Pergamon

*Tetrahedron Letters*, Vol. 37, No. 43, pp. 7845-7848, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01746-7

# Transition Metal-Catalyzed Diastereoselective Aldol Reactions of Prochiral Ketones with Methyl Isocyanoacetate

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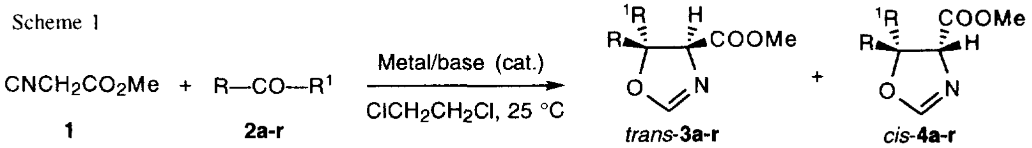
***Abstract*:** Systematic study of the transition metal-catalyzed aldol reactions of certain prochiral ketones with methyl isocyanoacetate has been made. High diastereoselectivity (80-98% de) of these condensations, leading to methyl (4*R**,5*R**)-4,5-dihydro-5,5-(disubstituted)-4-oxazolecarboxylates was shown to be controlled by the nature of both catalyst and substituents on the starting ketone. Copyright © 1996 Elsevier Science Ltd

Sterically constrained β,β-disubstituted-β-hydroxy-α-amino carboxylic acids are of exciting potential interest in the *de novo* design of peptides with specific conformational and physiological properties.[2] The most direct access to these amino acids might be provided by the aldol condensations between an equivalent of nucleophilic glycine and an appropriate prochiral ketone. However, due to the poor electrophilicity of ketones and generally limited stereochemical control of their addition reactions, the stereoselective aldol methodology involving prochiral ketones is virtually undeveloped.[3] Recently we have disclosed that aryl polyfluoroalkyl ketones undergo silver(I)/triethylamine-catalyzed aldol reactions with methyl isocyanoacetate (**1**) giving rise in highly diastereoselective manner (up to 90% de) to the corresponding oxazolines in excellent chemical yields.[4] We would like to report further that a) metal/base catalyst effects both the rate and the diastereoselectivity of these aldol reactions and previously reported diastereoselectivity[4] can be sizably increased (up to >98% de) with a proper choice of the catalyst; b) apart from aryl fluoroalkyl ketones, electrophilic aliphatic ketones can be readily involved in this aldol condensation providing concise and generalized entry to the particularly interesting type of stereochemically defined β,β-disubstituted-β-hydroxy-α-amino acids.[5]

To survey the effect of the both metal and base components of the catalyst on the stereoselectivity of the condensations, we carried out series of experiments varying the base ($NMe_3$, $NEt_3$, *i*-$Pr_2NEt$, PyH) and metal [Ag(I), Au(I), Cu(I), Rh(I), Pd(II)] used. The most representative results obtained are collected in Table 1. The first conclusion which can be drawn from the table 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 **2a** with **1** a remarkable influence on the diastereoselectivity by the steric bulk of the amine was revealed

Scheme 1



| | R | $R^1$ | | R | $R^1$ | | R | $R^1$ | | R | $R^1$ | | R | $R^1$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **a** | $C_6F_5$ | $CF_3$ | **e** | Ph | $CF_3$ | **i** | Me | $CHCl_2$ | **m** | *n*-Oct | $CF_3$ | **q** | Me | Et |
| **b** | Ph | $CClF_2$ | **f** | Me | $CH_2OMe$ | **j** | Me | $CCl_3$ | **n** | *c*-Hex | $CF_3$ | **r** | Me | *c*-Hex |
| **c** | Ph | $C_2F_5$ | **g** | Me | $CH_2F$ | **k** | Me | $CF_3$ | **o** | C≡C-Ph | $CF_3$ | | | |
| **d** | Ph | $C_4F_9$ | **h** | Me | $CH_2Cl$ | **l** | *n*-Hep | $CF_3$ | **p** | C≡C-*n*-Hex | $CF_3$ | | | |

**Table 1.** Catalytic Aldol Reactions of Aromatic Ketones **2** with Methyl Isocyanoacetate (**1**)[a]

| Entry | Ketone | Catalyst,[b] mol % | Time | Yield[c], % | Ratio[d] | |
|---|---|---|---|---|---|---|
| | | | | | *trans*-**3** | *cis*-**4** |
| 1 | (**a**) $C_6F_5COCF_3$ | 1% Ag(I)/*i*-$Pr_2NEt$ | 12 h | 96 | 83 | 17 |
| 2 | (**a**) $C_6F_5COCF_3$ | 1% Ag(I)/$NEt_3$ | 3.5 h | 92 | 94[e] | 6 |
| 3 | (**a**) $C_6F_5COCF_3$ | 1% Ag(I)/$NMe_3$[f] | 3.5 h | 97 | 98 | 2 |
| 4 | (**a**) $C_6F_5COCF_3$ | 1% Ag(I)/PyH | 45 h | 99 | 64 | 36 |
| 5 | (**b**) $C_6H_5COCClF_2$ | 1% Rh(I)/$NEt_3$ | 10 h | 98 | 90 | 10 |
| 6 | (**b**) $C_6H_5COCClF_2$ | 1% Pd(II)/$NEt_3$ | 5 h | 93 | 85 | 15 |
| 7 | (**b**) $C_6H_5COCClF_2$ | 10% Cu(I)/$NEt_3$ | 10 min | 92 | >99 (93)[e] | <1 |
| 8 | (**c**) $C_6H_5COC_2F_5$ | 10% Cu(I)/$NEt_3$ | 10 min | 94 | >99 (95)[e] | <1 |
| 9 | (**d**) $C_6H_5COC_4F_9$ | 10% Cu(I)/$NEt_3$ | 10 min | 87 | >99 | <1 |
| 10 | (**e**) $C_6H_5COCF_3$ | 1% Au(I) or Rh(I)/$NEt_3$ | 5 h | 94 | 89 (86)[e] | 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 **1**/**2** = 1/1.1; 1-5 mmol scale. Reactions were monitored by GLC and upon the completion products were isolated by bulb-to-bulb distillation. [b] Ag(I) is $AgClO_4$; Rh(I) — $[Rh(NBD)_2]BF_4$; Pd(II) — $PdCl_2(MeCN)_2$; Cu(I) — CuCl; Au(I) — $[Au(c\text{-}HexNC)_2]BF_4$. [c] Isolated yield. [d] Determined by GLC and $^1H$ NMR analyses. Relative configuration was determined as described in ref. 4. [e] Previously reported values for Ag(I)/$NEt_3$-catalyzed reactions; see ref. 4. [f] 1,2-Dichloroethane saturated with $NMe_3$ was used.

(entries 1-3). Thus, Ag(I)/*i*-$Pr_2NEt$-catalyzed reaction (entry 1) afforded a mixture of oxazolines **3,4a** with modest diastereoselectivity, while the condensation catalyzed with Ag(I)/$NMe_3$ (entry 3) furnished *trans*-oxazoline **3a** with higher de than previously reported for Ag(I)/$NEt_3$-catalyzed reaction (entry 2).[4] By contrast, condensation of octafluoroacetophenone with isocyanoacetate **1** catalyzed by 1 mol% of Ag(I)/PyH proceeded with low reaction rate and gave a mixture of oxazolines **3**, **4** with poor diastereoselectivity (entry 4).

The nature of the metal in the catalyst was also found to be important for high diastereoselectivity to be achieved. Selection of the proper metal for each ketone condensation allowed us to improve the previously reported diastereoselectivity of Ag(I)-catalyzed reactions.[4] We have found that stereochemical outcome of chloro-difluoroacetophenone **2b** reaction with isocyanoacetate **1** is very sensitive to the metal used, varying from 70-80% de (entries 5,6) to virtually stereospecific formation of *trans*-oxazoline **3a**, if catalyzed by CuCl (entry 7). The same catalyst, CuCl/$NEt_3$, was shown to be the best for the reactions of aryl perfluoroalkyl ketones **2c,d** giving rise to the targeted *trans*-**3c,d** as the single reaction products with excellent chemical yield (entries 8,9). By contrast, for trifluoroacetophenone **2e** condensation with **1**, the best value of diastereoselectivity, 89% of *trans*-**3e**, was achieved with Au(I) or Rh(I)/$NEt_3$ catalysts (entry 10).

Next, to explore generality of this reaction we carried out series of the condensations between isocyanoacetate **1** and a variety of prochiral aliphatic ketones. The most striking results are given in Table 2. In the CuCl/$NEt_3$-catalyzed reactions of mono-substituted acetones **2f-h** with methyl isocyanoacetate (**1**) low-to-modest diastereoselectivity was obtained (entries 1-3). A remarkable increase in the *trans*-diastereoselectivity was observed for the condensations of dichloromethyl **2i** and trichloromethyl ketones **2j** with **1** (entries 4,5). The stereochemical outcome of the series of mono-, di- and trichlorosubstituted acetones **2h-j** reactions (entries 3-5) clearly shows the steric influences in the diastereoselection process in these aldol condensations. Reaction of trifluoroacetone **2k** with **1** was found to proceed also with excellent diastereoselectivity (entry 6) while the condensation of *n*-heptyl trifluoromethyl ketone (**2l**) gave a mixture of oxazolines **3,4l** with a modest domination of *trans*-diastereomer **3l** (entry 7). However, the stereochemical outcome of the reactions of *n*-alkyl trifluoromethyl ketones **2lm** with **1** could be improved to 80% de with application of Ag(I)/$NEt_3$ as the catalyst (entry 8,9). In sharp contrast to the reactions of methyl **2k**, and *n*-alkyl ketones **2l,m**, Cu(I)/$NEt_3$-catalyzed condensation of *c*-hexyl trifluoromethyl ketone (**2n**) proceeded with the opposite sense of stereochemical preferences furnishing *cis*-oxazoline **4n** as the major diastereomer, albeit with low de (entry 10). Application of

**Table 2.** Metal/$NEt_3$-Catalyzed Reactions of Aliphatic Ketones **2f-s** with Methyl Isocyanoacetate (**1**)[a]

| Entry | Ketone R | $R^1$ | Catalyst, mol %[b] | Time | Yield[c], % | Ratio[d] trans-**3**[e] | cis-**4**[e] |
|---|---|---|---|---|---|---|---|
| 1 | (**f**) Me | $CH_2OMe$ | 10% Cu(I) | 20 h | 74 | 56 | 44 |
| 2 | (**g**) Me | $CH_2F$ | 10% Cu(I) | 0.5 h | 93 | 71 | 29 |
| 3 | (**h**) Me | $CH_2Cl$ | 10% Cu(I) | 0.5 h | 97 | 74 | 26 |
| 4 | (**i**) Me | $CHCl_2$ | 10% Cu(I) | 0.5 h | 99 | 92 | 8 |
| 5 | (**j**) Me | $CCl_3$ | 10% Cu(I) | 0.5 h | 95 | >99 | <1 |
| 6 | (**k**) Me | $CF_3$ | 10% Cu(I)[f] | 0.5 h | 91 | 99 | 1 |
| 7 | (**l**) *n*-Hep | $CF_3$ | 10% Cu(I) | 1 h | 91 | 76 | 24 |
| 8 | (**l**) *n*-Hep | $CF_3$ | 2% Ag(I) | 1 h | 93 | 90 | 10 |
| 9 | (**m**) *n*-Oct | $CF_3$ | 5% Ag(I) | 1 h | 95 | 91 | 9 |
| 10 | (**n**) *c*-Hex | $CF_3$ | 10% Cu(I) | 5 h | 87 | 35 | 65 |
| 11 | (**n**) *c*-Hex | $CF_3$ | 5% Ag(I) | 10 h | 91 | 43 | 57 |
| 12 | (**o**) C≡C-Ph | $CF_3$ | 2% Ag(I) | 10 min | 96 | >99 | <1 |
| 13 | (**p**) C≡C-*n*-Hex | $CF_3$ | 2% Ag(I) | 10 min | 96 | >99 | <1 |
| 14 | (**q**) Me | Et | 10% Cu(I) | 24 h | 37[g] | 60 | 40 |
| 15 | (**r**) Me | *c*-Hex | 10% Cu(I) | 24 h | 24[g] | 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 **1**/**2** = 1/1.1; 1-5 mmol scale. Reactions were monitored by GLC and upon the completion products were isolated by bulb-to-bulb distillation. [b] Cu(I) is the complex $CuCl/NEt_3$; Ag(I) — $AgClO_4/NEt_3$. [c] Isolated yield. [d] Determined by GLC and $^1H$ NMR analyses. [e] Relative configuration was determined as described in ref. 6. [f] At 0 °C. [g] Less then 50% conversion of starting materials.

Ag(I)/$NEt_3$, as the catalyst in this reaction, gave a mixture of oxazolines **3,4n** with lower diastereoselectivity (entry 11).

Excellent diastereoselectivity was achieved also in the reactions of α-acetylenic α'-trifluoromethyl ketones **2o,p** with isocyanoacetate **1**. Due to the high electrophilicity of ketones **2o,p** their Ag(I)/$NEt_3$-catalyzed condensations with **1** occurred with very high reaction rates and gave the desired *trans*-oxazolines **3o,p** as individual products (entry 12,13).

Finally, Cu(I)/$NEt_3$-catalyzed reactions of unsubstituted prochiral hydrocarbon ketones with isocyanoacetate **1** were investigated. We found that the condensation of ethyl methyl ketone (**2q**) with **1**, proceeded with low stereoselection (entry 14), while *c*-hexyl methyl ketone (**2r**) reacted with **1** giving rise to *trans*-oxazoline **3r** with markedly higher diastereoselectivity (entry 15). It is worth noting that the diastereodirecting effect of the *c*-hexyl group in the reaction of **2r** with **1** (entry 15) was less pronounced than that of trifluoromethyl one in the condensation of **2k** with **1** (entry 6), while the direct competition of these substituents in the reaction of *c*-hexyl trifluoromethyl ketone (**2n**) with **1** (entry 10,11) showed a preference to *c*-hexyl group.

In conclusion, we have found that metal/base-catalyzed condensations of methyl isocyanoacetate with electrophilic prochiral ketones would be of general importance for preparing stereochemically defined methyl 4,5-dihydro-5,5-(disubstituted)-4-oxazolecarboxylates and further, upon acidic hydrolysis, β,β-disubstituted-β-hydroxy-α-amino carboxylic acids of biomedicinal interest. The results presented here, highlight pronounced influences of the steric properties of substituents on the starting ketone in the diastereoselection processes in these reactions. However, stereochemical outcome of the reactions can not be rationalized by means of steric factors only and might involve electronic features of the substituents and the nature of the catalyst as well. Investigation of these issues on the reactions of a more wide range of prochiral carbonyl compounds is currently under study.

**Acknowledgment.** We thank the JSPS Foundation (Japan), Ministry of Education, Japan, for a Grant-in-Aid for Scientific Research, Uehara Memorial Foundation, International Science Foundation (U6M000, U6M200), INTAS (Network 93-799) for partial financial support of this work.

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6. Relative *trans*-configuration of oxazoline **3k** was confirmed *via* its acidic hydrolysis to the corresponding amino acid, (2*R**,3*R**)-configuration of which was established by comparison with the sample of known absolute stereochemistry; see ref. 5. Similarly, *trans*-configuration of **3l,m** was confirmed. To the rest of oxazolines **3f-j,n-p** *trans*-configuration was assigned on the basis of an apparent similarity of their NMR spectra to the patterns of **3k-m**; see ref. 7. In the case of hydrocarbon derivatives **3q,r**, relative configuration of the dominant diastereomer has not been established, but is assumed to be *trans* on the basis of similarity of their NMR spectra to the patterns of **3f-p**, and stereochemical preferences revealed for these reactions.
7. For aromatic derivatives **3,4a-e**, see ref. 4. $^1$H NMR (299.95 MHz, TMS, $CDCl_3$): **3f**: 1.23 (s, 3 H), 3.38 (s, 3 H), 3.41-3.52 (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). **4f**: 1.47 (s, 3 H), 3.23 (s, 3 H), 3.41-3.52 (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). **3g**: 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). **4g**: 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). **3h**: 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). **4h**: 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). **3i**: 1.56 (s, 3 H), 3.81 (s, 3 H), 4.91 (m, 1 H), 5.73 (d, $J$ = 0.66 Hz, 1 H), 6.98 (d, $J$ = 1.3 Hz, 1 H). **4i**: 1.76 (s, 3 H), 3.80 (s, 3 H), 4.56 (m, 1 H), 6.20 (s, 1 H), one resonance is obscured. **3j**: 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). **3k**: 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). **3l**: 0.84-0.89 (m, 3 H), 1.24-1.41 (m, 10 H), 1.82-2.05 (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). **3m**: 0.85-0.90 (m, 3 H), 1.25-1.41 (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). **4n**: 0.93-2.20 (m, 11 H), 3.78 (s, 3 H), 4.78 (d, $J$ = 2.0 Hz, 1 H), 6.97 (d, $J$ = 2.3 Hz, 1 H). **3o**: 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). **3p**: 0.81-0.88 (m, 3 H), 1.22-1.40 (m, 8 H), 1.83-2.07 (m, 2 H), 3.81 (s, 3 H), 4.99 (d, $J$ = 2.0 Hz, 1 H), 7.07 (d, $J$ = 2.0 Hz, 1 H). **3q**: 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). **4q**: 0.94 (t, $J$ = 7.6 Hz, 3 H), 1.48 (s, 3 H), 1.65 (m, 2H), 3.75 (s, 3 H), 4.40 (d, $J$ = 2.2 Hz, 1 H), one resonance is obscured. **3r**: 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).

(*Received in UK* 29 *July* 1996; *accepted* 6 *September* 1996)