Tetrahedron Letters, Vol.31, No.45, pp 6553-6556, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

COMPLEX-INDUCED PROXIMITY EFFECTS IN ENOLATE FORMATION. HIGHLY DIASTEREOSELECTIVE α-METHYLATION OF BINAPHTHYL ESTERS OF ARYLACETIC ACIDS.

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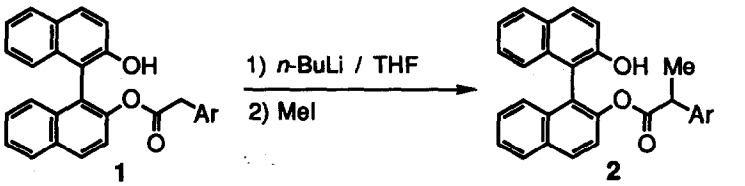
Abstract: Highly diastereoselective methylation of binaphthyl esters of arylacetic acids and its application to the syntheses of antiinflammatory drugs, (*S*)- suprofen and (*S*)-naproxen.

Recently, we reported a synthesis of optically active 2-arylalkanoic acids *via* diastereoselective alkylation of enolates generated from binaphthyl esters of arylacetic acids in tetrahydrofuran (THF)-hexamethylphosphoramide (HMPA).[1] Though a high degree of diastereoselectivity was recognized with bulky alkylating agents such as isopropyl iodide, less bulky alkylating agents resulted in a lower ratio of the products. Since 2-arylpropionic acids are an important class of nonsteroidal antiinflammatory drugs,[2] increase in diastereoselectivity of methylation has been desired to yield these drugs in optically pure form. Here, we report a dramatic improvement of diastereoselectivity in methylation, when *n*-butyllithium was used as a base in THF.

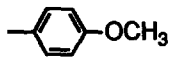
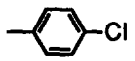
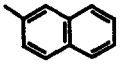
Generally, *n*-butyllithium has not been used for α-deprotonation of esters due to its nucleophilicity.[3] We were delighted to find that binaphthyl ester **1** was deptotonated with *n*-butyllithium in THF and gave the methylated product **2** in high diastereomeric ratio rich in (R^*,R^*)-isomer.[4] Results are listed in the Table.

A question to be answered is why *n*-butyllithium can be used as a base in the present enolization. Methylation of **3** and **4** under the standard conditions [4,6] afforded **5** and **6** in 60% and 25% yield, respectively. A 25% yield of **7** was obtained in the latter case indicating that approximately half of *n*-butyllithium was employed as a nucleophile rather than a base. 2-Naphthylester **9**, lacking a top half of binaphthol, was not deprotonated smoothly but afforded an approximately 1:1 mixture of **8** and **10**. External addition of 2-naphthol (**11**) gave similar results, indicating that an internal oxygen function is indispensable for the observed deprotonation of binaphthyl esters **1**. Complex-induced proximity effects[7] explain unexpectedly smooth enolization. Thus, *n*-butyllithium forms a complex with the oxygen function at C-2' in binaphthol prior to deprotonation. An enhanced acidity

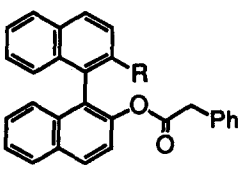
Table. Diastereoselective Methylation of Binaphthyl Esters **1** of Arylacetic Acids



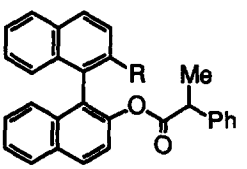
1 **2**

Ar	temp, °C	time, h	yield,%	*R*,R* : R*,S**
	-78	4.0	86	96 : 4
	-78~-25	4.3	72	87 : 13[a]
	-78~-30	2.0	97	92 : 8[b]
	-78~-30	3.5	78	95 : 5
	-78~-30	4.0	76	93 : 7

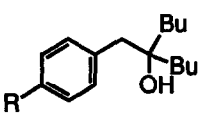
[a] A ratio of 53:47 with LDA in THF/HMPA was reported. See ref. 1.
[b] See ref. 5.



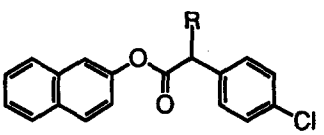
3, R = OMe
4, R = Me



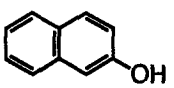
5, R = OMe
6, R = Me



7, R = H
8, R = Cl



9, R = H
10, R = Me



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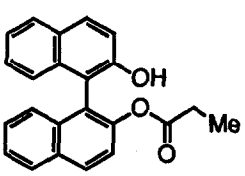

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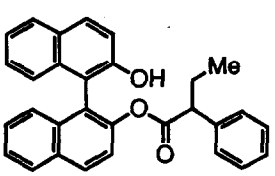

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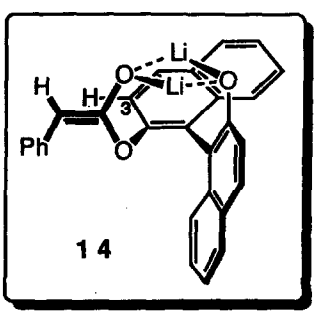

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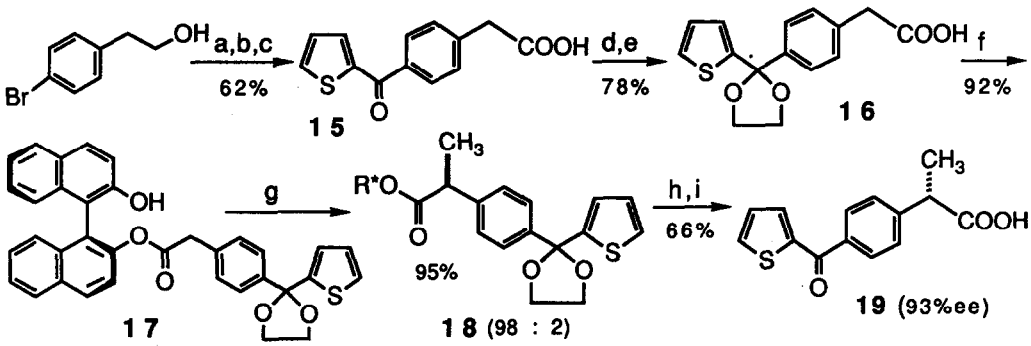
of a proton at the α-position of esters is also important, because binaphthyl esters **12** and **13** failed in methylation under standard conditions.[8]

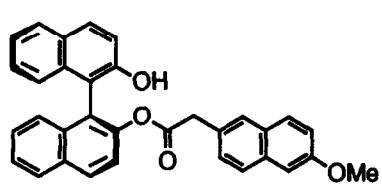
Although the detailed mechanism remains to be studied, an intermediate (*E*)-enolate **14**[9] captured by two lithium atoms offers a plausible explanation for the observed stereoselectivity in methylation. The *si*-face of the nucleophilic carbon in **14** is more congested due to the H-3 than the *re*-face, when (*R*)-binaphthol is used as a chiral auxiliary.

Scheme. Synthesis of (*S*)-(+)-Suprofen (**19**).

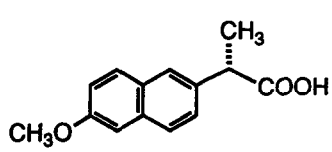


a)TBSCl, b)*n*-BuLi/2-thiophenecarboxaldehyde, c)Jones' oxid, d)ethylene glycol/TsOH, e)NaOH f)R*OH/WSC/DMAP, g)*n*-BuLi/THF,MeI, h)LiOH, i)HCl. (R*OH = (*S*)-2,2'-binaphthol).

Diastereoselective methylation of binaphthyl esters was applied to the syntheses of clinically important antiinflammatory drugs, (*S*)-suprofen (**19**)[11] and (*S*)-naproxen (**21**).[12] A synthetic route to (*S*)-suprofen (**19**) utilized acetalization of an aromatic ketone **15**, prepared from 4-bromophenethyl alcohol in three steps, to yield **16** (Scheme). Esterification with (*S*)-binaphthol gave a desired ester **17**, which was alkylated to afford a 95% yield of **18** contaminated with 2% of *S,R*-isomer. Hydrolysis with lithium hydroxide followed by the treatment with acid yielded (*S*)-(+)-suprofen (**19**)[13] of 93% ee[14] ($[\alpha]_D^{28}$ +39.5°, $CHCl_3$). (*S*)-(+)-Naproxen (**21**)[14] of 82% ee[13] ($[\alpha]_D^{28}$ +52.6°, $CHCl_3$) was prepared by the diastereoselective methylation (94%, 92:8) of **20** followed by the basic hydrolysis.



20



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3. An enolate of a sterically congested ester has been prepared with *n*-butyllithium. See, D. Seebach, R. Amstutz, T. Laube, W. B. Schweizer, and J. D. Dunitz, *J. Am. Chem. Soc.*, **1985**, *107*, 5403.
4. Typical procedure : To a solution of binaphthyl ester **1** (Ar = Ph, 0.2 mmol) in anhydrous THF (3 mL) was added a solution of *n*-butyllithium in hexane (1.57 M, 2.1 eq.) at -78°C. After 5 min., methyl iodide (20 eq.) was added and the mixture was stirred at -78°C for 4 h. Usual extractive workup followed by preparative TLC (silica gel, AcOEt : hexane = 1 : 3.5) gave a 86% yield of **2** (Ar = Ph). The diastereomeric ratio was shown to be 96:4 by ^{1}H NMR measurement, which was consistent with that of crude extracts.
5. Alkylation with *i*-propyl iodide afforded a 96:4 mixture of *R*,R**- and *R*,S**-isomers in 80% yield. Addition of HMPA is indispensable to prevent the decomposition of an enolate.
6. A 1.1 eq. of *n*-butyllithium was used.
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8. 2,2'-Binaphthol was obtained in high yield.
9. Though exclusive formation (*E*)-enolates from esters with LDA in THF is well known,[9] conclusive evidence for the formation of the same enolate with *n*-butyllithium has not been obtained. However, the chelated (Z)-enolate cannot explain the observed stereochemistry.
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(Received in Japan 30 July 1990)