

CHIRAL AMINAL TEMPLATES 4¹. CHIRAL ARYL METALLIC REAGENTS : REACTIONS WITH ALDEHYDES

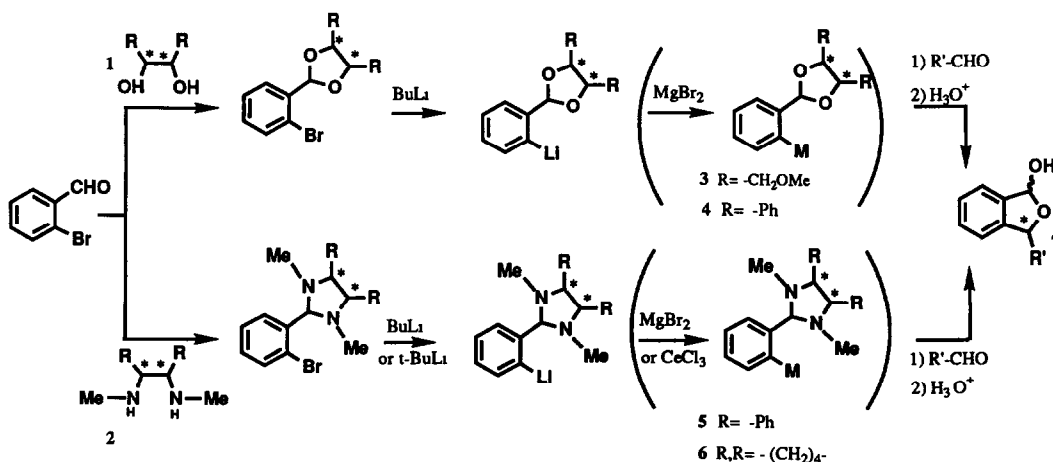
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(Received 5 March 1990)

Abstract. Chiral aryl metallic derivatives are generated from chiral *o*-bromo imidazolidines or acetals, prepared from chiral diols or diamines having a C₂ axis of symmetry. These reagents react with aldehydes with moderate to high diastereoselectivities. Removal of the chiral auxiliary, then, leads to homochiral lactols 7.

Much attention has been paid to reactions involving the diastereoselective addition of an achiral organometallic derivative on a prochiral carbonyl derivative using neighbouring acetal or imidazolidine groups as chiral auxiliaries². On the other hand the addition of organometallic derivatives, bearing such a chiral functionality to prochiral carbonyl compounds has led to very few studies. As a model, we have studied the diastereoselective addition of chiral aryl-metallic derivatives to aldehydes¹. By analogy with the works of Meyers³ and Mukaiyama⁴, the chirality was introduced in ortho position. As chiral auxiliaries, we have used dioxolanes or imidazolidines prepared from homochiral diols 1 or diamines 2⁵, having a C₂ axis of symmetry. Following a similar approach, Yamamoto described the addition of homochiral aryl Grignard reagents, bearing an ortho dioxane ring, on carbonyl compounds. In this case, the best diastereoselectivity was obtained with benzaldehyde (d.e. 88%)⁶.



The preparation of the chiral metallic reagents and their reactions with aldehydes are represented in the preceding scheme. Halogen metal exchange was performed with organolithium derivatives (BuLi or $t\text{-BuLi}$) Metal-metal exchange was then effected using MgBr_2 or CeCl_3 . Aldehydes were added *in situ* to metallated acetals **3** and **4** or imidazolidines **5** and **6**, affording after acidic hydrolysis, the lactol **7**. The enantiomeric excess was determined from the corresponding diacetates **8** and the absolute configuration of the new chiral carbon from the lactone **9**.

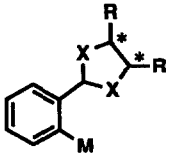


Our results are summarized in the table. First assays were effected using acetal **3** (runs 1-2). We choose the acetal derived from (2*S*, 3*S*)-(-)-1,4 dimethoxy-2,3 butanediol because of the possible chelation of the metallic atom by one of the methoxy oxygen atoms. Relatively poor asymmetric induction was observed in this case either with lithium or magnesium derivatives. In both cases, THF is a more effective solvent than ether. However in ether, with the lithium derivative (run 1) we observed an inverse selectivity as compared to the magnesium case. These observations are in favour of a steric control rather than a chelation one. In such acetals, the influence of the intramolecular coordination of the metal to one of the methoxy oxygen atoms competes with the steric effect of the bulky acetal moiety. Indeed with acetal **4** prepared from 1,2-diphenyl ethanediol (run 3), the diastereoselectivity, obtained in ether, is quite similar to the selectivity observed in THF with acetal **3** (run 2). In order to increase steric effects, we decided to use aminals **5** and **6** prepared from chiral symmetrical diamines⁵ (runs 4-16).

Under the same conditions as those used for acetal **4** (ether without LiBr , run 3) we observed an increase in the stereoselectivity (runs 4 and 8). As shown in the table, the optical yields obtained with lithiated aminals are very sensitive to the reaction conditions (solvent, absence or presence and concentration of a lithium salt). For aminal **5** prepared from homochiral 1,2-bis *N*-methylamino-1,2-diphenyl ethane (runs 4-7), the best stereoselectivity is obtained in ether without lithium salts. On the contrary, for aminal **6** prepared from homochiral 1,2-bis *N*-methylamino cyclohexane the best selectivity is obtained in THF with an excess of lithium salt (run 11). Under these conditions, extremely high stereoselectivity was observed with pentanal ($ee > 95\%$).

The stereoselectivity is also sensitive to the nature of the aldehyde used for the reaction. With benzaldehyde (run 14) a low optical yield was observed and with isobutyraldehyde we obtained a low chemical yield and no control at all (run 15). By using ceric derivatives, excellent chemical yield was obtained but without selectivity. The obtention of an extremely high stereoselectivity in the reaction of aminal **6** with linear aldehydes, without substitution in α position, might be rationalized by an intramolecular coordination of the lithium atom by one of the nitrogen atoms of the aminal. The metallic derivative (prepared from *S,S* aminal **6**) adds, then, on the *SI* face of the aldehyde as shown in fig. 1 rather than on the *RE* face because of steric interaction between the bulky substituent of the aldehyde and the *N*-methyl group (fig. 2).

TABLE

Run		LiBr (equivalents)	Solvent	R'-CHO R' =	yield ^{a)} %	e.e. %	config. ^{b)}
1	3 Li	-	Et ₂ O	Bu	50	12	R
	3 MgBr	-	Et ₂ O	Bu	11	3	S
2	3 Li	-	THF	Bu	66	25	S
	3 MgBr	-	THF	Bu	32	37	S
3	4 Li	-	Et ₂ O	Bu	52	21	S
4	5 Li	-	Et ₂ O	Bu	40	38	S
5	5 Li	1	Et ₂ O	Bu	75	4	R
6	5 Li	-	THF	Bu	20	13	S
7	5 Li	4	THF	Bu	40	7	S
8	6 Li	-	Et ₂ O	Bu	70	42	S
9	6 Li	1	Et ₂ O	Bu	65	59	S
10	6 Li	1	THF	Bu	80	87	S
11	6 Li	4	THF	Bu	80	96	S
12	6 Li	1	THF	i-Bu	85	50	S
13	6 Li	4	THF	i-Bu	90	98	S
14	6 Li	4	THF	Ph	60	52	S
15	6 Li	4	THF	i-Pr	10	0	-
16	6 CeCl ₃	4	THF	i-Pr	90	28	S

a) Yield of isolated diacetate **8**

b) starting from S,S diols or S,S diamines

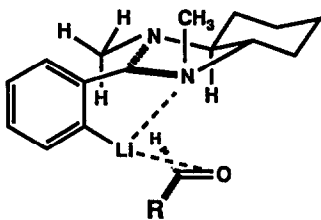


fig. 1

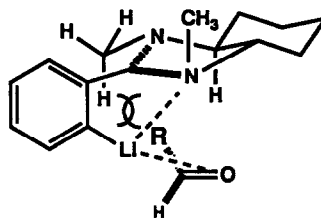


fig. 2

The advantage in using such chiral auxiliaries lies in their ease of preparation without creation of a new chiral center during their formation (thanks to the C_2 axis of symmetry) and their availability in both enantiomeric forms. Further studies are in progress to generalize and improve these reactions.

Acknowledgements : The authors thank prof J -F Normant for our fruitful discussions

References and notes

- 1 . The complementary approach is described in the preceding paper, *viz* the diastereoselective addition of an organometallic reagent to a chiral aryl aldehyde derivative Part 3 · Alexakis, A , Sedrani, R , Normant, J , Mangeney, P. *Tetrahedron Asymmetry* 1990 0000
- 2 . Fujioka, H.; Annoura, H , Murano, K., Kita, Y , Tamura, Y. *Chem Pharm Bull* , 1989, 37, 2047 and references cited therein
- 3 . Meyers, A I. , Hanagan, M.A , Trefonas, L.M. , Baker, R.V. *Tetrahedron Lett* , 1983, 39, 1991
- 4 . Asami, M , Mukaiyama, T. *Chem Lett* , 1980, 17
- 5 . a) Mangeney, P , Tejero, T , Alexakis, A , Grojean, F. , Normant, J -F. *Synthesis*, 1988, 255
b) Mangeney, P. , Alexakis, A , Normant, J -F. *Tetrahedron Lett* , 1988, 29, 2677
- 6 . Kaino, M. , Ishihara, K , Yamamoto, H *Bull Chem Soc , Jpn*, 1989, 62, 3736
- 7 . Imamoto, T , Kusumoto, T ; Tawarayama, Y. , Sugura, Y , Mita, T , Hatanaka, Y. , Yokoyama, M. *J Org Chem* , 1984, 49, 3904.