5b**, **6h**, and **11b**,**h**, quantities of starting compounds, and reaction conditions are listed below. *trans*-(4*S*,5*R*)-Oxazoline **5b**: 395.96 mg (88.7%), starting from 273.05 mg (2.2 mmol) of *p*-fluorobenzaldehyde (**1b**), 198.18 mg (2 mmol) of isocyanoacetate **2a**, 9.76 mg (0.02 mmol) of **3** and 15.9 mg (0.022 mmol) of ferrocenylphosphine ligand **4a**, stirring in 4 mL of dichloromethane at 0 °C for 100 hrs, isolated by preparative MPLC; *cis*-(4*S*,5*S*)-**6h**: 335.3 mg (56.8%), [165.88 mg (28.1%) of **5h**], from 431.35 mg (2.2 mmol) of pentafluorobenzaldehyde (**1h**), 198 mg (2 mmol) of isocyanoacetate **1a**, 19.5 mg (0.04 mmol) of **3** and 31.9 mg (0.044 mmol) of ligand **4b**, stirring in 4 mL of dichloromethane at 0 °C for 100 hrs., isolated by preparative MPLC; *trans*-(4*S*,5*R*)-**11b**: 366.2 mg (77.5%), starting from 322.69 mg (2.6 mmol) of *p*-fluorobenzaldehyde (**1b**), 224.26 mg (2 mmol) of isocyanoacetamide **2b**, 19.5 mg (0.04 mmol) of **3** and 31.8 mg (0.044 mmol) of ferrocenylphosphine ligand **4a**, stirring in 4 mL of dichloromethane at 20 °C for 24 hrs., isolated by preparative TLC; *trans*-(4*S*,5*R*)-**11h**: 380.3 mg (61.7%), from 509.8 mg (2.6 mmol) of pentafluorobenzaldehyde (**1h**), 224.26 mg (2 mmol) of isocyanoacetamide **2b**, 19.5 mg (0.04 mmol) of **3** and 31.8 mg (0.044 mmol) of ligand **4a**, were mixed in 4 mL of dichloromethane at 0 °C and then stirred at 15 °C for 48 hrs., isolated by preparative TLC. Each of the oxazolines **5b**, **6h**, **11b**,**h** was dissolved in 20 mL MeOH, treated with 3 mL conc. HCl, and stirred at 50 °C for 2 hrs.. and then solution was evaporated under reduced pressure to dryness. The residual material was dissolved in 10 mL 6 *N* HCl and heated at 90-100 °C for 24 hrs.., for **7b** and **8h** from **5b**, **6h**,

respectively, and at 100 °C for 43 hrs.. (sealed tube), for **7b,h** from **11b,h**, and evaporated to dryness. The residual material was dissolved in methanol (15 mL) and treated with propylene oxide. Precipitated free amino acid was filtered off, washed with MeOH and dried in vacuum. Yields and $[\alpha]_D$ of amino acids **7b,h**, **8h** obtained were as follows: (2*S*,3*R*)-**7b**, 307 mg (87% from **5b**, and 71% (220 mg) from **11b**), $[\alpha]_D^{25}$ -20.0 (*c* 1, H_2O), lit.[5d] for (2*R*,3*S*)-enantiomer: $[\alpha]_D^{25}$ +20.5; (2*S*,3*S*)-**8h**, 258.7 mg (84% from **6h**), $[\alpha]_D^{25}$ +35.8 (*c* 1, 6 *N* HCl), lit.[5d] $[\alpha]_D^{25}$ +37.4; (2*S*,3*R*)-**7h**, 230.9 mg (69% from **11h**), $[\alpha]_D^{25}$ +12.1 (*c* 0.5, 6 *N* HCl), lit.[5d] $[\alpha]_D^{25}$ +13.03.

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