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BINAPHTHOL AS A CHIRAL AUXILIARY: DIASTEREOSELECTIVE ALKYLATION OF BINAPHTHYL ESTERS OF α,β -UNSATURATED CARBOXYLIC ACIDS

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Abstract: Binaphthyl esters of α,β-unsaturated carboxylic acids are alkylated at the α-position concomitant with the migration of the double bond to the β,γ-position with high diastereoselectivity.

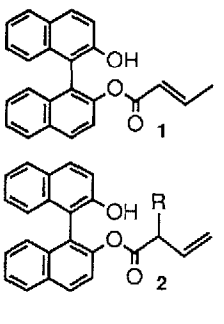
Recently, we reported highly diasteroselective alkylations of enolates generated from binaphthyl esters of arylacetic acids.[1,2] Though asymmetric alkylation of derivatives of carboxylic acids has been studied extensively,[3] no paper has appeared on the asymmetric alkylation of α,β-unsaturated carboxylic acids. As an extension of our work, asymmetric alkylation of binaphthyl esters of α,β-unsaturated carboxylic acids were studied.

Initially the alkylation of the binaphthyl ester **1** of crotonic acid was examined. The enolate of **1** generated with lithium diisopropylamide (LDA) in tetrahydrofuran (THF)-hexamethylphosphoric triamide (HMPA) at -78°C was treated with alkyl halides to afford α-alkylated product **2** exclusively.[4] The results are compiled in Table I. Addition of HMPA was indispensable for the alkylation, otherwise the unconjugated ester **2** (R = H) was recovered. High diastereoselectivity (ca 9 : 1) was observed for all of reactions regardless of the bulkiness of the alkylating agent. Diastereomeric mixture of chiral **2** (R = *i*-Pr) obtained from (*R*)-binaphthyl crotonate (*R*)-**1** was recrystallized from CH_2Cl_2-hexane to yield the major diastereomer **3** of 97% optical purity. The major isomer was converted into (*S*) -2 -ethyl-3-methyl-1-butanol (**4**) by hydrogenation followed by the reduction with $LiAlH_4$. The absolute configuration of **4** was determined by the optical rotation of its α-naphthylurethan **5** ($[\alpha]_D^{24}$ -3.5°, *c* 1.5, $CHCl_3$; lit.[5] $[\alpha]_D^{25}$ -3.8°, *c* 2.1, $CHCl_3$). Thus, the absolute structure **3** for the major diasteromer of isopropylation of (*R*)-**1** was confirmed to be *R, R*. Though there is no direct evidence for the stereochemistry of other alkylated products, it is much more likely that major diastereomers have the same stereochemistry as that for **3**.

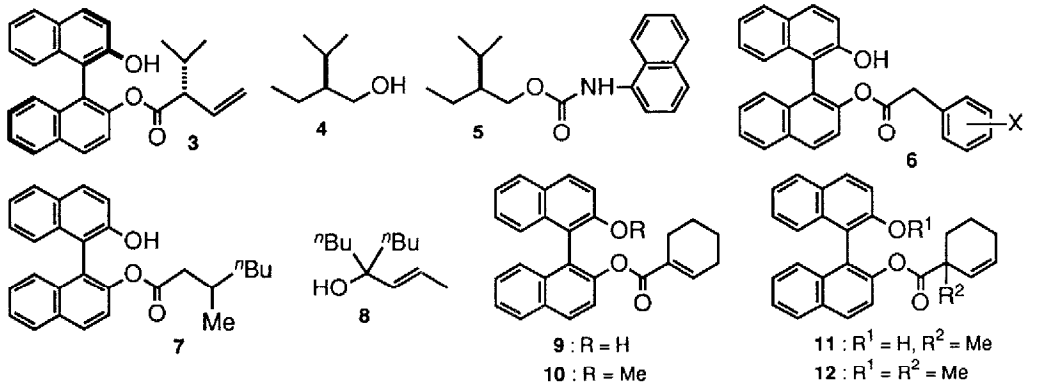
Table I. Alkylation of **1** giving **2**.[a)]

run	RX	temp.,°C	time, h	R =	yield, %	product ratio[b)]
1[c)]	EtI	-78	19	Et	0[d)]	-
2	EtI	-78	0.5	Et	53[e)]	93 : 7
3	$PhCH_2Br$	-78	0.7	$PhCH_2$	83	90 : 10
4	*i*-PrI	-78 ~ -45	2.3	*i*-Pr	64	90 : 10
5	*i*-BuI	-78 ~ -45	1.5	*i*-Bu	32	92 : 8

[a)] *dl* -Binaphthol was used. [b)] Determined by ^{1}H-NMR. [c)] Without HMPA. [d)] A 67% of **2** (R = H) was obtained. [e)] A 21% of diethylated product was obtained.



We have shown that diastereoselectivity was improved dramatically in the alkylation of binaphthyl arylacetate **6**, when *n*-BuLi in THF was used as a base to generate the enolate.[2] With the hope of successful generation of enolate and improvement of diastereomeric ratio, **1** was treated with 2.1 mol eq. of *n*-BuLi. The products were analyzed after quenched with dil. HCl. Major products included **7** (28%) and **8** (24%) resulting from the nucleophilic attack of *n*-BuLi in 1,4- and 1,2-sense, respectively. The compound **2** (R=H) with the unconjugated double bond was also obtained in 10% yield as well as the starting material **1** (6%). Though the formation of **2** (R=H) is the indication for the generation of the enolate, these findings show that *n*-BuLi acts mainly as a nucleophilic but as a base. The (*R*)-binaphthyl ester **2** (R = H) of vinylacetic acid was, however, deprotonated with *n*-BuLi in THF. After the addition of HMPA, the enolate was alkylated with *i*-PrI to afford **3** with a slightly higher selectivity (95 : 5). Easy formation of the enolate from **2** (R= H) can be rationalized by the higher acidity of the hydrogen at α-position of the carbonyl group in **2** (R=H) than that at the γ-position in **1**. It is beyond doubt that the complex-induced proximity effect[6] of the phenolic hydroxyl group plays an important role in abstracting the α-hydrogen as in the case of **6**.[2]



Methylation of the *dl*-ester **9** of 1-cyclohexenecarboxylic acid gave a 81 : 19 mixture of α-methylated products **11** in 71% yield.[7] Both the yield and the product ratio were decreased to 54% and 74 : 26, respectively, when *i*-PrI was used for alkylation. Importance of hydroxyl group was again demonstrated for the observed diastereoselectivity, because methylation of the methyl ether **10** afforded an approximately 1:1 mixture of **12**. Detailed studies on the mechanism and the extension of this alkylation to other substrates are currently under way in our laboratory.

References and Notes

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2. Fuji, K.; Node, M.; Tanaka, F. *Tetrahedron Lett.* **1990**, *31*, 6553.
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4. Alkylation of α,β-unsaturated esters has been reported to give α-alkylated products exclusively. See Kende, A. S.; Toder, B. H. *J. Org. Chem.* **1982**, *47*, 163 and references cited therein.
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7. Stereochemistries of the products were not determined

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