HETEROCYCLES, Vol. 97, No. 2, 2018, pp. 708 - 711. © 2018 The Japan Institute of Heterocyclic Chemistry
Received, 15th February, 2018, Accepted, 20th March, 2018, Published online, 29th March, 2018
DOI: 10.3987/COM-18-S(T)63

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

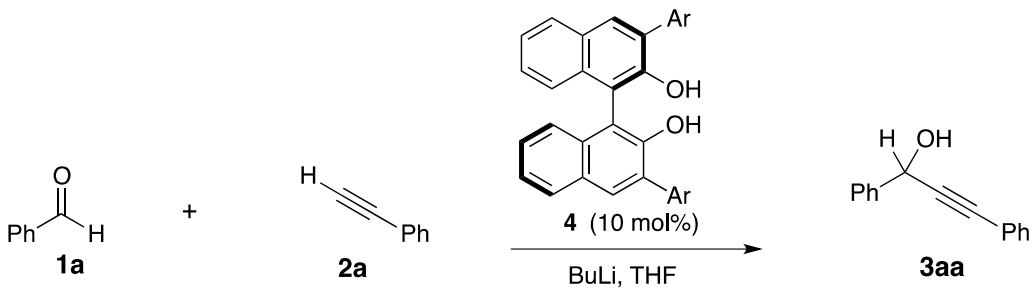
Makoto Nakajima,* Rika Watanabe, Kazuki Osakama, Midori Sakamoto, Daijiro Takemoto, and Kenji Kukita

Graduate School of Pharmaceutical Sciences, Kumamoto University, 5-1, Oe-honmachi, Chuo-ku, Kumamoto, 862-0973 Japan.
nakajima@gpo.kumamoto-u.ac.jp

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]

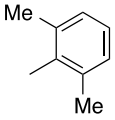
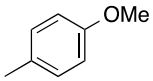
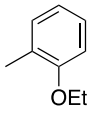
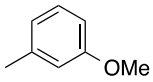
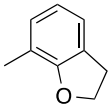
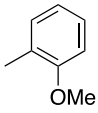
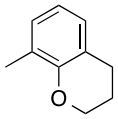
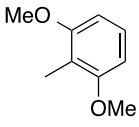
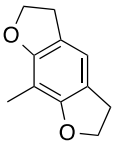
Using the reaction conditions reported previously,[2] we investigated the propargylation of benzaldehyde (**1a**) with phenylacetylene (**2a**) using various binaphthol derivatives as catalyst precursors. As demonstrated previously,[2] 3,3'-diphenylbinaphthol (**4a**) gave the corresponding propargylic 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

Dedicated with respect to Professor Kiyoshi Tomioka on the occasion of his 70th birthday

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 (*S*)	6	**4f**, 	95	12 (*S*)
2	**4b**, 	91	70 (*S*)	7	**4g**, 	94	7 (*S*)
3	**4c**, 	90	50 (*S*)	8	**4h**, 	90	75 (*R*)
4	**4d**, 	99	70 (*R*)	9	**4i**, 	92	57 (*R*)
5	**4e**, 	95	73 (*R*)	10	**4j**, 	99	77 (*R*)

[a] benzaldehde:3,3'-biarylnaphthol:phenylaectylene: 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).

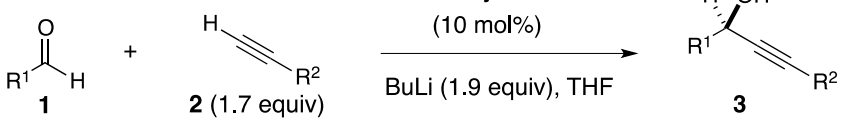
We found that small changes in the reagent equivalents significantly affected the enantioselectivity. We therefore optimized the equivalents.[7] After considerable screening, we found 0.1 equivalents of **4j**, 1.7 equivalents of phenylacetylene, and 1.9 equivalents of BuLi gave the best result.

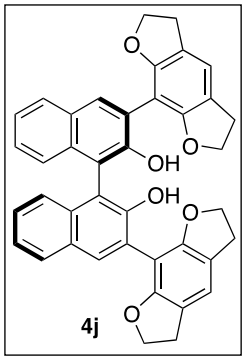
The results obtained from the enantioselective propargylation of benzaldehyde with various acetylenes shown in Table 2.[8] In each case reaction proceeded smoothly and the product with the same configuration was obtained. No acetylene reagents gave better results than phenylacetylene (entries 1-3).

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 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 (*R*)
2	**1a**, Ph	**2b**, *n*-C_4H_8	**3ab**	99	66 (*R*)
3	**1a**, Ph	**2c**, $PhCH_2OCH_2$	**3ac**	98	69 (*R*)
4	**1b**, $PhCH_2CH_2$	**2a**, Ph	**3ba**	72	27 (*R*)
5	**1c**, PhCH=CH	**2a**, Ph	**3ca**	99	41 (*R*)
6	**1d**, 2-naphthyl	**2a**, Ph	**3da**	94	86 (*R*)
7	**1e**, 4-Cl-C_6H_4	**2a**, Ph	**3ea**	94	63 (*R*)
8	**1f**, 4-Me_2N-C_6H_4	**2a**, Ph	**3fa**	76	84 (*R*)
9	**1g**, 4-MeO-C_6H_4	**2a**, Ph	**3ga**	97	93 (*R*)
10	**1h**, 3,4,5-$(MeO)_3C_6H_2$	**2a**, Ph	**3ha**	97	93 (*R*)

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.

ACKNOWLEDGEMENTS

This study was supported in part by grants from the Naito Foundation and the Ministry of Education, Culture, Sports, Science and Technology-Japan.

REFERENCES AND NOTES

1. (a) V. Bisai and V. K. Singh, *Tetrahedron Lett.*, 2016, **57**, 4771; (b) T. Ohshima, H. Morimoto, and

Morisaki, In *Comprehensive Chirality*, ed. by E. M. Carreira and H. Yamamoto, Elsevier: Oxford, U.K., 2012; Vol. 4, p 355; (c) P. G. Cozzi, R. Hilgraf, and N. Zimmermann, *Eur. J. Org. Chem.*, 4095; (d) B. M. Trost and A. H. Weiss, *Adv. Synth. Catal.*, 2009, **351**, 963.

2. (a) K. Tanaka, K. Kukita, T. Ichibakase, S. Kotani, and M. Nakajima, *Chem. Commun.*, 2011, **47**, 5614; (b) S. Kotani, K. Kukita, K. Tanaka, T. Ichibakase, and M. Nakajima, *J. Org. Chem.*, 2014, **79**, 4817.
3. Other binaphtholate catalysis developed recently in our laboratory: (a) T. Ichibakase and M. Nakajima, *Org. Lett.*, 2011, **13**, 1579; (b) K. Osakama and M. Nakajima, *Org. Lett.*, 2016, **18**, 236; (c) M. Sakamoto, T. Kaneko, Y. Orito, and M. Nakajima, *Synlett*, 2016, **27**, 2477; (d) S. Kotani, T. Asano, M. Moritani, and M. Nakajima, *Tetrahedron Lett.*, 2016, **57**, 4217.
4. Catalyst precursors **4a**, **4b**, and **4d-4f** were prepared by the method in literatures as follows: (a) T. R. Wu, L. Shen, and J. M. Chong, *Org. Lett.*, 2004, **6**, 2701; (b) K. Ishihara, H. Kurihara, M. Matsumoto, and H. Yamamoto, *J. Am. Chem. Soc.*, 1998, **120**, 6920; (c) X.-L. Liu, Z.-B. Yu, B.-W. Pan, L. Chen, T.-T. Feng, and Y. Zhou, *J. Heterocycl. Chem.*, 2015, **52**, 628; (d) K. B. Simonsen, K. V. Gothelf, and K. A. Jørgensen, *J. Org. Chem.*, 1998, **63**, 7536.
5. Catalyst precursors **4c** and **4g-4j** were prepared by Suzuki coupling between MOM-protected 3,3'-I_2BINOL and the corresponding borane derivative ($Pd(PPh_3)_4$, Na_2CO_3, aq. DME), followed by deprotection of MOM group (HCl, CH_2Cl_2, MeOH) according to the method in literatures.[4a,4c]
6. An example of dramatic enantioselectivity change upon a slight modification of ligand: K. Tomioka, M. Nakajima, and K. Koga, *Tetrahedron Lett.*, 1990, **31**, 1741.
7. 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.
8. The absolute configurations of the products were determined by HPLC data reported in reference 2b.
9. 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. NH_4Cl and the mixture was extracted with AcOEt (3 × 10 mL). The organic layer was washed with brine. After drying over Na_2SO_4, the solvent was removed, and the residue was purified by silica gel column chromatography (hexane/CH_2Cl_2=1/1 SiO_2 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.