Transition Metal/Base-Catalyzed Aldol Reactions of Isocyanoacetic Acid Derivatives with Prochiral Ketones, a Straightforward Approach to Stereochemically Defined β,β-Disubstituted-β-hydroxy-α-amino Acids.[1] Scope and Limitations

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A systematic study of the transition metal/base-catalyzed aldol reactions of methyl isocyanoacetate with a wide range of prochiral ketones, giving rise to the 4-(methoxycarbonyl)-5,5-disubstituted-2-oxazolines, has been made. The diastereoselectivity of these reactions was found to be influenced by a mix of several factors, including steric characteristic of the substituents, nature of the catalyst, electrostatic, and electron donor−acceptor type interactions. The former factor, a stereochemical discrimination between the substituents at the ketone carbon, was shown to be the most pronounced in controlling of the stereochemical outcome, which could be markedly improved with a proper choice of the catalyst. In particular, for the reactions of methyl isocyanoacetate with polyhaloalkyl aryl(alkyl) ketones, high diastereoselectivity (80−98% de) was achieved, thus allowing for straightforward and generalized access to the corresponding (2*R**,3*R**)-β,β-disubstituted-β-hydroxy-α-amino carboxylic acid.

Introduction

Over the past 15 years the art of stereoselective aldol methodology has been advanced to the state that could rival enzymatic systems for the synthetic efficiency and control over relative and absolute stereochemistry of the products.[2] However, the overwhelming majority of the strategies developed in this area are suitable for the additions to aldehydes, while the involvement of prochiral ketones in the stereoselective aldol reactions has yet to meet with such success.[2,3] In particular, highly diastereoselective condensations between glycine α-anion equivalents and prochiral ketones are virtually unknown.[4] It was recognized that poor electrophilicity and steric shielding of the carbonyl group, as well as greater difficulty in the stereodiscrimination between the two carbon-containing substituents in ketones, impose serious limitations on the control of chemo-, regio-, and stereoselective outcomes of the corresponding aldol addition reactions. Apart from the methodological challenge, aldol reactions between the nucleophilic glycine equivalents and prochiral ketones attract our attention also because this approach would provide the most straightforward access to the sterically constrained β,β-disubstituted-β-hydroxy-α-amino carboxylic acids, which are of exciting potential interest in the *de novo* design of peptides and peptidomimetics with specific conformational and physiological properties.[5]

Recently we have disclosed that trifluoromethyl ketones react with a Ni(II) complex of the Schiff base of glycine with (*S*)-*o*-[*N*-(*N*-benzylprolyl)amino]benzophenone to afford the targeted aldol products in a highly diastereoselective manner (90−98% de) and in respected chemical yields (56−87%).[6] Unfortunately, the scope of this approach was found to be limited to the reactions of the trifluoromethyl *n*-alkyl ketones, while sterically demanding aryl and *sec*-alkyl trifluoromethyl ketones and less electrophilic fluorine-free ketones failed to react with the Ni(II) complex.[6c]

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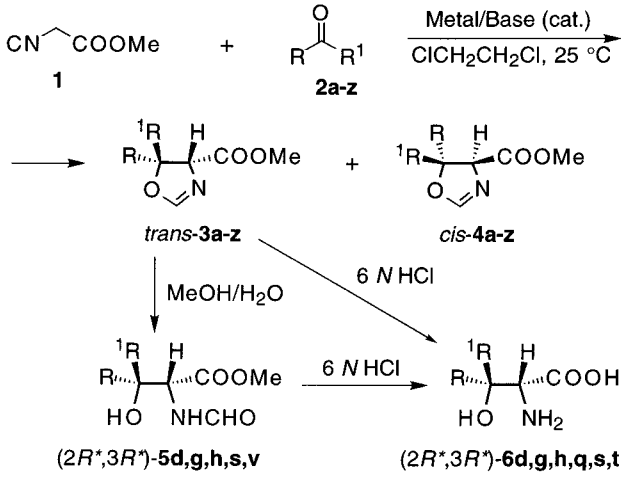
Our experience in the aldol reactions clearly revealed that one serious obstacle to the successful condensation between a nucleophilic glycine equivalent and a ketone is the reversibility of the reaction, the equilibrium of which nearly entirely lies on the side of starting compounds. From this point of view, aldol-type reactions between isocyanoacetic acid derivatives and carbonyl compounds, one of the useful methods for preparing β-hydroxy-α-amino acids, hold an apparent advantage, as these condensations could proceed irreversibly, giving rise to the corresponding oxazolinecarboxylates.[7] Moreover, these reactions were shown to be effectively catalyzed by certain transition metals that could allow for the rational influence of the regio- and diastereochemical outcomes of these transformations.[8] This study gains also an additional impetus when considering the fact that for aldehyde series this method was brought to a high level of sophistication with the development of catalytic enantioselective synthesis of β-hydroxy-α-amino acids by use of a well-designed chiral ferrocenylbisphosphine−gold(I)[9,10] or −silver(I)[11] catalyst.

For the reactions of isocyanoacetic acid derivatives with prochiral ketones, only a handful of examples are extant.[8,12] It was reported that certain alkyl α,β-alkenyl and α-chloroalkyl alkyl(aryl) ketones in the presence of Cu(I) (Cu_2O, CuCl) smoothly react with the ethyl isocyanoacetate to afford a mixture of the corresponding *trans*/*cis*-oxazolines with diastereoselectivity ranging from 0 to 80% de,[12] while, under the similar reaction conditions, the condensation of acetophenone gives a 1 to 1 mixture of the diastereomeric products.[8b]

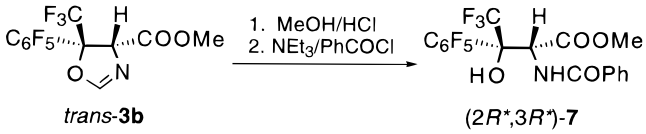
In the work described here, following a systematic study, we have examined the diastereoselectivity of the transition metal/base-catalyzed reactions between methyl isocyanoacetate and a wide range of prochiral ketones **2a**−**z**. Our study indicates that the stereochemical outcome of these reactions is influenced by a mix of several factors, including steric characteristic of the ketone substituents, the nature of the catalyst (metal and base) employed, and, in some cases, the electrostatic, donor−acceptor type interactions. The resultant oxazoline diastereomer ratios appear to be determined primarily by the steric influence of the ketone substituents; however, they were found to be tunable depending on a proper choice of the catalyst. In particular, for the reactions of methyl isocyanoacetate **1** with polyhaloalkyl aryl(alkyl) ketones, a high, synthetically useful level stereoselectivity (80−98% de) was achieved, allowing straightforward and generalized access to the corresponding (2*R**,3*R**)-β,β-disubstituted-β-hydroxy-α-amino carboxylic acid of biomedicinal importance. Apart from the synthetic results, the data presented here shed light on some of the intricacies of these metal/base-catalyzed reactions, and should allow for the design of more general and practical catalytic and enantioselective aldol-type processes in the future.

Scheme 1



	R	R^1		R	R^1
a	C_6H_5	Me	**n**	Me	$CHCl_2$
b	C_6F_5	CF_3	**o**	Me	CCl_3
c	C_6F_5	Me	**p**	CH_2Cl	$CHCl_2$
d	C_6H_5	CF_3	**q**	Me	CF_3
e	4-CF_3-C_6H_4	CF_3	**r**	Me	C_3F_7
f	4-MeO-C_6H_4	CF_3	**s**	*n*-Hep	CF_3
g	C_6H_5	$CClF_2$	**t**	*n*-Oct	CF_3
h	C_6H_5	C_2F_5	**u**	*c*-Hex	CF_3
i	C_6H_5	C_4F_9	**v**	C≡C-Ph	CF_3
j	C_6H_5	CN	**w**	CH_2COOEt	CF_3
k	Me	CH_2OMe	**x**	Me	Et
l	Me	CH_2F	**y**	Me	*n*-Pr
m	Me	CH_2Cl	**z**	Me	*c*-Hex

Scheme 2



Results

We have reacted methyl α-isocyanoacetate (**1**) (Scheme 1) with prochiral ketones **2a**−**z** to give the corresponding diastereomeric oxazolines[13] **3**,**4a**−**z**. The most represen-

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Table 1. Catalytic Aldol Reactions of Ketones 2a−z with Methyl Isocyanoacetate 1a[a]

	ketone		catalyst,[b]				ratio[d]	
entry	R	R^1	metal/base	mol %	time	yield,[c] %	*trans*-**3**	*cis*-**4**
1 (**a**)	C_6H_5	Me	Cu(I)/NEt_3	10	24 h[e]	80	53	47
2 (**b**)	C_6F_5	CF_3	Cu(I)/NEt_3	10	10 min	93	91	9
3 (**b**)	C_6F_5	CF_3	Cu(I)/NEt_3	10	10 h	91	91	9
4 (**b**)	C_6F_5	CF_3	Au(I)/NEt_3	1	4 h	95	92	8
5 (**b**)	C_6F_5	CF_3	Ag(I)/NEt_3	1	3.5 h	92	94	6
6 (**b**)	C_6F_5	CF_3	Ag(I)/*i*-Pr_2NEt	1	12 h	96	83	17
7 (**b**)	C_6F_5	CF_3	Ag(I)/NMe_3[f]	1	3.5 h	97	98	2
8 (**b**)	C_6F_5	CF_3	Ag(I)/PyH	1	45 h	99	64	36
9 (**b**)	C_6F_5	CF_3	Ag(I)/PS[g]	1	12 h	94	77	23
10 (**b**)	C_6F_5	CF_3	Cu(I)	10	20 h	78	73	27
11 (**b**)	C_6F_5	CF_3	NEt_3	25	50 h	60	95	5
12 (**b**)	C_6F_5	CF_3			96 h	54	80	20
13 (**c**)	C_6F_5	CH_3	Ag(I)/NEt_3	1	48 h	85	41	59
14 (**c**)	C_6F_5	CH_3	Cu(I)/NEt_3	1	50 h	83	37	63
15 (**c**)	C_6F_5	CH_3	Au(I)/NEt_3	1	50 h	77	48	52
16 (**c**)	C_6F_5	CH_3	Pd(II)/NEt_3	1	60 h	84	50	50
17 (**d**)	C_6H_5	CF_3	Ag(I)/NEt_3	1	5 h	92	86	14
18 (**d**)	C_6H_5	CF_3	Au(I)/NEt_3	1	5 h	94	89	11
19 (**d**)	C_6H_5	CF_3	Rh(I)/NEt_3	1	5 h	95	89	11
20 (**d**)	C_6H_5	CF_3	Cu(I)/NEt_3	10	7 h	93	88	12
21 (**e**)	4-CF_3-C_6H_4	CF_3	Ag(I)/NEt_3	1	5 h	94	88	12
22 (**f**)	4-CH_3O-C_6H_4	CF_3	Ag(I)/NEt_3	1	6 h	89	87	13
23 (**g**)	C_6H_5	$CClF_2$	Ag(I)/NEt_3	1	5 h	96	93	7
24 (**g**)	C_6H_5	$CClF_2$	Rh(I)/NEt_3	1	10 h	98	92	8
25 (**g**)	C_6H_5	$CClF_2$	Pd(II)/NEt_3	1	5 h	93	85	15
26 (**g**)	C_6H_5	$CClF_2$	Cu(I)/NEt_3	10	10 min	92	>99	<1
27 (**g**)	C_6H_5	$CClF_2$	NEt_3	200	1 h	95	94	6
28 (**h**)	C_6H_5	C_2F_5	Ag(I)/NEt_3	1	6 h	93	95	5
29 (**h**)	C_6H_5	C_2F_5	Cu(I)/NEt_3	10	10 min	94	>99	<1
30 (**i**)	C_6H_5	*n*-C_4F_9	Cu(I)/NEt_3	10	10 min	87	>99	<1
31 (**j**)	C_6H_5	CN	Cu(I)/NEt_3	10	10 min	81	18	82
32 (**k**)	Me	CH_2OMe	Cu(I)/NEt_3	10	20 h	74	56	44
33 (**l**)	Me	CH_2F	Cu(I)/NEt_3	10	0.5 h	93	71	29
34 (**m**)	Me	CH_2Cl	Cu(I)/NEt_3	10	0.5 h	97	74	26
35 (**m**)	Me	CH_2Cl	Ag(I)/NEt_3	2	0.5 h	94	79	21
36 (**n**)	Me	$CHCl_2$	Cu(I)/NEt_3	10	0.5 h	99	92	8
37 (**o**)	Me	CCl_3	Cu(I)/NEt_3	10	0.5 h	95	>99	<1
38 (**p**)	CH_2Cl	$CHCl_2$	Cu(I)/NEt_3	10	0.5 h	89	71	29
39 (**q**)	Me	CF_3	Cu(I)/NEt_3	10	0.5 h[h]	91	99	1
40 (**r**)	Me	*n*-C_3F_7	Cu(I)/NEt_3	10	0.5 h[h]	88	>99	<1
41 (**s**)	*n*-Hep	CF_3	Cu(I)/NEt_3	10	1 h	91	76	24
42 (**s**)	*n*-Hep	CF_3	Ag(I)/NEt_3	2	1 h	93	90	10
43 (**s**)	*n*-Hep	CF_3	NEt_3	200	2 h	89	86	14
44 (**t**)	*n*-Oct	CF_3	Ag(I)/NEt_3	5	1 h	95	91	9
45 (**t**)	*n*-Oct	CF_3	NEt_3	200	2 h	94	84	16
46 (**u**)	*c*-Hex.	CF_3	Cu(I)/NEt_3	10	5 h	87	35	65
47 (**u**)	*c*-Hex.	CF_3	Ag(I)/NEt_3	5	10 h	91	43	57
48 (**v**)	C≡C-Ph	CF_3	Ag(I)/NEt_3	2	10 min[h]	96	>99	<1
49 (**w**)	CH_2COOEt	CF_3	Au(I)/NEt_3	2	0.5 h	87	62	38
50 (**w**)	CH_2COOEt	CF_3	Cu(I)/NEt_3	10	1 h	83	84	16
51 (**w**)	CH_2COOEt	CF_3	Ag(I)/NEt_3	2	0.5 h	91	91	9
52 (**w**)	CH_2COOEt	CF_3	NEt_3	100	24 h	NR		
53 (**x**)	Me	Et	Cu(I)/NEt_3	10	24 h	37[i]	60	40
54 (**y**)	Me	*n*-Pr	Cu(I)/NEt_3	10	24 h	31[i]	62	38
55 (**z**)	Me	*c*-Hex	Cu(I)/NEt_3	10	24 h	24[i]	89	11

[a] All reactions were run in 1,2-dichloroethane at 18−23 °C in the presence of the catalyst indicated in the table. Ratio **1a**/**2a**−**z** = 1/1.1; 1-5 mmol scale. Reactions were monitored by GLC, and upon completion, the products were isolated by bulb-to-bulb distillation. [b] Cu(I) is CuCl; Ag(I), $AgClO_4$ or $AgBF_4$; Rh(I), $[Rh(NBD)_2]BF_4$; Pd(II), $PdCl_2(MeCN)_2$; Au(I), $[Au(c\text{-}HexNC)_2]BF_4$; ratio metal/base 1/1-2. [c] Isolated yield. [d] Determined by GLC and ^1H and ^{19}F NMR analyses. [e] At 50 °C. [f] 1,2-Dichloroethane saturated with NMe_3 was used. [g] PS is "Proton Sponge", 1,8-diaminonaphthalene. [h] Reaction was started at 0 °C and then warmed to room temperature. [i] Less than 50% conversion of the starting materials.

tative results obtained are collected in Table 1. All reactions were performed under the similar reaction conditions, in dry 1,2-dichloroethane at ambient temperature in the presence of 1−10 mol % of the transition metal/base catalyst, except for the condensation of acetophenone (**2a**) with **1** which, presumably due to the poor electrophilicity and steric shielding of the carbonyl in **2a**, necessitated an elevated temperature to proceed (Table 1, entry 1). In most cases CuCl and triethylamine (TEA), in a 1/1−2 ratio, was used as the catalyst. To explore the effect of both the metal and base components of the catalyst on the stereochemical outcome, we carried out a series of isocyanoacetate **1** condensations varying the base, *i*-Pr_2NEt (Table 1, entry 6), NMe_3 (entry 7), PyH (entry 8), 1,8-diaminonaphtalene (entry 9), and the metal used, Ag(I) ($AgClO_4$ or $AgBF_4$) (entries 5−9, 13, 17, 21−23, 28, 35, 42, 44, 47, 48, 51), Au(I) {$[Au(c\text{-}HexNC)_2]BF_4$} (entries 4, 15, 18, 49), and Rh(I) {$[Rh(NBD)_2]BF_4$} (entries 19, 24), and Pd(II) [$PdCl_2(MeCN)_2$] (entries 16, 25). For some ketones we also investigated the diastereoselectivity of the reactions with **1** catalyzed separately by the metal

(13) The common name, 2-oxazoline, is used throughout. Following nomenclature rules, the systematic name for **3** and **4** is 4,5-dihydro-5-(substituent)-5-(substituent)-4-oxazolecarboxylic acid, methyl ester.

(CuCl, entry 10) and by the base (TEA, entries 11, 27, 43, 45, 52), as well as uncatalyzed condensation of highly electrophilic octafluoroacetophenone **2b** (entry 12). Regardless of the nature of starting ketones and the catalyst employed, all reactions proceeded irreversibly and were very clean, as no byproducts detectable by NMR were observed. In the series of isocyanoacetate **1** reactions with **2a**−**z** the conversions of the starting materials and the yields of the targeted oxazolines were generally quite high, except for the reactions of **1** with ketones **2x**−**z**, which proceeded with very low reaction rates, apparently due to the poor electrophilicity of the ketones (Scheme 1, Table 1). The stereochemical outcome of the reactions is assumed to be kinetically controlled since no time-dependent alterations in the diastereoselectivity were detected (entry 2 *vs* 3). Moreover, additional experiments have shown that the ratio of diastereomeric oxazolines **3** and **4** does not change while standing in neat TEA solution at rt, thus allowing us to neglect the possibility of diastereomer epimerization at the α-position to the methoxycarbonyl group in **3** and **4**.

The ratio of diastereomers **3**/**4** was determined by GLC and/or NMR analysis on the crude reaction mixture, before removal of the solvent and distillation, and by NMR (^{1}H and ^{19}F, where possible) analysis on the distilled products. The ratios determined by NMR analysis were comparable (±1%) with those determined by GLC analysis. In order to avoid complication of Scheme 1, the *trans*/*cis* definition for **3**/**4** is used throughout with respect to the relationship between the substituent R^1 and the methoxycarbonyl group. Thus, compounds **3**, bearing *trans*-disposed R^1 and COOMe groups, are defined as *trans*-**3** and the diastereomeric oxazolines **4**, with R^1 and COOMe groups in *cis*-disposition to each other, are *cis*-**4**. These assignments are correct for most of the products **3** and **4** (**b**,**d**−**z**) except only for 5-aryl-5-methyl derivatives **3**,**4a**,**c**, where, according to the CIP priority rules,[14] diastereomers **3** and **4** are *cis* and *trans*, respectively.

The determination of relative configuration for the products **3**,**4a**−**z** was based on NMR chemical shifts, X-ray analysis and comparison with the literature examples. For the series of 5-phenyl-containing derivatives **3**,**4a**,**d**−**j** relative configuration was unambiguously assigned using an apparent difference in the chemical shifts of the methoxy (COOMe) protons of diastereomers **3**,**4a**,**d**−**j**. As established previously for the relative oxazolines derived from aromatic aldehydes and **1**, the methoxy protons of the diastereomer with *cis*-disposed phenyl and the methoxycarbonyl group, due to the shielding effect of the aromatic ring,[15] are shifted strongly upfield (3.25−3.28 ppm), as compared with those of the opposite diastereomer (3.82−3.84 ppm).[9] For the derivatives **3**,**4a**,**d**−**j** we observed the same pattern of the chemical shifts. Thus, in *trans*-oxazolines **3a**,**d**−**j**, bearing *cis*-disposed aryl and COOMe groups, the protons of the latter are substantially shifted upfield (3.16−3.33 ppm) as compared with the chemical shifts of the methoxy group in *cis*-oxazolines **4** (3.86−3.93 ppm). Moreover, in the series of 5-fluoroalkyl-substituted **3**,**4d**−**i**, fluorine resonances of the minor *cis*-diastereomers **4d-i**, with *cis*-disposed fluoroalkyl and COOMe groups, presumably due to the deshielding effect of the carbonyl group,[15] are shifted downfield as compared with ^{19}F NMR chemical shifts of *trans*-**3d**−**i**. Although the pattern of ^{1}H NMR spectra of oxazolines **3**,**4b**,**c** was quite similar to that of the 5-phenyl-substituted derivatives **3**,**4d-i**, the difference between chemical shifts of the methoxy protons of the diastereomers was much less pronounced. Since we failed to find in the literature reliable data on the shielding−deshielding effects of the pentafluorophenyl ring, we have established configuration of the dominant diastereomer **3b** by X-ray analysis of its crystalline derivative **7**, which was prepared as shown in Scheme 2. As revealed by X-ray analysis,[1a] compound **7** has a (2*R**,3*R**)-configuration[16] that corresponds to the *trans* relative configuration of the oxazoline **3b**. Accordingly, oxazolines **4b**,**c** and **3c** were assigned as *cis* and *trans* diastereoisomers, respectively. In the aliphatic series, relative configurations of *trans*-**3m** and *cis*-**4m** were determined by comparison of ^{1}H NMR data obtained for the diastereomers **3m**,**4m** with those reported in the literature for *trans*/*cis*-4-(ethoxycarbonyl)-5-(chloromethyl)-5-methyl-2-oxazolines.[12] Relative *trans*-configuration of the oxazolines **3q**,**s**,**t** was confirmed *via* their acidic hydrolysis to the corresponding amino acid **6q**,**s**,**t**, the (2*R**,3*R**)-configuration of which was established by comparison with the samples of known stereochemistry.[6] To the rest of oxazolines **3k**,**l**,**n**−**r**,**u**,**v**,**x**−**z** *trans* configuration, and consequently *cis* to **4k**,**l**,**n**−**r**,**u**,**v**,**x**−**z** diastereomers, was assigned on the basis of an apparent similarity of their NMR spectra to the patterns of **3**,**4m**,**q**,**s**,**t**. The most characteristic difference in ^{1}H NMR spectra of the diastereomers **3**,**4k**−**v**,**x**−**z** is the chemical shifts of the proton at C4. Thus, for the *cis* diastereomers **4k**−**v**,**x**−**z**, the resonance of this proton is shifted upfield relative to the corresponding resonance of the *trans*-configured products **3**,**4k**−**v**,**x**−**z**. This trend is also observed in the spectra of aromatic derivatives **3**,**4a**−**j** and is in an agreement with the data reported for the oxazolines derived from α-chloroalkyl alkyl(aryl) ketones and ethyl isocyanoacetate.[12] Moreover, in the series of 5-(trifluoromethyl)-containing compounds **3**,**4q**,**s**−**v**, chemical shifts of the trifluoromethyl groups of *cis* diastereomers **4q,s**−**v** are shifted downfield relative to ^{19}F NMR chemical shifts of *trans*-**3q,s**−**v**, repeating the trend observed for aromatic derivatives **3**,**4d**−**i**. The assignment of configuration of **3**,**4w** requires an additional comment. The reaction of β-keto ester **2w** with isocyanoacetate **1** follows the usual course and gives the oxazolines **3**,**4w** with sizable domination of one of the diastereomers, as disclosed by NMR. In this case, the resonance of the proton at C4 of the dominant diastereomer is shifted upfield (4.94 ppm, d, J = 2.6 Hz) relative to the corresponding resonance of the minor diastereomer (5.43 ppm, d, J = 2.3 Hz). However, considering the half-width of the doublets, the one at 4.94 ppm with the half-width of 1.6 Hz might be ascribed to the *trans*-**3w**, since the signal at 5.43 ppm has the half-width of 3.1 Hz that could be caused by a small coupling constant between the *trans*-disposed α-proton and the trifluoromethyl group. This trend is observed for all trifluoromethyl-containing oxazolines **3**,**4q,s**−**v**: the half-width of the resonance of the proton at C4 of *cis* diastereomer **4q,s**−**v** is sizably bigger than that of *trans* isomer **3q,s**−**v**.

The results, collected in Table 1, indicate that the stereochemical outcome of the reaction studied is a function of the nature of the starting ketone, as well as the catalyst employed (*vide infra*). For some cases, the

(14) Cahn, R. S.; Ingold, C.; Prelog, V. *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 385.

(15) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 3rd ed.; Wiley: New York, 1974.

(16) The (2*R**,3*R**)-configuration, a consequence of the Cahn−Ingold−Prelog priority (ref 14), is stereochemically equivalent to the (2*R**,3*S**)-configuration in the hydrocarbon analogs.

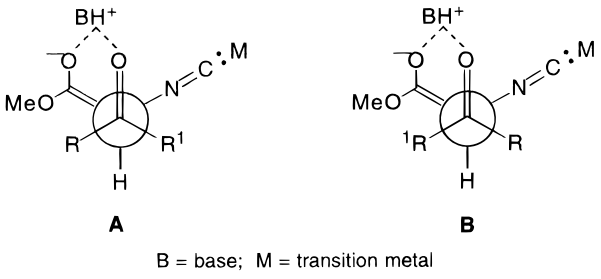

Figure 1. Proposed transition states **A** and **B** for the aldol reactions of isocyanoacetate **1** with prochiral ketones **2a**−**z**.

reactions of **1** with ketones **2b**,**d**−**i**,**n**,**m**,**q**−**t**,**w** (Table 1, entries 5, 20−22, 26, 29, 30, 36, 37, 39, 40, 42, 44, 48, 51), high chemical yields, and appreciable diastereoselectivity render this method synthetically useful for preparing targeted *β*,*β*-disubstituted-*β*-hydroxy-α-amino carboxylic acid. Hydrolysis of oxazolines of this type to the corresponding amino acids is a well-established procedure normally carried out under the mild acidic conditions.[7−12] In this work, we have demonstrated this transformation with the preparation of certain representative (2*R**,3*R**)-*β*,*β*-disubstituted-*β*-hydroxy-α-amino acids **6d**,**g**,**h**,**q**,**s**,**t** in diastereomerically pure state using one- and two-stage hydrolysis procedures (Scheme 1). First, we hydrolyzed oxazolines **3**,**4d**,**g**,**h**,**s** (79−99% de of *trans*-**3**) in aqueous methanol in the presence of catalytic amounts of HCl to afford the corresponding *N*-formyl derivatives **5d**,**g**,**h**,**s**. Products **5d**,**g**,**h**,**s** are crystalline compounds and could be easily purified to the diastereomerically pure form by a conventional crystallization. Further hydrolysis of **5d**,**g**,**h**,**s** to give targeted amino acids **6d**,**g**,**h**,**s** was accomplished by heating of a solution of **5d**,**g**,**h**,**s** in 6 N HCl. Direct hydrolyses of oxazolines are represented by the synthesis of amino acids **6d**,**g**,**h**,**q**,**s**,**t** from the corresponding oxazolines **3**,**4d**,**g**,**h**,**q**,**s**,**t**. In this case, resultant amino acids were crystallized from water to furnish diastereomerically pure compounds.

Discussion

Mechanistic Background; Transition States in the Reactions of Isocyanoacetate 1 with Ketones 2a−z. An examination of Table 1 reveals that the diastereoselectivity of the reactions under study is determined primarily by the steric properties of the ketone substituents. On the other hand, the effect of the catalyst on the ratio of oxazolines **3**,**4a**−**z** normally is less pronounced; however, in some cases, the nature of the catalyst can dramatically influence the stereochemical result (e.g., entry 5 *vs* 8, 9; 14 *vs* 16; 25 *vs* 26; 41 *vs* 42; 44 *vs* 45; 49 *vs* 51). To account for these general trends, by analogy with the reactions of α-isocyanoacetic acid derivatives with aldehydes,[7−11] we can propose two possible transition states, **A** and **B** (Figure 1), for the reactions between methyl isocyanoacetate **1** and ketones **2a**−**z**. In **A**, the substituent R^1 is pointing away from the enolate moiety and interacts with the sterically undemanding proton and linear isocyano group, while the substituent R in **A** interacts unfavorably with the enolate methoxy group pointed toward it. It follows that the transition state **A**, leading to the formation of *trans* oxazolines **3**, might be realized in the cases when the substituent R^1 is more sterically demanding relative to the R. The transition state **B**, giving rise to *cis* oxazolines **4**, might be favored relative to **A** when the substituent R is sterically larger than R^1. According to the proposed transition states **A** and **B**, the effects of the catalyst on the diastereoselectivity should be rather small, as both the base and metal are distant from the reaction site. However, they still could influence stereochemical preferences by the interaction with the substituents R and R^1.

Steric Effects of Ketone Substituents on the Stereochemical Outcome. While the importance of steric requirements of substituents, among other factors influencing the stereoselectivity in aldol reactions, is well-known and rationalized,[2] some of the stereochemical preferences observed in this study were rather unexpected and thus worthy of discussion. The stereochemical outcome of the sluggish condensation of acetophenone (**2a**) and **1** suggests that there is no significant stereodiscrimination between the phenyl and the methyl, and apparently, the reaction proceeded through both transition states **A** and **B** with comparable reaction rates (entry 1). In sharp contrast, the exothermic condensation of octafluoroacetophenone (**2b**) with **1** afforded the product **3**,**4b** with remarkable domination of *trans* diastereomer **3b** (entry 2). The diastereoselectivity in this reaction was found to be influenced by the catalyst employed (*vide infra*) and could be enhanced up to the value of 96% de (entry 7 *vs* 2). To get insight in the origin of this surprising stereocontrol, we investigated the diastereoselectivity in the reactions of **1** with acetophenones **2c**,**2d**, bearing separately pentafluorophenyl and trifluoromethyl moieties of **2b**, as well as the reaction with ketone **2j**, the CN group of which, being a sterically innocuous substituent, would mimic the strong electron-withdrawing effect of the trifluoromethyl group.[17] The results shown in entries 13, 17, 20, and 31 strongly suggest that in the reactions of isocyanoacetate **1** with ketones **2b**,**d** the trifluoromethyl group plays the role of the stereocontrolling substituent, as if it were a group larger than a phenyl. We found next that electron-withdrawing and electron-releasing substituents on the phenyl of trifluoroacetophenone, ketones **2e**,**f**, respectively, do not influence high *trans* diastereoselectivity (entries 21, 22 *vs* 17), while a substitution of the trifluoromethyl by the bulkier chlorodifluoromethyl and perfluoroalkyl groups, ketones **2g**−**i**, respectively, enhances further the diastereoselectivity to the level of complete stereocontrol, allowing an efficient preparation of diastereomerically pure *trans* oxazolines **3g**−**i** (entries 26, 28, 29). These data clearly demonstrate that in the reactions under study trifluoromethyl, or more generally the perfluoroalkyl group, acts as a substituent sterically bulkier than a phenyl or pentafluorophenyl group. To account for these results, we can assume that in the transition state **A**, leading to *trans*-oxazolines **3**, the phenyl or its substituted analogs, due to the flat shape of these groups, might more effectively minimize unfavorable steric interactions than the trifluoromethyl or perfluoroalkyl group could do, occupying the sterically unfavorable position in the transition state **B**. Apart from purely steric reasons, we believe that a plausible explanation of the phenomenon observed might involve also nonbonding, repulsive interactions between the perfluoroalkyl group and the enolate moiety[6] (*vide infra*).

Aliphatic amino compounds make up a large body of naturally occurring and medicinally important compounds. Therefore, it was of particular interest to us to

(17) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*; Wiley: New York, 1979.

investigate the condensations of isocyanoacetate **1** with aliphatic ketones. In the CuCl/NEt_3-catalyzed reactions of **1** with mono-substituted acetones **2k**−**m** low-to-modest diastereoselectivities were obtained (entries 32−34). It is interesting to note the sizable difference in the diastereoselectivity of the condensations of **1** with monofluoro- (**2l**) and methoxyacetones (**2k**) (entries 32 *vs* 33), as it is stated that "F and OH are chemical isosteres".[18] A remarkable increase in the *trans* diastereoselectivity was observed for the condensations of dichloromethyl (**2n**) and trichloromethyl (**2o**) ketones with **1** (entries 36, 37), while the diastereoselectivity of the reaction between **1** and dichloromethyl chloromethyl ketone (**2p**) was found to be comparable with the stereochemical outcome of the corresponding condensation of monochloroacetone (**2m**) (entry 38 *vs* 34). The diastereoselectivities obtained in the series of mono-, di-, and trichloro-substituted acetones **2m**−**p** reactions (entries 34−38) clearly show the steric influences of the substituents on the starting ketone in the diastereoselection process in these aldol condensations.

With these results in hand and in view of the above-mentioned data on the condensations of trifluoromethyl-containing ketones with a Ni(II) complex of the Schiff base of glycine,[6] we anticipated high diastereoselectivity in the reactions of isocyanoacetate **1** with alkyl trifluoromethyl(perfluoroalkyl) ketones. Indeed, the condensations between **1** and methyl trifluoromethyl (**2q**) and methyl *n*-heptafluoropropyl (**2r**) ketones, catalyzed by Cu(I)/TEA, shown excellent (entry 39) and complete (entry 40) stereochemical discrimination between the methyl and the perfluoroalkyl groups, respectively, affording diastereomerically pure *trans* oxazolines **3q**,**r** in high yield. Excellent diastereoselectivity was achieved also in the reaction of α-acetylenic α'-trifluoromethyl ketone **2v** with isocyanoacetate **1**. Due to the high electrophilicity of ketone **2v**, its Ag(I)/NEt_3-catalyzed condensation with **1** occurred with a very high reaction rate and gave the desired *trans*-oxazoline **3v** as an individual product in high chemical yield (entry 48). However, Cu(I)/TEA-catalyzed reaction of *n*-heptyl trifluoromethyl ketone (**2s**) with **1** gave the targeted oxazolines **3**,**4s** with remarkably reduced *trans* diastereoselectivity (entry 41). Despite the stereoselectivity of this reaction being to 80% de with an application of Ag(I)/TEA as the catalyst (entry 42), this value remains still lower compared with the diastereoselectivity of >98% reported for the reaction of ketone **2s** with a Ni(II) complex of the chiral Schiff base of glycine.[6] A similar stereochemical result was obtained in the condensation of *n*-octyl trifluoromethyl ketone (**2t**) with **1** (entry 44). These data suggest once again that, while important, steric reasons alone fail to rationalize the stereochemical outcome of the reactions under study (*vide infra*). In sharp contrast to the reactions of trifluoromethyl-containing aryl **2b**,**d**−**f**, and *n*-alkyl ketones **2q**,**s**,**t**, Cu(I)/NEt_3-catalyzed condensation of cyclohexyl trifluoromethyl ketone (**2u**) with **1** proceeded with the opposite sense of stereochemical preferences, furnishing *cis*-oxazoline **4u** as the major diastereomer, albeit with low diastereoselectivity (entry 46). Application of Ag(I)/NEt_3 as the catalyst in this reaction gave a mixture of oxazolines **3**,**4u** with lower diastereoselectivity (entry 47). Condensation of β-keto ester **2w** with **1** was of particular interest, since highly enolizable **2w** normally does not enter aldol reactions under basic reaction conditions (entry 52). The diastereoselectivity of this reaction was found to be highly dependent on the catalyst employed (entries 49−51) but comparable in value with that of *n*-alkyl ketones **2s**,**t** reactions with **1** (entries 42, 44 *vs* 51).

Finally, Cu(I)/NEt_3-catalyzed reactions of unsubstituted prochiral hydrocarbon ketones with isocyanoacetate **1** were investigated. We found that the condensations of ethyl methyl and *n*-propyl methyl ketones (**2x**,**y**) with **1** proceeded with low stereoselection (entries 53, 54), while cyclohexyl methyl ketone (**2z**) reacted with **1**, giving rise to *trans*-oxazoline **3z** with markedly higher diastereoselectivity (entry 55). It is worth noting that the diastereodirecting effect of the cyclohexyl group in the reaction of **2z** with **1** (entry 55) was less pronounced than that of trifluoromethyl in the condensation of **2q** with **1** (entry 39), while the direct competition of these substituents in the reaction of cyclohexyl trifluoromethyl ketone (**2n**) with **1** (entries 46,47) showed a preference for the cyclohexyl group.

The results discussed here clearly demonstrate the pivotal role of the steric parameters of substituents on the starting ketone in the origin of stereocontrol in the reactions under study. However, steric interactions alone probably cannot account for the sense and the values of the diastereoselectivities observed. Thus, while for the hydrocarbon series (reactions of **1** with **2x**−**z**) a plot of the E_s[19] and $E_{s'}$[20] constants for the substituents Et, *n*-Pr, *c*-Hex versus log *trans*/*cis* ratios of **3**,**4x**−**z** gives an acceptable linear correlation, the diastereoselectivities obtained in the reactions of **1** with halo-substituted ketones are much higher to follow this correlation.

Effect of Electrostatic Interactions on the Stereochemical Outcome. An evaluation and use of the steric substituent constants E_s[19] and $E_{s'}$[20] as a measure of steric requirements is of great importance to the problems of mechanistic studies, when it is applied to the substituents of similar nature. However, attempts to describe the stereochemical behavior of the different in nature substituents merely by the means of their steric constants or van der Waals radii[21] usually give controversial results. In particular, direct comparison of the steric characteristic of fluorocarbon and hydrocarbon substituents seems to be rather inappropriate and methodologically misleading.[22] Thus, whereas the $E_{s'}$ value of a phenyl group (2.31) is much larger than that of a trifluoromethyl group (0.78),[20] the results reported on asymmetric reductions of trifluoroacetophenone **2d** show that the sense and value of the asymmetric outcome heavily depends on the reducing reagent employed.[23] For instance, the reduction of ketone **2d** with alpine-borane afforded the corresponding carbinol (54% ee) of (*R*)-configuration, that is the same as compared to the stereochemistry observed in the reduction of fluorine-free acetophenone, while the reduction of **2d** with DIP-Cl gave the opposite stereochemical result.[23l] Since the steric bulkiness of the substituents could not "depend" on the reaction condition employed, an explanation for these anomalous data might involve, apart from steric proper-

(18) Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E.; Smart, B. E.; Tatlow, J. C., Eds.; Plenum Press: New York, 1994; pp. 57−88.

(19) Taft, R. W. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; Wiley: New York, 1956; p 556.

(20) MacPhee, A.; Panaye, A.; Dubois, J.-E. *Tetrahedron* **1978**, *34*, 3553.

(21) Bott, G.; Field, L. D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618.

(22) For instance, such statements as "CF_3 is sterically at least as large as $CH(CH_3)_2$"; see ref 18. For asymmetric results, which do not follow this statement, and the corresponding rationale, see ref 23k.

ties, some other features of the substituents, such as the electronic and electrostatic properties.

Thus, a dramatic difference between the stereochemical outcomes of the reactions of isocyanoacetate **1** with acetophenone (**2a**) and its trifluoromethyl analogs **2b**,**d**−**f** could be reasonably ascribed, as proposed above, to the larger steric requirements of the spherical trifluoromethyl group being larger than that of the flat phenyl in the transition states **B** and **A** (Figure 1), respectively. However, by analogy with the mechanistic rationale for the high diastereoselectivity observed in the reactions of trifluoromethyl ketones with a Ni(II) complex of the chiral Schiff base of glycine,[6] we can assume that the transition state **B** could be additionally destabilized by the repulsive electrostatic interactions between the negatively charged enolate moiety and the trifluoromethyl group. These effects might take place also in the reactions of isocyanoacetate **1** with per(poly)fluoroalkyl alkyl-(aryl) ketones **2g**−**i**,**q**−**w** and, in general, with other halogen-containing ketones, influencing the stereoselectivity in these condensations. In particular, the results obtained allow us to conclude that, in the reactions under study, a trifluoromethyl group acts as a sterically larger substituent than a thin and flexible *n*-alkyl or a flat phenyl groups, even though the total steric volume of these groups is much larger than that of the trifluoromethyl.

Other stereochemical results which are difficult to explain on the basis of purely steric reasons are the higher values of diastereoselectivities observed in the reactions of **1** with pentafluorophenyl-containing ketones **2b**,**c** as compared with that of acetophenone (**2a**) and trifluoroacetophenone **2d** condensations with **1** (e.g., entry 1 *vs* 14, and 5 *vs* 17). Recently we have shown that in the reactions of methyl isocyanoacetate **1** with fluorobenzaldehydes the number of fluorine atoms on the phenyl ring of the starting aldehyde controls the stereochemical outcome of the condensation, giving rise in the case of polyfluorobenzaldehydes reactions to the corresponding *cis*-oxazolines.[9a] Our working rationale for this *cis* diastereoselectivity involves an electron donor−acceptor type attractive interaction between the enolate oxygen and the polyfluorophenyl ring. We can assume that the same type of the interactions could take place in the reactions of **1** with ketones **2b**,**c**. Thus, an attractive interaction between negatively charged enolate moiety and electron-deficient pentafluorophenyl ring would stabilized the transition state **A**, giving some preference for *trans*-oxazolines **3b**,**c** formation. This assumption is strongly supported by the results reported previously by *Ojima* and *Kwon* on the addition reactions to a pentafluorophenyl-containing chiral iron acyl complex (PFCHIRAC).[24] The authors had proven that the opposite sense of stereodifferentiation, disclosed for the addition reactions of PFCHIRAC and fluorine-free CHIRAC,[25] is caused by the electron donor−acceptor type attractive interaction between the enolate oxygen and the pentafluorophenyl ring.[24]

On the basis of these and literature data,[6,23,24,26−28] we can suggest that the stereochemical outcome of the reactions, proceeding with an involvement of the fluorine-containing substituent into the stereoselective step, might be rationalized as the balance between steric and electronic/electrostatic effects influencing the pattern of stereochemical preferences. Under the certain reaction conditions the former or the latter effects could dominate and the both could work for the same or different stereochemical result. Obviously, the stereochemical behavior of fluorine must await further investigations.[29]

Catalyst Effect on Reaction Rate and Stereoselectivity. An important advantage of the transition metal catalysis in the reactions under study is that the coordination of a transition metal to the isocyano moiety increases substantially the C−H acidity of the methylene group of isocyanoacetate, allowing the reaction to proceed under more gentle conditions and to enjoy wider functional group tolerance as compared with those of the old-fashioned protocol relying on strongly basic conditions.[7,8] Thus, *Ito* has shown that while CuCl alone is capable of catalyzing the condensation of ethyl isocyanoacetate with carbonyl compounds, addition of TEA to the CuCl causes a remarkable acceleration of the reaction rate.[8a] However, no data on the relevance of the catalyst to the diastereoselectivity of the reactions have been reported.

Given the example of the reaction between isocyanoacetate **1** with octafluoroacetophenone (**2b**) (entries 2−12), we investigated the effect of both the metal and base components of the catalyst on the stereochemical outcome, as, due to high reactivity of the ketone **2b**, it was possible to explore also the diastereoselectivity of the reactions catalyzed separately by the metal (entry 10) and the base (entry 11), as well as the uncatalyzed condensation (entry 12). The first conclusion which can be drawn from the results obtained is the dramatic influence of the base in the catalyst on the rate and the diastereoselectivity of the reactions. In the series of Ag(I)/trialkylamine-catalyzed reactions of ketone **2b** with **1** (entries 4−9), the remarkable influence on the diastereoselectivity of the nature, particularly the steric bulk, of the amine was revealed. Thus, Ag(I)/*i*-Pr_2NEt-catalyzed reaction (entry 6) afforded a mixture of oxazolines **3**,**4b** with modest diastereoselectivity, while the condensation catalyzed with Ag(I)/NMe_3 (entry 7) furnished *trans*-oxazoline **3b** in excellent de (96%). The

(23) (a) Aaron, C.; Dull, D.; Schmiegel, J. L.; Jaeger, D.; Ohashi, Y. O.; Mosher, H. S. *J. Org. Chem.* **1967**, *32*, 2797. (b) Nasipuri, D.; Bhattacharya, P. K. *J. Chem. Soc. Perkin Trans 1* **1977**, 576. (c) Midland, M. M.; Kazubski, A. *J. Org. Chem.* **1982**, *47*, 2495. (d) Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *Synthesis* **1983**, 897. (e) Brown, H. C.; Pai, G. G. *J. Org. Chem.* **1985**, *50*, 1384. (f) Brown, H. C.; Cho, B. T.; Park, W. S. *J. Org. Chem.* **1988**, *53*, 1231. (g) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (h) Chong, J. M.; Mar, E. K. *J. Org. Chem.* **1991**, *56*, 893. (i) Corey, E. J.; Link, J. O.; Sarshar, S.; Shao, Y. *Tetrahedron Lett.* **1992**, *33*, 7103. (j) Corey, E. J.; Link, J. O.; Bakshi, R. K. *Tetrahedron Lett.* **1992**, *33*, 7107. (k) Ramachandran, P. V.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1725. (l) Ramachandran, P. V.; Teodorovic, A. V.; Gong, B.; Brown, H. C. *Tetrahedron: Asymmetry* **1994**, *5*, 1075.

(24) PFCHIRAC is an abbreviation for [$(C_6F_5)Ph_2P$](CO)CpFeCOMe (Cp = η^5-cyclopentadienyl); Ojima, I.; Kwon, H. B. *J. Am. Chem. Soc.* **1988**, *110*, 5617.

(25) CHIRAC is an abbreviation for (Ph_3P)(CO)CpFeCOMe; see for examples: (a) Davies, S. G.; Walker, J. C. *J. Chem. Soc., Chem. Commun.* **1985**, 209. (b) Liebeskind, L. S.; Welker, M. E.; Fengle, R. W. *J. Am. Chem. Soc.* **1986**, *108*, 6328.

(26) (a) (*Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; *Tetrahedron*: *Asymmetry*, *Special Issue*; Hayashi, T.; Soloshonok, V. A., Eds.) (b) *Tetrahedron* **1996**, *52*, No 1 (*Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards*; Resnati, G.; Soloshonok, V. A. Eds.; *Tetrahedron Symposium-in-Print No. 58*). (c) *EPC-Synthesis of Fluoro-Organic Compounds: Stereochemical Challenges and Biomedicinal Targets*; Soloshonok, V. A. Ed.; Wiley: Chichester, scheduled to appear in 1997.

(27) Soloshonok, V. A. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I.; McCarthy, J. R.; Welch, J. T. Eds.; ACS Symposium Series 639; American Chemical Society: Washington, D. C., 1996, pp 26−41.

(28) Schlosser, M.; Michel, D. *Tetrahedron* **1996**, *52*, 99.

(29) The state of controversy in this area was best exemplified recently by Schlosser: "All in all, the more results one sees, the more one feels frustrated. Whenever the question about the effective size of fluorine is asked again, a different answer is obtained." See ref. 28.

reaction catalyzed by Ag(I)/TEA showned lower stereoselectivity (entry 5). In contrast, the condensation of **2b** with isocyanoacetate **1**, catalyzed by 1 mol % of Ag(I)/PyH or Ag(I)/PS, proceeded with low reaction rates and gave a mixture of oxazolines **3** and **4** with poor diastereoselectivities (entries 8,9). The effect of the metal used for catalyzing the reaction of **1** with **2b** was less pronounced (entries 3−5). Surprisingly, the reactions catalyzed separately by CuCl and TEA showed quite different values of the diastereoselectivity (entry 10 *vs* 11). Considering also the stereochemical outcome of the uncatalyzed condensation (entry 12), we can assume that the use of a sterically undemanding base is essential for high reaction rate and diastereoselectivity to be achieved. Presumably, the presence of the base is critical for organization of the transition states **A** and **B** and their thermodynamic preferences are influenced by the stereochemical properties of the base. Despite the higher diastereoselectivity in the reactions of **1** with ketone **2b** that was obtained with the use of trimethylamine (entry 7 *vs* 5), for the rest of the study we chose to apply TEA, since the latter is much more easy to handle and its accurate concentration can be controlled.

The use of the metal in the catalyst and its nature were also found to be important for high diastereoselectivity to be achieved. Thus, in all condensations catalyzed by TEA alone, the stereoselectivities obtained were sizably lower compared with that of transition metal/TEA-catalyzed reactions (entry 27 *vs* 26, 43 *vs* 42, 45 *vs* 44). The reaction of **1** with keto ester **2w** is particularly noticeable, since it did not proceed at all if the transition metal is not present (entry 52 *vs* 49−51). Selection of the proper metal for each ketone condensation allowed us to improve the diastereoselectivity in many cases. We have found that the stereochemical outcome of the chlorodifluoroacetophenone **2g** reaction with isocyanoacetate **1** is very sensitive to the metal used, varying from 70−84% de (entries 23−25) to virtually stereospecific formation of *trans*-oxazoline **3g**, if catalyzed by CuCl (entry 26). The same catalyst, $CuCl/NEt_3$, was shown to be the best for the reactions of aryl perfluoroalkyl ketones **2h**,**i**, giving rise to the targeted *trans*-**3h**,**i** as the single reaction products with excellent chemical yields (entries 29, 30). A similar but even more pronounced change in the diastereoselectivity, depending on the metal used, was observed also in the reactions of **1** with trifluoromethyl alkyl ketones. Here Cu(I) or Au(I)/TEA catalysts gave a mixture of oxazolines **3**,**4s**,**t**,**w** with remarkably lower diastereoselectivity (entries 41, 46, 49, 50) as compared with the synthetically useful *trans* stereoselectivity (90% de and over) obtained in the reactions catalyzed by Ag(I)/TEA (entries 42, 44, 48, 51). Interestingly, even in the reaction of **1** with ketone **2u**, where the trifluoromethyl does not play the role of a diastereodirecting group, an application of Ag(I)/TEA as the catalyst increased the ratio of *trans*-oxazoline **3u** in a mixture with the dominant **4u**.

Given the diversity of the coordination numbers of the transition metal used, as well as the ligands they are bearing, it is unlikely that a single mechanistic rationale for their influence in the stereodiscrimination process through the transition states **A** and **B** could be proposed. However, the results obtained strongly suggest that Cu(I) and Ag(I) are rather superior over the rest of the metals explored and could be recommended, in a complex with TEA, as the catalysts of choice for this type of diastereoselective aldol reaction of isocyanoacetate **1** with prochiral ketones.

Summary. The results presented here indicate that the stereochemical outcome of the transition metal/base-catalyzed aldol type addition reaction between methyl isocyanoacetate **1** and prochiral ketones **2a**−**z** is subject to a number of substrate and catalyst influences, including the steric and electronic/electrostatic properties of the substituents on the starting ketone and the nature of both metal and base in the catalyst. The results suggest that some of the factors, in essence, could be manipulated to afford synthetically useful diastereoselectivity in these reactions.

Experimental Section

General. All reagents, unless otherwise stated, are commercially available and were used as received. *p*-Methoxyphenyl trifluoromethyl ketone (**2f**),[30] 1,1,1-trifluoro-4-phenyl-3-butyn-2-one (**2v**),[31] *n*-heptyl trifluoromethyl ketone (**2s**),[23k] *n*-octyl trifluoromethyl ketone (**2t**),[23k] cyclohexyl trifluoromethyl ketone (**2u**),[23k] and Au(*c*-HexNC)$_2$]BF_4[32] were prepared according to the corresponding literature procedures. Melting points were taken in open capillaries and are uncorrected. Monitoring of the reactions by GLC was performed using a fused silica capillary column. ^{1}H and ^{19}F NMR spectra were measured at 299.95 and 282.24 MHz, respectively. Unless indicated, NMR spectra were taken in $CDCl_3$ solutions using tetramethylsilane (TMS) and $CFCl_3$ as the internal standards.

X-ray analysis of the compound **7** was performed on an Rigaku AFC-5S diffractometer. A total of 1386 unique reflections were considered and used in the analysis. The structure was solved by the TEXSAN method. The R and R_w factors were of 0.056 and 0.052. A number of heavy atoms were refined (31) (C, N, O, F). Crystals of **7** were grown from diethyl ether and pentane. Crystal data for **7**: $C_{18}H_{11}F_8NO_4$, monoclinic, space group *C*2/*c*. Radiation: graphite monochromatized Cu Kα radiation. Crystal size: 0.8 × 0.2 × 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}.[33]

Unless otherwise stated, yields refer to isolated yields of products of greater than 95% purity as estimated by capillary GC and/or ^{1}H and ^{19}F NMR spectrometry. All new compounds were characterized by ^{1}H and ^{19}F NMR and elemental analysis.

Aldol Reactions of α-Methyl Isocyanoacetate (1) with Ketones 2a−z. General Procedure. To a magnetically stirred solution of the corresponding transition metal/base (1−10 mol %, as indicated in Table 1) and methyl isocyanoacetate (typically 1 mmol) in 2 mL of freshly distilled 1,2-dichloroethane was added an appropriate ketone **2** (1.1 mmol) under dry nitrogen atmosphere at room temperature (20−22 °C). Stirring was continued until complete consumption of the starting **1**, or the reaction mixture was stirred for a longer time (Table 1) to attain a suitable conversion. The progress of the reaction was monitored by GLC. The solvent was removed *in vacuo* and aldol products were isolated via bulb-to-bulb distillation. The ratio of diastereomers **3**/**4** was determined by GLC analysis on the crude reaction mixture, before removal of the solvent and distillation, and by NMR (^{1}H and ^{19}F, where possible) analysis on the distilled products. The ratios determined by NMR analysis were comparable (±1%) with those determined by GLC analysis. NMR spectra and microanalytical data for the oxazolines **3**,**4a**−**z** are listed below.

4-(Methoxycarbonyl)-5-methyl-5-phenyl-2-oxazolines (3,4a). *trans*-**3a**: ^{1}H NMR δ 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). *cis*-**4a**: ^{1}H NMR δ 1.61 (br s, 3 H), 3.86 (s, 3

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(32) Bonati, F.; Minghetti, G. G. *Gazz. Chim. Ital.* **1973**, *103*, 373.
(33) Atomic coordinates for the structure (**9**)have been deposited with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request from The Director, Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EW, UK.

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). Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.88; H, 6.09; N, 6.17.

4-(Methoxycarbonyl)-5-(trifluoromethyl)-5-(pentafluorophenyl)-2-oxazolines (3,4b). *trans*-**3b**, ^{1}H NMR δ 3,71 (s, 3 H), 5.32 (m, 1 H), 7.15 (d, J = 1.8 Hz, 1 H). *cis*-**4b**: ^{1}H NMR δ 3.86 (s, 3 H), 5.31 (m, 1 H), 7.14 (d, J = 1.8 Hz, 1 H). Anal. Calcd for $C_{12}H_5F_8NO_3$: C, 39.69; H, 1.39; N, 3.86; F, 41.85. Found: C, 39.83; H, 1.34; N, 4.02; F, 41.64.

4-(Methoxycarbonyl)-5-methyl-5-(pentafluorophenyl)-2-oxazolines (3,4c). *trans*-**3c**: ^{1}H NMR δ 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). *cis*-**4c**: ^{1}H NMR δ 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). Anal. Calcd for $C_{12}H_8F_5NO_3$: C, 46.62; H, 2.61; N, 4.53; F, 30.72. Found: C, 46.43; H, 2.67; N, 4.61; F, 31.00.

4-(Methoxycarbonyl)-5-(trifluoromethyl)-5-phenyl-2-oxazolines (3,4d). *trans*-**3d**: ^{1}H NMR δ 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); ^{19}F NMR δ −80.05 (s). *cis*-**4d**: ^{1}H NMR δ 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); ^{19}F NMR δ −75.97 (s). Anal. Calcd for $C_{12}H_{10}F_3NO_3$: C, 52.76; H, 3.69; N, 5.13; F, 20.86. Found: C, 52.65; H, 3.71; N, 5.17; F, 20.94.

4-(Methoxycarbonyl)-5-(trifluoromethyl)-5-[4-(trifluoromethyl)phenyl]-2-oxazolines (3,4e). *trans*-**3e**: ^{1}H NMR δ 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). *cis*-**4e**: ^{1}H NMR δ 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). Anal. Calcd for $C_{13}H_9F_6NO_3$: C, 45.76; H, 2.66; N, 4.11; F, 33.41. Found: C, 45.69; H, 2.61; N, 4.09; F, 33.34.

4-(Methoxycarbonyl)-5-(trifluoromethyl)-5-(4-methoxyphenyl)-2-oxazolines (3,4f). *trans*-**3f**: ^{1}H NMR δ 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); ^{19}F NMR δ −80.07 (s). *cis*-**4f**: ^{1}H NMR δ 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); ^{19}F NMR δ −75.93 (s). Anal. Calcd for $C_{13}H_{12}F_3NO_4$: C, 51.49; H, 3.99; N, 4.62; F, 18.80. Found: C, 51.53; H, 3.94; N, 4.67; F, 18.71.

4-(Methoxycarbonyl)-5-(chlorodifluoromethyl)-5-phenyl-2-oxazolines (3,4g). *trans*-**3g**: ^{1}H NMR δ 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); ^{19}F NMR δ −66.00, −67.10 (AB, J = 173.4 Hz). *cis*-**4g**: ^{1}H NMR δ 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); ^{19}F NMR δ −62.75, −63.60 (AB, J = 173.0 Hz). Anal. Calcd for $C_{12}H_{10}ClF_2NO_3$: C, 49.76; H, 3.48; N, 4.84; F, 13.12. Found: C, 49.77; H, 3.50; N, 4.85; F, 13.11.

4-(Methoxycarbonyl)-5-(pentafluoroethyl)-5-phenyl-2-oxazolines (3,4h). *trans*-**3h**: ^{1}H NMR δ 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); ^{19}F NMR δ −79.02 (br s, 3F), −123.01, −125.16 (AB, J = 302.3 Hz, 2 F). *cis*-**4h**: ^{1}H NMR δ 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). Anal. Calcd for $C_{13}H_{10}F_5NO_3$: C, 48.31; H, 3.12; N, 4.33; F, 29.39. Found: C, 48.45; H, 3.21; N, 4.44; F, 29.17.

***trans*-4-(Methoxycarbonyl)-5-(heptafluoropropyl)-5-phenyl-2-oxazoline:** ^{1}H NMR δ 3.29 (s, 3 H), 5.41 (d, J = 2.2 Hz, 1 H), 7.20 (d, J = 2.2 Hz, 1 H), 7.36−7.42 (m, 3 H), 7.43−7.47 (m, 2 H); ^{19}F NMR δ −81.60 (m, 3F), −118.81, −121.86 (AB, J = 288.2 Hz, 2 F), −120.70, −125.82 (ABX, J = 289.1 Hz, J = 11.5 Hz, 2 F). Anal. Calcd for $C_{14}H_{10}F_7NO_3$: C, 45.05; H, 2.70; N, 3.75; F, 35.63. Found: C, 45.12; H, 2.74; N, 3.81; F, 35.49.

4-(Methoxycarbonyl)-5-cyano-5-phenyl-2-oxazolines (3,4j). *trans*-**3j**: ^{1}H NMR δ 3.20 (s, 3 H), 5.41 (d, J = 2.0 Hz, 1 H), 7.29 (d, J = 2.0 Hz, 1 H), 7.42−7.74 (m, 5 H). *cis*-**3j**: ^{1}H NMR δ 3.90 (s, 3 H), 5.00 (d, J = 2.3 Hz, 1 H), 7.19 (d, J = 2.3 Hz, 1 H), 7.42−7.74 (m, 5 H). Anal. Calcd for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.79; H, 4.42; N, 12.19.

4-(Methoxycarbonyl)-5-(methoxymethyl)-5-methyl-2-oxazolines (3,4k). *trans*-**3k**: ^{1}H NMR δ 1.23 (s, 3 H), 3.38 (s, 3 H), 3.41−3.44 (m, 2H), 3.73 (s, 3 H), 4.62 (d, J = 2.0 Hz, 1 H), 6.89 (d, J = 2.0 Hz, 1 H). *cis*-**4k**: ^{1}H NMR δ 1.47 (s, 3 H), 3.23 (s, 3 H), 3.48−3.52 (m, 2H), 3.72 (s, 3 H), 4.33 (d, J = 2.0 Hz, 1 H), 6.90 (d, J = 2.0 Hz, 1 H). Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.41; H, 6.94; N, 7.50.

4-(Methoxycarbonyl)-5-(fluoromethyl)-5-methyl-2-oxazolines (3,4l). *trans*-**3l**: ^{1}H NMR δ 1.31 (d, J = 2.0 Hz, 3 H), 3.80 (s, 3 H), 4.39, 4.51 (ABX, J_{AB} = 9.9 Hz, J_{AX} = 47.6 Hz, J_{BX} = 46.7 Hz, 2 H), 4.66 (d, J = 2.0 Hz, 1 H), 6.96 (d, J = 2.0 Hz, 1 H). *cis*-**4l**: ^{1}H NMR δ 1.55 (d, J = 2.0 Hz, 3 H), 3.79 (s, 3 H), 4.44, 4.53 (ABX, J_{AB} = 9.9 Hz, J_{AX} = 46.8 Hz, J_{BX} = 45.2 Hz, 2 H), 4.48 (d, J = 2.0 Hz, 1 H), 6.97 (d, J = 2.0 Hz, 1 H). Anal. Calcd for $C_7H_{10}FNO_3$: C, 48.00; H, 5.75; N, 8.00; F, 10.85. Found: C, 47.94; H, 5.77; N, 7.89; F, 10.76.

4-(Methoxycarbonyl)-5-(chloromethyl)-5-methyl-2-oxazolines (3,4m). *trans*-**3m**: ^{1}H NMR δ 1.41 (s, 3 H), 3.65, 3.73 (AB, J_{AB} = 11.9 Hz, 2 H), 3.80 (s, 3 H), 4.73 (d, J = 2.0 Hz, 1 H), 6.96 (d, J = 2.0 Hz, 1 H). *cis*-**4m**: ^{1}H NMR δ 1.56 (s, 3 H), 3.67, 3.75 (AB, J_{AB} = 11.9 Hz, 2 H), 3.79 (s, 3 H), 4.50 (d, J = 2.0 Hz, 1 H), 6.97 (d, J = 2.0 Hz, 1 H). Anal. Calcd for $C_7H_{10}ClNO_3$: C, 43.88; H, 5.26; N, 7.31; Cl, 18.50. Found: C, 43.92; H, 5.27; N, 7.44; Cl, 18.39.

4-(Methoxycarbonyl)-5-(dichloromethyl)-5-methyl-2-oxazolines (3,4n). *trans*-**3n**: ^{1}H NMR δ 1.56 (s, 3 H), 3.81 (s, 3 H), 4.91 (d, J = 2.0 Hz, 1 H), 5.73 (s, 1 H), 6.98 (d, J = 2.0 Hz, 1 H). *cis*-**4n**: ^{1}H NMR δ 1.76 (s, 3 H), 3.80 (s, 3 H), 4.56 (m, 1 H), 6.20 (s, 1 H), one resonance is obscured. Anal. Calcd for $C_7H_9Cl_2NO_3$: C, 37.19; H, 4.01; N, 6.20; Cl, 31.37. Found: C, 37.24; H, 4.05; N, 6.27; Cl, 31.22.

***trans*-4-(Methoxycarbonyl)-5-(trichloromethyl)-5-methyl-2-oxazoline (3o)**: ^{1}H NMR δ 1.75 (s, 3 H), 3.83 (s, 3 H), 5.07 (d, J = 2.0 Hz, 1 H), 7.04 (d, J = 2.0 Hz, 1 H). Anal. Calcd for $C_7H_8Cl_3NO_3$: C, 32.28; H, 3.09; N, 5.38; Cl, 40.83. Found: C, 32.34; H, 3.14; N, 5.41; Cl, 40.61.

4-(Methoxycarbonyl)-5-(dichloromethyl)-5-(chloromethyl)-2-oxazolines (3,4p). *trans*-**3p**: ^{1}H NMR δ 3.81 (s, 3 H), 3.98 (AB, J = 12.2 Hz, 2 H), 5.08 (d, J = 2.0 Hz, 1 H), 6.21 (s, 1 H), 7.02 (br d, J = 2.0 Hz, 1 H). *cis*-**4p**: ^{1}H NMR δ 3.81 (s, 3 H), 4.06 (AB, J = 11.9 Hz, 2 H), 5.04 (d, J = 2.0 Hz, 1 H), 6.36 (s, 1 H), 7.02 (br d, J = 2.0 Hz, 1 H). Anal. Calcd for $C_7H_8Cl_3NO_3$: C, 32.28; H, 3.09; N, 5.38. Found: C, 32.37; H, 3.12; N, 5.39.

4-(Methoxycarbonyl)-5-(trifluoromethyl)-5-methyl-2-oxazolines (3,4q). *trans*-**3q**: ^{1}H NMR δ 1.51 (s, 3 H), 3.82 (s, 3 H), 4.90 (d, J = 2.0 Hz, 1 H), 6.98 (d, J = 2.0 Hz, 1 H); ^{19}F NMR δ −80.78 (s). *cis*-**4q**: 1.75 (s, 3 H), 3.81 (s, 3 H), 4.64 (d, J = 2.0 Hz, 1 H), 7.01 (d, J = 2.0 Hz, 1 H); ^{19}F NMR δ −76.57 (s). Anal. Calcd for $C_7H_8F_3NO_3$: C, 39.82; H, 3.82; N, 6.64; F, 27.00. Found: C, 39.85; H, 3.84; N, 6.69; F, 26.93.

***trans*-4-(Methoxycarbonyl)-5-(heptafluoropropyl)-5-methyl-2-oxazoline (3r)**: ^{1}H NMR δ 1.53 (s, 3 H), 3.84 (s, 3 H), 4.95 (d, J = 2.0 Hz, 1 H), 6.99 (d, J = 2.0 Hz, 1 H). Anal. Calcd for $C_9H_8F_7NO_3$: C, 34.74; H, 2.59; N, 4.50; F, 42.74. Found: C, 34.85; H, 2.62; N, 4.57; F, 42.51.

4-(Methoxycarbonyl)-5-(trifluoromethyl)-5-*n*-heptyl-2-oxazolines (3,4s). *trans*-**3s**: ^{1}H NMR δ 0.87 (t, J = 6.5 Hz, 3 H), 1.24−1.40 (m, 10 H), 1.82−1.97 (m, 2 H), 3.81 (s, 3 H), 4.90 (d, J = 2.0 Hz, 1 H), 6.98 (d, J = 2.0 Hz, 1 H); ^{19}F NMR δ −80.81 (s). *cis*-**4s**: ^{1}H NMR δ 0.88 (t, J = 6.6 Hz, 3 H), 1.24−1.40 (m, 10 H), 1.82−2.20 (m, 2 H), 3.80 (s, 3 H), 4.72 (d, J = 2.0 Hz, 1 H), 6.99 (d, J = 2.0 Hz, 1 H); ^{19}F NMR δ −76.53 (s). Anal. Calcd for $C_{13}H_{20}F_3NO_3$: C, 52.87; H, 6.83; N, 4.74; F, 19.30. Found: C, 52.94; H, 6.89; N, 4.67; F, 19.25.

4-(Methoxycarbonyl)-5-(trifluoromethyl)-5-*n*-octyl-2-oxazolines (3,4t). *trans*-**3t**: ^{1}H NMR δ 0.87 (t, J = 6.5 Hz, 3 H), 1.25−1.37 (m, 12 H), 1.82−1.98 (m, 2 H), 3.82 (s, 3 H), 4.91 (d, J = 2.3 Hz, 1 H), 6.99 (d, J = 2.3 Hz, 1 H); ^{19}F NMR δ −80.80 (s). *cis*-**4t**: ^{1}H NMR δ 0.88 (t, J = 6.5 Hz, 3 H), 1.25−1.41 (m, 12 H), 1.82−2.20 (m, 2 H), 3.80 (s, 3 H), 4.72 (d, J = 2.3 Hz, 1 H), 7.00 (d, J = 2.3 Hz, 1 H); ^{19}F NMR δ −76.55 (s). Anal. Calcd for $C_{14}H_{22}F_3NO_3$: C, 54.36; H, 7.17; N, 4.53; F, 18.43. Found: C, 54.44; H, 7.21; N, 4.50; F, 18.32.

4-(Methoxycarbonyl)-5-(trifluoromethyl)-5-cyclohexyl-2-oxazolines (3,4u). *trans*-**3u**: ^{1}H NMR δ 0.99−2.20 (m, 11 H), 3.82 (s, 3 H), 4.94 (d, J = 2.0 Hz, 1 H), 7.00 (d, J = 2.0 Hz, 1 H); ^{19}F NMR δ −80.82 (s). *cis*-**4u**: 0.93−2.20 (m, 11 H), 3.80 (s, 3 H), 4.80 (d, J = 2.0 Hz, 1 H), 7.00 (d, J = 2.0 Hz, 1 H); ^{19}F NMR δ −76.53 (s). Anal. Calcd for $C_{12}H_{16}F_3NO_3$: C, 51.61; H, 5.78; N, 5.02; F, 20.41. Found: C, 51.63; H, 5.77; N, 5.06; F, 20.38.

***trans*-4-(Methoxycarbonyl)-5-(trifluoromethyl)-5-(2-phenylethynyl)-2-oxazoline (3v)**: ^{1}H NMR δ, 3.81 (s, 3 H), 5.10 (d, J = 2.1 Hz, 1 H), 7.08 (d, J = 2.1 Hz, 1 H), 7.26−7.48 (m, 5 H); ^{19}F NMR δ −80.99 (s). Anal. Calcd for $C_{14}H_{10}F_3NO_3$: C, 56.57; H, 3.39; N, 4.71; F, 19.18. Found: C, 56.55; H, 3.42; N, 4.78; F, 19.09.

4-(Methoxycarbonyl)-5-(trifluoromethyl)-5-[2-(ethoxycarbonyl)ethyl]-2-oxazolines (3,4w). *trans*-**3w**: ^{1}H NMR δ 1.24 (t, J = 7.3 Hz, 3H), 3.13, 3.42 (AB, J = 17.5 Hz, 2H), 3.79 (s, 3H), 4.11 (m, J = 3.3 and 7.3 Hz, 2H), 4.94 (d, J = 2.6 Hz, 1H), 6.94 (d, J = 2.6 Hz, 1H); ^{19}F NMR δ −80.85 (s). *cis*-**4w**: ^{1}H NMR δ 1.28 (t, J = 7.0 Hz, 3H), 3.03, 3.16 (AB, J = 16.0 Hz, 2H), 3.81 (s, 3H), 4.20 (q, J = 7.0 Hz, 2H), 5.43 (d, J = 2.3 Hz, 1H), 6.96 (d, J = 2.3 Hz, 1H); ^{19}F NMR δ −76.58 (s). Anal. Calcd for $C_{10}H_{12}F_3NO_5$: C, 42.41; H, 4.27; N, 4.95; F, 20.13. Found: C, 42.53; H, 4.25; N, 4.99; F, 20.08.

4-(Methoxycarbonyl)-5-ethyl-5-methyl-2-oxazolines (3,4x). *trans*-**3x**: ^{1}H NMR δ 0.97 (t, J = 7.6 Hz, 3 H), 1.27 (s, 3 H), 1.79 (q d, J = 7.6 Hz, J = 1.8 Hz, 2H), 3.76 (s, 3 H), 4.42 (d, J = 2.0 Hz, 1 H), 6.92 (m, 1 H). *cis*-**4x**: ^{1}H NMR δ 0.94 (t, J = 7.6 Hz, 3 H), 1.48 (s, 3 H), 1.55, 1.65 (ABX, J = 7.6 Hz, J = 24.5 Hz, 2H), 3.75 (s, 3 H), 4.40 (d, J = 2.2 Hz, 1 H), 6.93 (m, 1 H). By ^{1}H NMR the product contains about 5% of starting methyl α-isocyanoacetate (**1**): ^{1}H NMR δ 3.82 (s, 3H), 4.23 (s, 2H).

4-(Methoxycarbonyl)-5-*n*-propyl-5-methyl-2-oxazolines 3,4y). *trans*-**3y**: ^{1}H NMR δ 0.96 (t, J = 7.3 Hz, 3 H), 1.27 (s, 3 H), 1.34−1.48 (m, 2H), 1.71−1.78 (m, 2H), 3.76 (s, 3 H), 4.44 (d, J = 1.8 Hz, 1 H), 6.93 (m, 1 H). *cis*-**4y**: ^{1}H NMR δ 0.90 (t, J = 7.6 Hz, 3 H), 1.49 (s, 3 H), 1.55, 1.65 (ABX, J = 7.6 Hz, J = 24.5 Hz, 2H), 3.75 (s, 3 H), 4.40 (d, J = 2.0 Hz, 1 H), 6.93 (m, 1 H). By ^{1}H NMR the product contains about 8% of starting methyl α-isocyanoacetate (**1**).

4-(Methoxycarbonyl)-5-cyclohexyl-5-methyl-2-oxazolines (3,4z). *trans*-**3z**: ^{1}H NMR δ 0.95−1.97 (m, 11 H), 1.24 (s, 3 H), 3.76 (s, 3 H), 4.52 (d, J = 2.0 Hz, 1 H), 6.92 (d, J = 2.0 Hz, 1 H). *cis*-**4z**: ^{1}H NMR δ 1.35 (s, 3H), 3.75 (s, 3 H), 4.35 (d, J = 1.9 Hz, 1 H), 6.96 (d, J = 1.9 Hz, 1 H), *c*-Hex resonances are obscured by those of the major isomer. Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.05; H, 8.53; N, 6.17.

General Method of Hydrolysis of the Oxazolines *trans*-3d,g,h,s,v to (2*R,3*R**)-Methyl *N*-Formyl-3,3-disubstituted-serinates 5d,g,h,s,v.** The starting oxazoline **5d**,**g**,**h**,**s**,**v** (typically 2 mmol) was dissolved in 3 mL of MeOH and 2 mL of water, and one drop of 2 *N* HCl was added under stirring at ambient temperature. The progress of the hydrolysis was monitored by TLC or GLC, and upon completion MeOH was evaporated *in vacuo*. The products **5d**,**g**,**h**,**s**,**v** were extracted by ethyl acetate and purified to a diastereomerically pure state by recrystallization from ethyl acetate/*n*-hexane 2/1. NMR spectra, melting point and microanalytical data for **5d**,**g**,**h**,**s**,**v** are listed below.

(2*R,3*R**)-Methyl *N*-formyl-3-(trifluoromethyl)-3-phenylserinate (5d)**: yield 84% (from **3,4d**); mp 124−125 °C; ^{1}H NMR δ 3.47 (s, 3 H), 4.71 (s, 1 H), 5.59 (d, J = 8.3 Hz, 1 H), 6.83 (d, J = 8.3 Hz, 1 H), 7.41 (m, 3 H), 7.60 (m, 2 H), 8.25 (s, 1 H); ^{19}F NMR δ −75.91 (s). NMR data for (2*R**,3*S**)-diastereomer: ^{1}H NMR δ 3.87 (s, 3 H), 4.76 (s, 1 H), 5.45 (d, J = 8.2 Hz, 1 H), 6.19 (d, J = 8.2 Hz, 1 H), 7.41 (m, 3 H), 7.60 (m, 2 H), 7.90 (s, 1 H); ^{19}F NMR δ −77.34 (s). Anal. Calcd for $C_{12}H_{12}F_3NO_4$: C, 49.49; H, 4.15; N, 4.81; F, 19.57. Found: C, 49.51; H, 4.17; N, 4.78; F, 19.44.

(2*R,3*R**)-Methyl *N*-formyl-3-(chlorodifluoromethyl)-3-phenylserinate (5g)**: yield 91% (from **3g**); mp 132−133 °C; ^{1}H NMR δ 3.44 (s, 3 H), 4.86 (s, 1 H), 5.67 (d, J = 8.3 Hz, 1 H), 6.95 (d, J = 8.3 Hz, 1 H), 7.41 (m, 3 H), 7.61 (m, 2 H), 8.23 (s, 1 H). Anal. Calcd for $C_{12}H_{12}ClF_2NO_4$: C, 46.84; H, 3.93; N, 4.55. Found: C, 46.93; H, 3.91; N, 4.47.

(2*R,3*R**)-Methyl *N*-formyl-3-(pentafluoroethyl)-3-phenylserinate (5h)**: yield 89% (from **3h**); mp 121−125 °C; ^{1}H NMR δ 3.45 (s, 3 H), 4.70 (s, 1 H), 5.63 (d, J = 8.6 Hz, 1 H), 6.63 (d, J = 8.6 Hz, 1 H), 7.41 (m, 3 H), 7.56 (m, 2 H), 8.25 (s, 1 H); ^{19}F NMR δ −78.88 (s, 3 F), −120.88 (m, 2 F). Anal. Calcd for $C_{13}H_{12}F_5NO_4$: C, 45.76; H, 3.54; N, 4.11; F, 27.84. Found: C, 45.83; H, 3.60; N, 4.05; F, 27.67.

(2*R,3*R**)-Methyl *N*-formyl-3-(trifluoromethyl)-3-*n*-heptylserinate (5s)**: yield 63% (from **3,4s**); mp 55 °C; ^{1}H NMR (CD_3COCD_3) δ 0.89 (t, J = 7.3 Hz, 3 H), 1.30 (m, 8 H), 1.52 (m, 2 H), 1.80 (m, 2 H), 3.76 (s, 3 H), 5.02 (br s, 1 H), 8.24 (s, 1 H). Anal. Calcd for $C_{13}H_{22}F_3NO_4$: C, 49.83; H, 7.08; N, 4.47; F, 18.19. Found: C, 49.88; H, 7.12; N, 4.43; F, 18.02.

(2*R,3*R**)-Methyl *N*-formyl-3-(trifluoromethyl)-3-(2-phenylethynyl)serinate (5v)**: yield 97% (from **3v**); mp 112−113 °C; ^{1}H NMR δ 3.83 (s, 3 H), 4.27 (s, 1 H), 5.31 (d, J = 8.0 Hz, 1 H), 6.56 (d, J = 8.0 Hz, 1 H), 7.38−7.47 (m, 5 H), 8.28 (s, 1 H). Anal. Calcd for $C_{14}H_{12}F_3NO_4$: C, 53.34; H, 3.84; N, 4.44; F, 18.08. Found: C, 53.42; H, 3.83; N, 4.49; F, 17.94.

Hydrolysis of the Oxazolines *trans*-3d,g,h,q,s,t or (2*R,3*R**)-Methyl *N*-Formyl-3,3-disubstituted-serinates 5d,g,h,s to (2*R**,3*R**)-3,3-Disubstituted-serines 6d,g,h,q,s,t.** The hydrolysis was accomplished according to the general procedure described in ref 9a. The targeted amino acids were purified by recrystallization from water. NMR spectra, melting points and microanalytical data for **6d**,**g**,**h**,**q**,**s**,**t** are listed below.

(2*R,3*R**)-3-(Trifluoromethyl)-3-phenylserine (6d)**: yield 62% from **3,4d**, 89% from (2*R**,3*R**)-**5d**; mp 204−207 °C (dec); ^{1}H NMR (CD_3SOCD_3) δ 3.90 (s, 1 H), 7.39 (m, 3 H), 7.60 (m, 2 H). Anal. Calcd for $C_{10}H_{10}F_3NO_3$: C, 48.20; H, 4.05; N, 5.62. Found: C, 47.93; H, 4.00; N, 5.41.

(2*R,3*R**)-3-(Chlorodifluoromethyl)-3-phenylserine (6g) (chlorohydrate)**: yield 74% from **3g**, 79% from (2*R**,3*R**)-**5g**; mp 172−173 °C (dec); ^{1}H NMR (CD_3SOCD_3) δ 4.63 (s, 1 H), 7.42 (m, 3 H), 7.61 (m, 2 H). Anal. Calcd for $C_{10}H_{10}ClF_2NO_3$·HCl: C, 39.76; H, 3.67; Cl, 23.47; N, 4.64. Found: C, 39.67; H, 3.61; Cl, 23.69; N, 4.55.

(2*R,3*R**)-3-(Trifluoromethyl)-3-methylserine (6q)**:[6] yield 78% from **3q**; mp 226−229 °C (dec); ^{1}H NMR (CD_3COCD_3) δ 1.22 (s, 3H), 4.22 (s, 1H); ^{19}F NMR (CD_3SOCD_3) δ −77.10 (s).

(2*S*,3*S*)-β-(Trifluoromethyl)-β-*n*-heptylserine (6s) (hydrochloride):[6c] yield 65% from **3**,**4s**, 81% from **5s**; mp 178−179 °C; ^{1}H NMR (CD_3COCD_3) δ 0.89 (t, J = 7.1 Hz, 3H), 1.17−1,73 (m, 12H), 4.32 (s, 1H); ^{19}F NMR (CD_3SOCD_3) −75.13 (s).

(2*S*,3*S*)-β-(Trifluoromethyl)-β-*n*-octylserine (6t) (hydrochloride):[6c] yield 59% from **3**,**4t**; mp 166−169 °C; ^{1}H NMR (CD_3COCD_3) δ 0.86 (t, J = 7.1 Hz, 3H), 1.18−1.78 (m, 14H), 4.31 (s, 1H); ^{19}F NMR (CD_3SOCD_3) δ −75.11 (s).

(2*R,3*R**)-Methyl *N*-Benzoyl-3-(trifluoromethyl)-3-(pentafluorophenyl)serinate (7).** To a solution of **3**,**4b** (diastereoisomers ratio 9:1) (240 mg) in MeOH (4 mL) was added concd 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 were added CH_2Cl_2 (6 mL), NEt_3 (0.4 mL), and PhCOCl (0.16 mL), and the mixture was stirred for 2 h at ambient temperature. After the usual workup, the crude product was purified by preparative TLC on silica gel using the mixture hexane/ethyl acetate (3:1) as an eluent: ^{1}H NMR 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). Anal. Calcd for $C_{18}H_{11}F_8NO_4$: C, 47.28; H, 2.43; N, 3.06; F, 33.24. Found: C, 47.34; H, 2.41; N, 3.11; F, 33.01.

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