114. Enantioselective Synthesis: Steric and Electronic Effects of the Substrates upon Stereoselectivity in the Gold(I)-Catalyzed Aldol Reaction with Chiral Ferrocenylamine Ligands

Preliminary Communication

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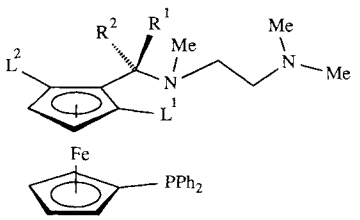
(16. III. 89)

Enantioselectivity in the gold(I)-catalyzed aldol reaction with chiral ferrocenylamine ligands is strongly dependent upon both the steric and electronic effects of the substrates. In the reaction of pyridine-2-, 3-, and 4-carbaldehydes with ethyl 2-isocyanoacetate, surprisingly and significantly different enantioselectivities were observed in the formation of the *cis*- and *trans*-dihydro-oxazoles that must be due to electronic rather than steric effects. The first example of double stereodifferentiation in the gold(I)-catalyzed aldol reaction is reported.

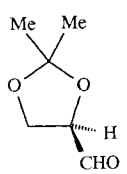
Introduction. – The development of synthetic methodology for enantioselective C–C bond formation is today a topic of fundamental importance. In particular, C–C bond-forming reactions whose diastereo- and enantioselectivity are derived through the use of catalytic quantities of chiral transition-metal catalysts are the focus of a considerable research effort [1].

In 1986, *Ito* and *Hayashi* reported an elegant asymmetric synthesis of dihydro-oxazoles by a Au(I)-catalyzed aldol reaction of aldehydes with 2-isocyanoacetate esters in the presence of the chiral ferrocenylamine **1** [2]. Later reports from the laboratories of *Ito* and *Hayashi* on the design of more efficient chiral ferrocenylamines [3] further suggested that the structure of the substrates can influence both diastereo- and enantioselectivity. We report herein a study primarily concerned with observing the effect of both changing



(*R,S*)-**1** R^1 = Me, R^2 = H, L^1 = PPh_2, L^2 = H
(*S,R*)-**1** R^1 = H, R^2 = Me, L^1 = H, L^2 = PPh_2

2 [(cyclo-$C_6H_{11}NC)_2Au$]BF_4



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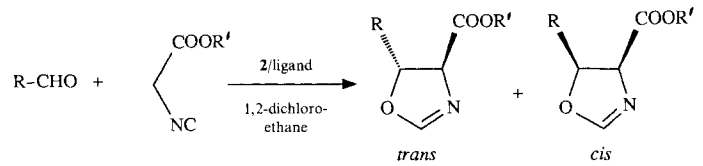
the steric and electronic requirements, and introducing chirality into the substrates. This as part of an effort in our laboratory directed towards *a)* better defining scope and limitations of this reaction with respect to applicability of a wide variety of substrates, and *b)* elucidating the nature of the stereoselective step in the Au(I)-catalyzed aldol reaction [4].

Results and Discussion. – 1. *Steric Effects.* In the condensation of the aldehyde with the alkyl 2-isocyanoacetate in the presence of bis(cyclohexyl isocyanide) Au(I) tetrafluoroborate (**2**) and the ligand **1** [5], we first investigated the influence of the size of the ester alkyl group (*Table 1, Entries 1–6;* for a general procedure, see [2]). An examination of the results obtained reveals a small increase in enantiomeric excess (ee) of the major *trans*-dihydro-oxazole isomer formed upon changing from the methyl to the ethyl ester. No change was observed in the ee of the *trans* product obtained by the reaction of the *tert*-butyl ester with benzaldehyde, whereas a decrease in ee was observed in the reaction with methacrolein. On the other hand, a significant increase in the ee of the *cis* product was observed for the reaction of either benzaldehyde or methacrolein with the *tert*-butyl ester. A reasonable interpretation of these results is that significantly different steric requirements exist for a particular substrate combination in the stereoselective transition state for attaining a maximum ee in the product. Furthermore, the steric requirements are clearly different for achieving maximum ee in the *cis* and *trans* dihydro-oxazole products. The improved *trans/cis* product ratios that were obtained by increasing the steric requirements of the aldehyde (*Table 1*, compare *Entries 7* and *8* with *1* and *2*) has been observed previously [2]. These observations are furthermore consistent with the lower stereoselectivity observed by *Ito* and *Hayashi* in the reaction of the sterically non-demanding substrate formaldehyde [3b].

2. *Electronic Effects.* Interestingly, both the sterically similar isomeric thiophene-2- and -3-carbaldehydes and furancarbaldehydes (*Table 1, Entries 15–18*), in which high *trans/cis* product ratios were obtained, gave a significantly different ee in the predominant *trans* product. The results obtained for the isomeric pyridinecarbaldehydes were even more surprising (*Table 1, Entries 19–21*). In the case of the pyridine-4-carbaldehyde, the reaction with the 2-isocyanoacetate gave a 88:12 *trans/cis* product ratio with high enantioselectivity on formation of both the *trans* (75% ee) and *cis* product (78% ee). Particularly striking were the results obtained in the reaction of pyridine-2-carbaldehyde. Although a relatively high 76:25 *trans/cis* product ratio was obtained, the *cis* product had a significantly greater ee (84% ee) than the *trans* product (6% ee).

The results obtained in the case of the isomeric pyridinecarbaldehydes cannot reasonably be explained by a steric argument because the sizes of the isomeric aldehydes are essentially the same. A comparison of the stereoselectivity obtained in the reaction of benzaldehyde (*Table 1, Entry 2*) with the stereoselectivity obtained using the isomeric pyridinecarbaldehydes, which have similar steric requirements, strongly argues against a steric explanation of the results. A change in stereoselectivity due to coordination of the heteroatom with the Au(I) cation seems equally unlikely. Both the O- and N-atom are known to be particularly poor ligands for Au(I) [6]. *Hayashi* and *Ito* have noted that coordination of the Au(I) cation to the P-atoms in **1** rather than the N-atoms is important to the success of the Au(I)-catalyzed aldol reaction. [2] A recently reported X-ray crystal structure of a Au(I) complex of **1** by *Togni* and *Rihs* supports this contention [7].

Table 1. *Reaction Conditions and Stereoselectivity in the Gold(I)-Catalyzed Reaction of Various Aldehydes with 2-Isocyanoacetates*



Entry	R	R′	Reaction time (h)	Reaction temp. [°][a]	Ligand	Dihydro-oxazole product		
						Yield [%][b]	*trans* [%]	*cis* [%]
1	Ph	Me	18	r.t.	(*R*,*S*)-**1**	99	90 (91 ee)	10 (7 ee)
2	Ph	Et	24	r.t.	(*R*,*S*)-**1**	88	89 (93 ee)	11 (17 ee)
3	Ph	*t*-Bu	40	r.t.	(*S*,*R*)-**1**	95	92 (93 ee)	8 (47 ee)
4	CH_2=C(CH_3)	Me	72	r.t.	(*R*,*S*)-**1**	56	92 (72 ee)	8 (13 ee)
5	CH_2=C(CH_3)	Et	72	r.t.	(*R*,*S*)-**1**	69	91 (78 ee)	9 (6 ee)
6	CH_2=C(CH_3)	*t*-Bu	72	r.t.	(*S*,*R*)-**1**	90	68 (54 ee)	32 (79 ee)
7	2,5-Me_2Ph	Me	20	r.t.	(*R*,*S*)-**1**	84	93 (95 ee)	7 (9 ee)
8	2,4,6-Me_3Ph	Et	24	50	(*R*,*S*)-**1**	57	100 (91 ee)	[c]
9	CH_2=C(CH_3)	(−)-Ment[d]	20	50	(*R*,*S*)-**1**	[h]	97 (88 de)	3 (15 de)
10	CH_2=C(CH_3)	(−)-Ment[d]	20	50	(*S*,*R*)-**1**	[h]	97 (89 de)[e]	3 (33 de)[f]
11	CH_2=C(CH_3)	(−)-Ment[d]	20	50	Et_3N	[h]	88 (12 de)[e]	12 (4 de)[e]
12	CH_2=C(CH_3)	(−)-Phet[g]	20	40	(*R*,*S*)-**1**	[h]	98 (81 de)	2 (40 de)
13	CH_2=C(CH_3)	(−)-Phet[g]	20	40	(*S*,*R*)-**1**	[h]	> 99 (80 de)[e]	< 0.5 (−)
14	CH_2=C(CH_3)	(−)-Phet[g]	20	40	Et_3N	[h]	94 (7 de)[f]	6 (5 de)
15	Thien-3-yl	Et	18	50	(*R*,*S*)-**1**	78	90 (78 ee)	3 (1 ee)
16	Thien-2-yl	Et	20	50	(*R*,*S*)-**1**	90	95 (33 ee)	5 (17 ee)
17	Fur-3-yl	Et	18	50	(*R*,*S*)-**1**	80	86 (87 ee)	14 (7 ee)
18	Fur-2-yl	Et	2.5	50	(*R*,*S*)-**1**	62	68 (32 ee)	32 (83 ee)
19	Pyridin-4-yl	Et	4	50	(*R*,*S*)-**1**	38	88 (75 ee)	12 (78 ee)
20	Pyridin-3-yl	Et	4	50	(*R*,*S*)-**1**	55	88 (79 ee)	12 (62 ee)
21	Pyridin-2-yl	Et	4	50	(*R*,*S*)-**1**	45	75 (6 ee)	25 (84 ee)
22	Ph	Me	40	r.t.	$Ph_3P/Me_2NCH_2CH_2NMe_2$	80	67 (0 ee)	33 (0 ee)
23	2,5-Me_2Ph	Me	20	r.t.	Diphos[i])/Et_3N	83	78 (0 ee)	22 (0 ee)
24	2,4,6-Me_3Ph	Et	24	50	Diphos[i])/Et_3N	21	78 (0 ee)	22 (0 ee)

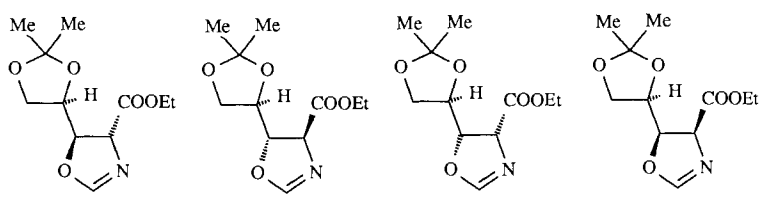
[a]) All reactions at r.t. were carried out in CH_2Cl_2.
[b]) Isolated yields after distillation; diastereoisomeric ratios were ascertained before and after distillation.
[c]) The *cis* isomer was not observed.
[d]) (1*R*,2*S*,5*R*)-Menthyl.
[e]) Opposite diastereoisomer formed in de to the previous entry.
[f]) The same diastereoisomer formed in de to the previous entry.
[g]) (*S*)-*sec*-Phenetyl.
[h]) Partial decomposition upon distillation.
[i]) 1,2-Bis(diphenylphosphino)ethane.

The unusual changes in enantioselectivity observed with the heteroaromatic aldehydes appears to be electronic in origin. A reasonable interpretation of these observations is that the electronegative heteroatom of the aldehyde causes a significant change in the $\Delta G^{\neq}$ leading to a particular *cis* or *trans* dihydro-oxazole enantiomer, which is due to a change in the relative energies of the possible diastereoisomeric conformations in the stereoselective transition state. The dependence of the product ee upon the electronic structure of the substrate has not previously been recognized in the Au(I)-catalyzed aldol reaction. The exact nature of this electronic perturbation is under active investigation in our laboratory and will be reported at a later date.

3. *Use of Chiral Isocyanoacetates and Chiral Aldehydes.* Recently, *Masamune et al.* advocated the powerful strategy of double stereodifferentiation (double asymmetric induction) for the predictable formation of new stereogenic centers [8]. The utilization of this stratagem with catalysts using chiral ferrocenylamine ligands is unreported in the literature. The reaction of (−)-menthyl or (−)-phenethyl 2-isocyanoacetate [9] with methacrolein in the presence of either (*R,S*)- or (*S,R*)-**1** gave both a nearly identical diastereoisomeric excess (de) in the predominant *trans* isomer and an almost identical *trans/cis* product ratio (*Table 1*, compare *Entries 9* and *12* with *10* and *13*, resp.). The observed increase in the *trans/cis* ratio over that of the control reaction without the ferrocenylamine (*Entries 11* and *14*) is not due to the use of a chiral 2-isocyano ester. This is supported by the observation of a similar increase in the *trans/cis* ratio when nonchiral esters are used (compare *Entries 1, 7,* and *8* with *22–24*).

The lack of double stereodifferentiation in the use of chiral esters could, in principle, be due to the distance of the chiral ester moiety from where the bond-forming process is taking place. Attempts to test this hypothesis through the use of the chiral aldehydes 2-methylbutanal and hydratropaldehyde (= 2-phenylpropanal) in which the stereogenic C-atom (chiral center) is proximate to the C—C bond being formed were thwarted by an inability to completely separate the diastereoisomeric pairs formed. On the other hand,

Table 2. *Distribution of Diastereoisomers Obtained in the Reaction of* **3** *with Ethyl 2-Isocyanoacetate*[a])



A **B** **C** **D**

Ligand	*trans*-Dihydro-oxazole		*cis*-Dihydro-oxazole	
	A [%]	**B** [%]	**C** [%]	**D** [%]
(*R,S*)-**1**	11	79	7	3
Diphos/Et_3N	22	57	3	18
(*S,R*)-**1**	45	44	1	10

[a]) The absolute configurations shown for the stereogenic centers in the dihydro-oxazole rings are tentative; their attribution is based on a comparison of the GLC retention times of **A**–**D** on *Chirasil-L-Val* with the ones of dihydro-oxazoles of known absolute configuration.

the four diastereoisomers formed on reaction of the chiral aldehyde **3** [10] with ethyl 2-isocyanoacetate could be cleanly separated by GLC with a *Chirasil*-L-*Val*® column *(Table 2)*. The use of **3** with (*R*,*S*)-**1** constitutes a matched pair, whereas the use of **3** with (*S*,*R*)-**1** constitutes a mismatched pair for the formation of the dominant *trans*-dihydro-oxazole. The opposite appears to be the case for the minor *cis*-dihydro-oxazole.

To our knowledge, these observations provide the first example of double stereo-differentiation between a substrate and a chiral ferrocenylamine catalyst in the Au(I)-catalyzed aldol reaction. It is relevant to note that the α-heteroatom effect mentioned above could play an important role in determining stereoselectivity (O-atom at C(α) in **3**). The relatively modest diastereoselectivity in the matched case, as well as the lack of diastereoselectivity in the mismatched case for the formation of the *trans* product, can tentatively be explained by the concurrent influence of both chirality and α-heteroatom effect.

These observations suggest that the application of the Au(I)-catalyzed aldol reaction to the construction of highly functionalized molecules potentially suffers from severe limitations, depending on the position of both chirality and/or heteroatom substituents in the substrates.

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