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ASYMMETRIC ADDITION OF ARYLLITHIUMS TO NAPHTHALENE BHA-ESTERS CATALYZED BY A CHIRAL LIGAND

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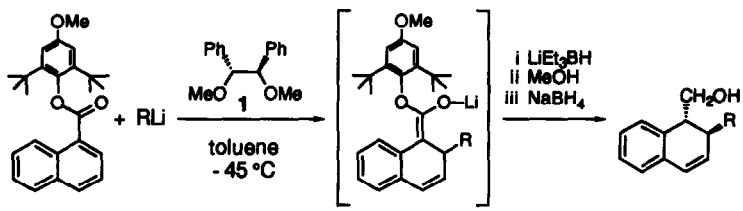
Summary: In the presence of both stoichiometric and catalytic amounts of a chiral dieter 1, aryllithiums reacted with BHA-esters of naphthalenecarboxylic acids 2, 5 to afford the corresponding adducts 4, 6 in high ee.

Enantioselective addition reaction is a rapidly developing area in synthetic chemistry.[1] Especially, a catalytic asymmetric conjugate addition reaction has been the recent focus.[2] We have previously described the asymmetric 1,4-addition of organolithiums to the cyclohexylimines derived from α,β-unsaturated or naphthalenecarbaldehydes by using a stoichiometric amount of a chiral ligand 1.[3] Attempted catalytic version of the reaction, however, was unsuccessful.

Based on the successful stoichiometric and catalytic asymmetric 1,2-addition reactions of organolithiums to imines derived from an arylamine,[4] we assumed that regeneration of active species, organolithium-ligand complex, would be rapid from lithium arylamide and sluggish from cyclohexylamide. Since a major difference is an acidity between arylamine ($pk_a \approx 27$) and cyclohexylamine ($pk_a \approx 35$), we then studied the reaction using an ester as a substrate. We now describe a catalytic asymmetric addition of aryllithiums to naphthalene 2,6-di-*tert*-butyl-4-methoxyphenyl (BHA)-esters **2**, **5** using the chiral diether mediator **1**.



2 **3** **4**

The stoichiometric asymmetric reaction of a BHA ester of 1-naphthalenecarboxylic acid **2** with phenyllithium in toluene provided, through a ketene-reduction one pot process,[5] the corresponding alcohol (1*R*,2*S*)-**4**[3] in 84% ee and 80% yield. The reaction with 1-naphthyllithium was much more selective to give **4**[6] in 91% ee and 82% yield. However, the reaction with butyllithium was not effective to give **4**[3] in 21% ee. Other reactions of a BHA ester of 2-naphthalenecarboxylic acid **5** with aryllithiums are also summarized in Table I (entries 1,3,5,7).

5 **6**

Table I. Enantioselective Conjugate Addition of Aryllithiums

entry	2,5	1 / RLi[a]	RLi	time / h	4,6	ee / %	yield / %
1	2	1.1	Ph	18	4	84	80
2	2	0.2	Ph	41	4	75	76
3[b]	2	1.1	1-Naph	4	4	91	82
4[b]	2	0.1	1-Naph	17	4	67	75
5	5	1.1	Ph	21	6	90	54
6	5	0.2	Ph	41	6	70	78
7	5	1.1	1-Naph	14	6	95	40
8	5	0.1	1-Naph	42	6	63	43

a) Equivalents of 1 to RLi. A 1.1~3.0 equivalent of RLi was used. PhLi was purchased from Aldrich, 1-NaphLi was prepared by treatment of 1-NaphBr with BuLi. b) A mixture of ether and toluene (1/3) was used.

As expected, a catalytic version was found to be successful. Thus, the reaction of 2 with phenyllithium in the presence of 20 mol% of 1 afforded 4 in 75% ee and 76% yield, indicating that a turnover of 1 exceeds 2 (entry 2). Other results are summarized in Table I (entries 2,4,6,8).

Typical reaction procedure is as follows (Table I, entry 2): To a solution of 2 (1 mmol) and 1 (0.3 mmol) in toluene 10 mL was added a solution of phenyllithium (0.74 mL, 1.3 mmol) in cyclohexane/ether (7/3). After stirring for 41 h at -45 °C, the mixture was successively treated with $LiEt_3BH$ in THF,[5] MeOH, and then $NaBH_4$ to give, after silica gel column chromatography (hexane/ether 4/1), 4 (R = Ph) in 75% ee and 76% yield. The absolute configuration and ee were determined by optical rotation and HPLC analysis using a chiral column.[3,6] The ligand 1 was recovered quantitatively.

The reaction of 2 with phenyllithium in toluene for 3 h at -45 °C in the absence of any ligand was sluggish to afford the addition product in 9% yield. Upon addition of 1 equivalent of DME, acceleration was dramatic to give, after 2 h, the product in 92% yield. These indicate that the ligand 1 accelerates the reaction to give the lithium enolate 3 probably complexed with 1. However, in the catalytic version, reactive species, RLi-1 complex, should be regenerated from the 3-1 complex through a ligand exchange.

The current focus of our studies is the chemistry of the catalyst turnover in the present catalytic asymmetric reaction.[7]

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