Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 4, pp. 541-544, 1994

0957-4166/94 $6.00+0.00

0957-4166(94)E0072-1

Enantioselective Aldol Reactions Using Homochiral Lithium Amides as Non-Covalently Bound Chiral Auxiliaries.

Yannick Landais* and Philippe Ogay

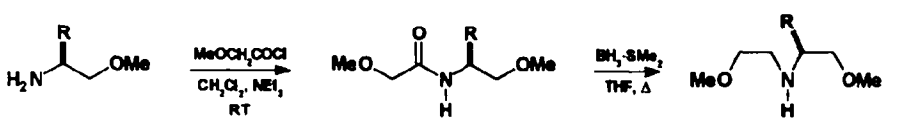
Institut de Chimie Organique, Université de Lausanne
Rue de la barre, 2, 1005 Lausanne, Switzerland

Abstract: *Syn* and *anti* aldols have been prepared from ketones and esters respectively with relatively high enantiomeric excesses, using a homochiral lithium amide possessing two co-ordinating sites, as non-covalently bound chiral auxiliary.

The interest in HomoChiral Lithium Amides (HCLAs) as either bases in asymmetric deprotonations, or as non-covalently bound chiral auxiliaries in aldol reactions, has steadily increased.[1] Although high enantioselectivities can be achieved using traditional covalently bound chiral auxiliaries, recent reports show that useful enantioselectivities can be obtained using HCLAs. However, to date few investigations have been undertaken about the enantioselectivities of HCLA mediated asymmetric aldol reactions using "convertible" carbonyls which have the potential to be functionalised after the aldol reaction.[2] We report herein our preliminary results concerning the asymmetric aldol reactions using Heathcock's versatile carbonyl substrates,[3] and two new HCLA bases possessing two co-ordinating groups (OMe).

The studies of Koga[2a] and Shioiri[2b-c] have shown that high selectivities can be obtained by using homochiral amines containing 1,2-amino-alcohol or 1,2-diamino moieties, which are known to efficiently coordinate to the lithium ions. It is likely that such co-ordinations rigidify the intermediate(s) involved in the transition state, thus increasing the enolate diastereofacial differentiation.[2d,4] Williard[5] recently proposed an aldol reaction sequence where he emphasises that mixed enolate-amide base aggregates might be among these important intermediates in the HCLA mediated aldol reactions. We thus devised our homochiral amine starting with the hypothesis that the presence of two chelating groups (OMe) co-ordinating the lithium ion should prove efficient in maintaining the rigidity of the intermediate (i.e. the mixed enolate-amide aggregate), leaving a free site on the lithium for the further co-ordination of the incoming aldehyde.

The amines **3a-b** were prepared using a two-step procedure, by acylation of the corresponding amino-ethers **1a-b** with α-methoxyacetyl chloride, to give the amides **2a-b**, followed by the reduction of the amide function with BH_3-DMS (Scheme 1)



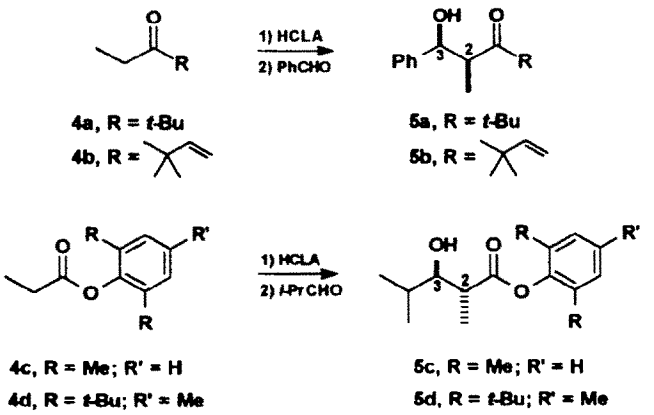
1a, R = *i*-Pr
1b, R = *t*-Bu

2a, R = *i*-Pr (82%)
2b, R = *t*-Bu (86%)

3a, R = *i*-Pr (86%)
3b, R = *t*-Bu (83%)

Scheme 1

We then studied the efficiency of the bases **3a-b** in the aldol condensations between substrates **4a-d** and various aldehydes (Scheme 2). The choice of these substrates was dictated by the fact that they give excellent simple diastereoselectivities, affording as sole products, the *syn* aldol for the ketones **4a**[2b] and **4b**[3a] and the *anti* aldol for the esters **4c-d**.[3b]



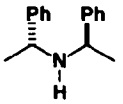
4a, R = *t*-Bu
4b, R =
5a, R = *t*-Bu
5b, R =
4c, R = Me; R' = H
4d, R = *t*-Bu; R' = Me
5c, R = Me; R' = H
5d, R = *t*-Bu; R' = Me

Scheme 2

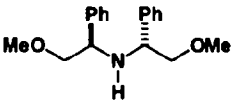
The results of our investigations are summarised in Table 1. Initial investigations were carried out on the reaction between the HCLA from amine **3a** (1.2 eq.), the ketone **4a** and benzaldehyde. A study of the effect on enantioselectivity of additives such as TMEDA, LDA, and *n*-BuLi was also made (entries 1-5).[2] The enantioselectivity of the reaction was determined from ^{1}H NMR of the Mosher esters, and the absolute configuration was determined by comparison (of optical rotations) with a sample prepared by using the conditions and an HCLA reported by Shioiri.[2b] While searching for the optimal stoechiometry recorded in entry 1,[6] a number of observations were made. The secondary amine (either **3a** or *i*-Pr$_2$NH) formed during the formation of the enolate must be re-deprotonated by the addition of *n*-BuLi (compare entry 1 with 5) As has already been observed by both Koga and Shioiri,[2a-c] the free chiral amine base is a poor chiral auxiliary which is not tightly bound to the enolate. Addition of TMEDA, in the ratio of one equivalent for every equivalent of amine base (both HCLA and LDA), before addition of the aldehyde, increased the enantioselectivity (compare entries 2 and 3 with 1). However, when this ratio is exceeded, the enantioselectivity dropped, presumably because of a change in the mixed enolate-HCLA aggregate structure (entries 1 and 4).[4] When the HCLA derived from the bulkier chiral amine **3b** was used (entry 6), the enantioselectivity dropped dramatically, suggesting that the formation of the enolate-HCLA aggregate is extremely affected by steric interactions.

Encouraged by these results, we then extended our investigations to the asymmetric aldol reactions of ketone **4b**. It was found that the enantioselectivity was slightly lower and that LDA had a detrimental effect on the enantioselectivity (entries 7 and 8). Finally, the absolute configuration of the aldol **5b** was found to be the same than that of aldol **5a**.[7]

Relatively few examples of HCLA mediated aldol reactions on esters have been reported so far and generally low enantioselectivities were observed.[1a,2d] We were pleased to find that the DMP ester **4c** gave useful enantioselectivities on reaction with isobutyraldehyde in the presence of amine **3a** (entry 9). It is also worthy of note that double recrystallisation of the aldol **5c** from hexane afforded the aldol in enantiomerically pure form. The absence of stereoselectivity in the aldol reaction with the bulky ester **4d** (entry 11) is in line with what was observed in entry 6 and indicates that the homochiral amide is tightly linked to the enolate and that the presence of large groups on the enolate (entry 11) or on the amide (entry 6) disrupts the HCLA-enolate complex. Finally, the absolute configuration of the aldol **5c**[8] suggests that the *E*-enolate of **4c**, like the *Z*-enolate of the ketones **4a** and **4b**, reacts on the *Si*-face of the aldehyde.



6a



6b

Scheme 3

We also studied the enantioselectivity of the C_2-symmetrical homochiral amines **6a**[1] and **6b**[9] (Scheme 3) in the aldol reactions with the carbonyl compounds **4b** and **4c**. The amine **6a** was found to give the aldol **5b** with lower e.e. than amine **3a** (entries 7 and 12), and surprisingly was totally non selective with the ester **4c** (entry 13). Contrary to **3a** and **6a**, **6b** was unable to deprotonate the ketone **4b** (entry 14), but when LDA (1 eq.) was used, **4b** afforded the aldol **5b** in good yield and higher e.e. than amine **6a** (entry 15). This indicates that the presence of additional co-ordinating groups around the N-Li bond might be necessary to ensure a good e.e., but also that steric effects are predominant both during the formation of the enolate and during the asymmetric C-C bond formation.

Table 1. Aldol reactions on substrates **4a-d** using HCLA bases (Scheme 2).

Entry	HCLA[a]	substrate[b]	BuLi (eq.)[c]	TMEDA (eq.)	LDA (eq.)	Yield (%)[d]	e.e (%)[e,f]	aldol[g]	config
1	**3a**	**4a**	**1.2**	**2.4**	**1.2**	**61**	**78**	**5a**	**2S,3S**
2	3a	4a	1.2	-	-	58	48	5a	"
3	3a	4a	1.2	1.2	-	60	62	5a	"
4	3a	4a	1.2	3.6	1.2	58	36	5a	"
5	3a	4a	-	2.4	1.2	59	5	5a	"
6	3b	4a	1.2	2.4	1.2	57	12	5a	"
7	**3a**	**4b**	**1.2**	**1.2**	-	**70**	**56**	**5b**	**2S,3S**
8	3a	4b	1.2	2.4	1.2	63	20	5b	"
9	**3a**	**4c**	**1.2**	**2.4**	**1.2**	**72**	**60**	**5c**	**2R,3R**
10	3a	4c	-	2.4	1.2	73	20	5c	"
11	3a	4d	1.2	2.4	1.2	90	0	5d	-
12	**6a**	**4b**	**1.2**	**1.2**	-	**65**	**40**	**5b**	**2S,3S**
13	6a	4c	1.2	2.4	1.2	88	8	5c	2R,3R
14	6b	4b	1.2	1.2	-	9	70	5b	2R,3R
15	**6b**	**4b**	**1.2**	**2.4**	**1.2**	**90**	**52**	**5b**	"

[a] HCLA generated from the corresponding amine (1.2 eq.) and *n*-BuLi (1.2 eq.) [b] 1 eq. [c] *n*-BuLi added after formation of the enolate. [d] Isolated yields. [e] determined from ^{1}H NMR of MTPA esters (aldols **5a** and **5b**). [f] determined by HPLC measurement on DAICEL® CHIRALCEL OD-H (aldol **5c**) [g] only one diastereoisomer was isolated in each case

The exact nature of the complex involved in the asymmetric aldol reaction is not known, but in the light of the recent report of Williard,[5] it is reasonable to postulate that a mixed HCLA-enolate aggregate is formed during our aldolisations (Fig -1). This is indeed supported by the stoechiometry of enolate-Li^+-base required for the reaction to take place with good stereocontrol.[2,6] We also observed in several cases (entries 6, 11), a dramatic effect of the steric hindrance on the stereochemical outcome of the reaction. Recent studies[10] have demonstrated that hindered lithium dialkylamide bases tend to be monomeric, and readily form mixed aggregates with ketone enolates. However, even if the mixed HCLA-enolate aggregate is present before addition of the aldehyde, it might not be the species involved in the asymmetric C-C bond formation.[4,5] As suggested by Williard,[5] it is likely that this mixed aggregate rearranges during aldolisation into more complex intermediates such as dimeric or tetrameric aggregates (Fig -1). Therefore, it is highly speculative to construct here a definitive intermediate which rationalises our findings

Finally, this HCLA mediated asymmetric aldol reaction on carbonyls **4b** and **4c** can give rise to all four *syn* and *anti* aldols, using L or D-amino-acids (entries 7 and 15), which is of major interest from the perspective of the total synthesis of natural compounds. Moreover, the homochiral amines are easily recovered in 80-90% yield, by a simple acidic workup followed by flash chromatography Further studies directed towards the development of more efficient HCLAs and clearer mechanistic rationales are now under way.

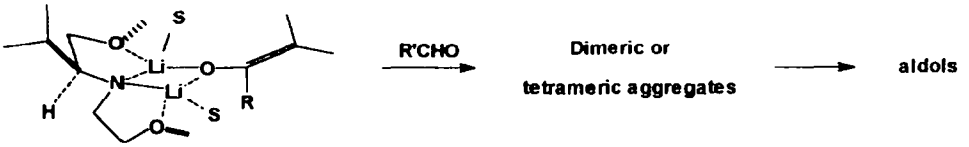
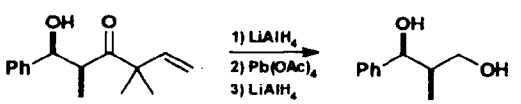


Fig.-1

Acknowledgements The authors gratefully acknowledge Pr P. Vogel and Dr. G. R. Jones for their interest in the project and Mr. V. Weber for technical assistance. We also thank the *Swiss National Science Foundation* and the *Fonds Herbette* for generous support

References and Notes

1. (a) For a review on the use of HCLAs in organic synthesis, see Cox, P J.; Simpkins, N S. *Tetrahedron Asymmetry*, **1991**, *2*, 1-26 and references cited therein, (b) Hasegawa, Y , Kawasaki, H , Koga, K. *Tetrahedron Lett.*, **1993**, *34*, 1963-1966; (c) Armer, R.; Begley, M J ; Cox, P.J ; Persad, A ; Simpkins, N.S *J. Chem. Soc., Perkin Trans. 1*, **1993**, 3099-3104; (d) Bunn, B.J.; Simpkins, N.S.; Spavold, Z ; Crimmin, M.J. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 3113-3116 and references cited therein.
2. (a) Muraoka, M., Kawasaki, H.; Koga, K. *Tetrahedron Lett.*, **1988**, *29*, 337-338; (b) Ando, A , Shioiri, T. *Tetrahedron*, **1989**, *45*, 4969-4988; (c) Ando, A., Tatematsu, T , Shioiri, T *Chem. Pharm. Bull.*, **1991**, *39*, 1967-1971; (d) Juaristi, E.; Beck, A K ; Hansen, J.; Matt, T ; Mukhopadhyay, T., Simson, M , Seebach, D *Synthesis*, **1993**, 1271-1290
3. (a) Mori, I ; Ishihara, K ; Heathcock, C.H. *J. Org. Chem.*, **1990**, *55*, 1114-1117, (b) Bal, B ; Buse, C T , Smith, K , Heathcock, C H. *Org. Synth.*, **1985**, *63*, 99-108 and references cited therein.
4. For a review on lithium enolate structures and reactivities, see Seebach, D *Angew. Chem. Int. Ed. Engl.*, **1988**, *27*, 1624-1654 and references cited therein.
5. Williard, P G ; Liu, Q -Y. *J. Am. Chem. Soc.*, **1993**, *115*, 3380-3381 and references cited therein.
6. To a solution of amine **3a** (1.2 mmol) and diisopropylamine (1.2 mmol) in dry THF (20 ml) was added at -30°C, a 1.6M solution of *n*-BuLi (2.4 mmol). The temperature was raised to -20°C, then TMEDA (2.4 mmol) was added and the mixture was cooled to -78°C. The ketone **4a** (1 mmol) in dry THF (2 ml) was then added and the resulting mixture was stirred for 30 minutes at -30°C. Then *n*-BuLi (1.2 mmol) was added at -30°C and the mixture was stirred at -30°C for 30 minutes. A cooled solution (-90°C) of benzaldehyde (1.2 mmol) in THF (1 ml) was then added at -100°C and the mixture was stirred for 15 minutes at -100°C, and then quenched with saturated 10% $NaHCO_3$. The organic layer was washed with 1M HCl and saturated $NaHCO_3$, dried over $MgSO_4$ and evaporated under reduced pressure to give an oil which was purified by chromatography on silica gel (hexane-ethyl acetate 96/4) to give the aldol **5a**[2b] as a colorless oil (61% yield)
7. Absolute configuration of the aldol **5b** was obtained by its conversion[3a] into the known diol 7 Davies, S.G ; Mortlock, A A *Tetrahedron Asymmetry*, **1991**, *2*, 1001-1004.



5b **7**

8. Duthaler, R.O.; Herold, P.; Wyler-Helfer, S.; Riedeker, M. *Helv. Chim. Acta*, **1990**, *73*, 659-673.
9. Barr, D.; Berrisford, D.J.; Jones, R.V.H.; Slawin, A W.Z.; Snaith, R.; Stoddart, J F.; Williams, D.J *Angew. Chem. Int. Ed. Engl.*, **1989**, *28*, 1044-1046.
10. Sakuma, K , Gilchrist, J.H.; Romesberg, F.E., Cajthami, C.E., Collum, D.B *Tetrahedron Lett.*, **1993**, *34*, 5213-5216.

(*Received in UK* 17 *February* 1994)