

Highly Diastereoselective Reduction and Addition of Nucleophiles to Binaphthol-protected Arylglyoxals¹

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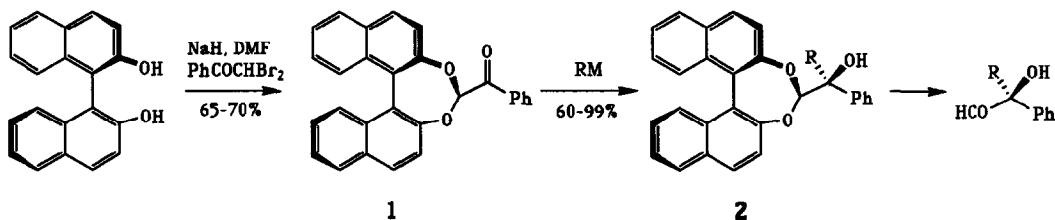
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Abstract: Arylglyoxals, protected at the aldehyde function with 1,1'-binaphthalene-2,2'-diol, are readily prepared by direct nucleophilic substitution of binaphthol-sodium salt on dibromoacetophenone and react highly diastereoselectively with lithium aluminium hydride and Grignard reagents to afford protected atrolactaldehyde and related compounds in high yield.

No preparations of arylglyoxals protected at the aldehyde function with chiral diols are known in the literature and generally only a few α -ketoacetals have been reported.⁴⁻⁶ The reason for the lack of reports may lay in the difficult preparation of vicinal ketoacetals as the few reported examples required multistep reaction sequences.⁷ Here, we report on the straightforward preparation and highly diastereoselective addition of hydride ion and Grignard reagents to binaphthol-derived phenylglyoxals. The products are precursors to natural atrolactic acid derivatives and of the intensively studied antiinflammatory drugs based on arylpropionic acids.

Reaction of the sodium salt of 1,1'-binaphthalene-2,2'-diol as obtained in DMF with NaH (60% toluene suspension) with dibromoacetophenone, produced ketone **1** directly in fairly good yield (65-70%, mp 206-7 °C from benzene).



The C₂-symmetry of the binaphthalene auxiliary can produce only a single isomer avoiding the production of diastereomeric mixtures which would arise from standard chiral auxiliaries. In contrast to binaphthol, aliphatic diols, for example ethylene glycol or tartaric acid derivatives, gave complex reaction mixtures of no practical use. This observation supports the rationale that the success of the reaction shown above is due to the lower basicity (or higher nucleophilicity) of the sodium salt of binaphthol with respect to that of aliphatic diols.

The results obtained in the reaction of **1** with lithium aluminium hydride and in the addition of nucleophiles are summarized in the Table. In a few instances the addition of the organometallic reagent was accompanied by partial reduction. In the case of *p*-MeC₆H₄MgBr, reduction was the only observed reaction path.

Table. Reaction conditions, yields, ratios and physical constants in the addition of nucleophiles to **1**.

RM	Reaction conditions ^a	Yield ^b	Diastereo- meric ratio ^b	Addition to reduction ratio ^b	mp (°C) of the major diastereoisomer (solv.)
LiAlH ₄	THF/Et ₂ O, -78°, 2h	97	98:2	-	142-3 (<i>i</i> -PrOH)
MeMgBr	THF, -78°, 2h	99	100:0	100:0	199-200 (<i>i</i> -PrOH)
MeLi ^c	Toluene, -83°, 2h	97	57:43	100:0	
ZnMe ₂	Et ₂ O, -20°, 2h	60 ^d	97:3	93:7 ^e	
EtMgBr	THF, -78°, 2h	96	100:0	93:7	180-1 (<i>i</i> -PrOH)
ZnEt ₂	Et ₂ O, -20°, 2h	80	92:8	93:7	
<i>i</i> -PrMgBr	THF, -78°, 2h	80	69:31	36:64 ^f	§
<i>n</i> -BuMgBr	THF, -78°, 2h	97	100:0	81:19	131-2 (<i>i</i> -PrOH)
<i>n</i> -BuLi ^h	Toluene, -83°, 2h	96	62:38	100:0	
PhMgBr	THF, -78°, 2h	99	-	92:8	218-9 (<i>i</i> -PrOH)
<i>p</i> -MeC ₆ H ₄ MgBr	THF, -78°, 2h	98	-	0:100 ⁱ	
<i>p</i> -Me ₂ NC ₆ H ₄ MgBr	THF, -78°, 2h	98	100:0	100:0	180-3 (<i>i</i> -PrOH)
<i>p</i> -FC ₆ H ₄ MgBr	THF, -78°, 2h	98	100:0	100:0	221-2 (<i>i</i> -PrOH)

^aAll reaction were carried out under argon with 1:10 substrate to RM ratio. ^bDetermined by NMR. ^c1.6 M in Et₂O. ^dCalculated with respect to recovered starting material. ^e93:7 ratio of the two diastereomeric secondary alcohols. ^f83:17 ratio of the two diastereomeric secondary alcohols. ^gnot determined. ^h1.6 M in *n*-hexane. ⁱ92:8 ratio of the two diastereomeric secondary alcohols.

While the reaction with lithium aluminium hydride and Grignard reagents afforded reaction mixtures composed of almost a single product (which can be obtained diastereomerically pure by a single recrystallization), little diastereoselectivity was observed with organolithium reagents. Organozinc compounds were far less reactive and slightly less diastereoselective. It should be noted that no reaction was observed with the Grignard reagent derived from methyl iodide.⁸

The stereochemistry of the addition was inferred by the X-ray structure determination of the product of addition of methylmagnesium bromide to ketone **1**. Suitable crystals were obtained after methylation of the hydroxy function and slow evaporation from a benzene solution.⁹ The ORTEP view is represented in the Figure. The stereochemistry encountered is not easily predictable on the assumption of a simple chelated intermediate between the substrate and the organomagnesium reagent as in related cases.⁵

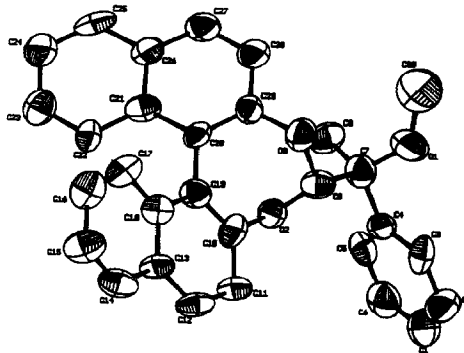


Figure. ORTEP representation of the adduct of methylmagnesium bromide to **1** after methylation.

From (*S*)-binaphthol ($\alpha_D^{25} = -33.8$, $c = 1.1$, THF), ketone **1** with $\alpha_D^{25} = +273.3$ ($c = 1$, THF) was obtained. Methylation of the latter gave **2** ($R = \text{Me}$) with $\alpha_D^{25} = +390.8$ ($c = 1$, THF). Preliminary deprotection experiments led to the optically active (*R*)-hydroxyaldehyde with retention of configuration, though as yet in poor yield.

References and Notes

- 1 Work supported by C.N.R. "Progetti Finalizzati".
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- 8 While this work was in progress a report on the preparation and reactivity of related 2-acyloxazolidines has been published: Ukaji, Y.; Yamamoto, K.; Fukui, M.; Fujisawa, T. *Tetrahedron Lett.*, **1991**, *32*, 2919.
- 9 MeMgI reacts with the dithioacetal instead: Delogu, G.; De Lucchi, O.; Maglioli, P.; Valle, G. *J. Org. Chem.* **1991**, *56*, 4467.
- 9 Unit cell parameters: $a = 10.188(2)$, $b = 14.417(2)$, $c = 7.820(1)$ Å, $\beta = 103.5(2)^\circ$; $C_{30}H_{24}O_3$; $Z = 8$; $D = 1.29$ g/cm³; monoclinic $P2_1$; λ (MoK α) = 0.7107 Å. The structure was phased by SHELX 86 program and refined by blocked full matrix least squares using SHELX 76 program. The final conventional R factor for the 1147 considered observed reflections [$F \geq 7\sigma(F)$] was 0.060.