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DRAMATIC ENANTIOSELECTIVITY REVERSAL IN THE PROPARGYLATION OF ALDEHYDE WITH ALKYNYL LITHIUM CATALYZED BY DILITHIUM BINAPHTHOLATE DERIVATIVES

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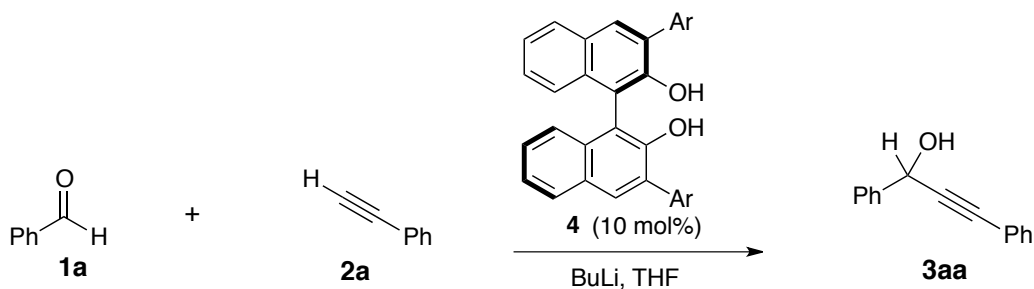
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Abstract – A slight structural modification of a chiral catalyst caused a dramatic reversal in the enantioselectivity of an aldehyde propargylation using alkynyllithium.


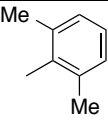
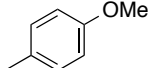
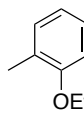
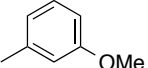
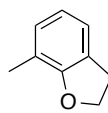
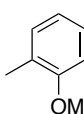
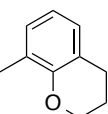
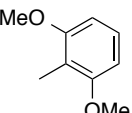
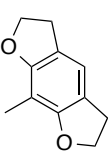
The enantioselective propargylation of carbonyl compounds is an important process for the preparation of optically active propargylic alcohols.¹ We previously reported an enantioselective propargylation of carbonyl compounds catalyzed by dilithium binaphtholate derivatives.^{2,3} In an effort to develop more effective propargylation methods, we designed and prepared binaphthol derivatives^{4,5} for use as catalyst precursors in this reaction. In this paper we report that only a slight structural modification of binaphthol dramatically reversed the enantioselectivity of the reaction.⁶

Using the reaction conditions reported previously,² we investigated the propargylation of benzaldehyde (**1a**) with phenylacetylene (**2a**) using various binaphthol derivatives as catalyst precursors. As demonstrated previously,² 3,3'-diphenylbinaphthol (**4a**) gave the corresponding propargylic alcohol in the *S*-configuration with a 75% ee (Table 1, entry 1). The introduction of methoxy groups at the *meta* or



Scheme 1. Enantioselective propargylation of aldehyde catalyzed by dilithium binaphtholate

Table 1. Enantioselective propargylation of **1a** with **2a** catalyzed by dilithium salt of binaphthol (**4**)^a

entry	BINOL, Ar	yield, %	ee, % (conf.)	entry	BINOL, Ar	yield, %	ee, % (conf.)
1	4a , 	97	75 (<i>S</i>)	6	4f , 	95	12 (<i>S</i>)
2	4b , 	91	70 (<i>S</i>)	7	4g , 	94	7 (<i>S</i>)
3	4c , 	90	50 (<i>S</i>)	8	4h , 	90	75 (<i>R</i>)
4	4d , 	99	70 (<i>R</i>)	9	4i , 	92	57 (<i>R</i>)
5	4e , 	95	73 (<i>R</i>)	10	4j , 	99	77 (<i>R</i>)

^a benzaldehyde:3,3'-biarylbinaphthol:phenylacetylene: BuLi=1.0:0.1:2.0:2.0

para positions of the phenyl group gave lower levels of the *S*-configuration (entries 2 and 3), whereas introduction of methoxy group at the *ortho* position gave the alcohol in *R*-configuration with a 70% ee (entry 4). We were surprised that only a slight structural modification of binaphthol dramatically reversed the sense of enantioselectivity of the reaction. Introduction of methoxy groups at the two *ortho* positions of the phenyl group gave better enantioselectivity (entry 5), but introduction of methyl groups on two *ortho* positions of the phenyl ring gave a very low selectivity (entry 6), suggesting that the coordination of a methoxy group to lithium plays an important role in enantio-differential step. The benzofuran derivative provided better result than methoxyphenyl derivative (entries 4 vs. 8). We therefore introduced two furan rings (benzodifuran) and found that it gave the highest enantioselectivity (entry 10).

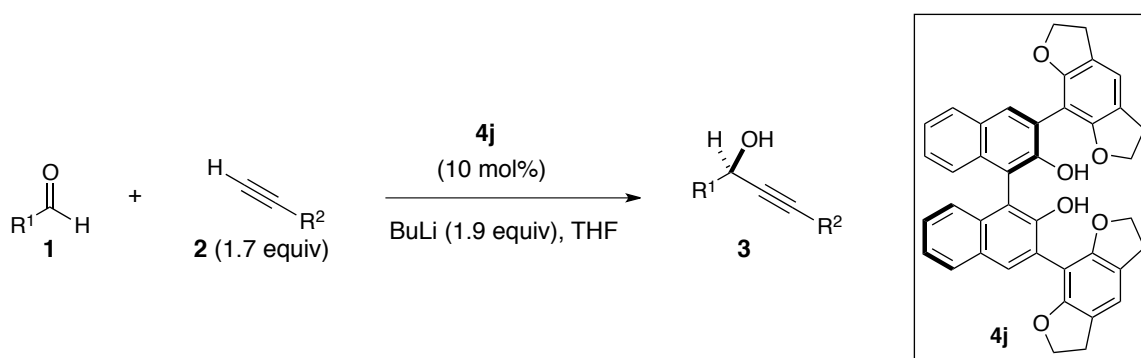
We found that small changes in the reagent equivalents significantly affected the enantioselectivity. We therefore optimized the equivalents.⁷ After considerable screening, we found 0.1 equivalents of **4j**, 1.7 equivalents of phenylacetylene, and 1.9 equivalents of BuLi gave the best result.

The results obtained from the enantioselective propargylation of benzaldehyde with various acetylenes are shown in Table 2.⁸ In each case reaction proceeded smoothly and the product with the same configuration was obtained. No acetylene reagents gave better results than phenylacetylene (entries 1-3).

We next investigated the propargylation of various aldehydes with phenylacetylene. Although hydrocinnamaldehyde (**1b**) and cinnamaldehyde (**1c**) gave low selectivities (entries 4 and 5), most of

benzaldehyde derivatives gave high selectivities with the identical enantioface differentiation. Benzaldehyde with chloro or dimethylamino group gave lower selectivity (entries 7 and 8), whereas 4-methoxybenzaldehyde (**1g**) and 3,4,5-trimethoxybenzaldehyde (**1h**) gave the products in 93% ee (entries 9 and 10), the highest enantioselectivity yet achieved in the propargylation of aldehyde using dilithium binaphtholate as a catalyst.

Table 2. Enantioselective propargylation catalyzed by dilithium salt of binaphthol **4j**⁹



entry	aldehyde, R ¹	acetylene, R ²	product	yield, %	ee, % (conf.)
1	1a , Ph	2a , Ph	3aa	99	87 (<i>R</i>)
2	1a , Ph	2b , <i>n</i> -C ₄ H ₈	3ab	99	66 (<i>R</i>)
3	1a , Ph	2c , PhCH ₂ OCH ₂	3ac	98	69 (<i>R</i>)
4	1b , PhCH ₂ CH ₂	2a , Ph	3ba	72	27 (<i>R</i>)
5	1c , PhCH=CH	2a , Ph	3ca	99	41 (<i>R</i>)
6	1d , 2-naphthyl	2a , Ph	3da	94	86 (<i>R</i>)
7	1e , 4-Cl-C ₆ H ₄	2a , Ph	3ea	94	63 (<i>R</i>)
8	1f , 4-Me ₂ N-C ₆ H ₄	2a , Ph	3fa	76	84 (<i>R</i>)
9	1g , 4-MeO-C ₆ H ₄	2a , Ph	3ga	97	93 (<i>R</i>)
10	1h , 3,4,5-(MeO) ₃ C ₆ H ₂	2a , Ph	3ha	97	93 (<i>R</i>)

Further studies toward the design of a much more sophisticated ligand structure and elucidation of the mechanism underlying the enantioselectivity are in progress in our laboratory.

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 - Catalyst precursors **4c** and **4g-4j** were prepared by Suzuki coupling between MOM-protected 3,3'-I₂BINOL and the corresponding borane derivative (Pd(PPh₃)₄, Na₂CO₃, aq. DME), followed by deprotection of MOM group (HCl, CH₂Cl₂, MeOH) according to the method in literatures.^{4a,4c}
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 - Selected data obtained from equivalent investigations are as follows, benzaldehyde:**4j**:phenylacetylene:BuLi=1.0:0.1:1.5:1.7; 93% yield, 68% ee, 1.0:0.1:1.8:2.0; 96% yield, 75% ee, 0.1:1.0:2.0:2.2; 98% yield, 73% ee.
 - The absolute configurations of the products were determined by HPLC data reported in reference 2b.
 - Under argon atmosphere, *n*-BuLi (1.6 M in hexane, 0.59 mL, 0.95 mmol) was added to a solution of **4j** (31 mg, 0.050 mmol) and phenylacetylene (**2a**) (0.10 mL, 0.85 mmol) in THF (1 mL) at -78 °C. To the mixture was added aldehyde **1h** (98 mg, 0.50 mmol) in THF (1 mL) over 10 min using syringe pump. The solution was stirred for an additional 20 min. The reaction was quenched with sat. aq. NH₄Cl and the mixture was extracted with AcOEt (3 × 10 mL). The organic layer was washed with brine. After drying over Na₂SO₄, the solvent was removed, and the residue was purified by silica gel column chromatography (hexane/CH₂Cl₂=1/1 SiO₂ 5 g), affording **3ha** (144 mg, 97% yield) as a colorless oil. The ee was determined by chiral HPLC (Chiralcel OD-H) to be 93% ee.