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INTRAMOLECULAR ASYMMETRIC TANDEM ADDITIONS TO CHIRAL NAPHTHYL OXAZOLINES

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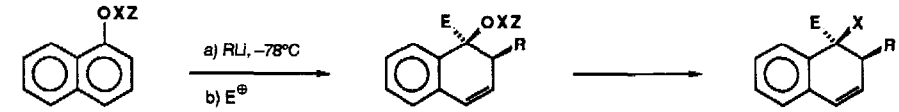
Summary: The addition of 1-lithio-4-chlorobutane to 1-naphthyl oxazoline leads to good yields of the annulated tricyclic systems **9** and **14** in greater than 96% ee.

Previous work from this laboratory demonstrated that oxazolines are excellent mediators of organolithium addition to the naphthalene nucleus. Thus, the use of the simple oxazoline **1**[1] or the chiral, nonracemic oxazoline **2**[2] allows a variety of lithium nucleophiles to furnish elaborated dihydronaphthalenes **3** and ultimately provide functionalized derivatives such as the acids **4**, aldehydes, **5** or the carbinols, **6**. We have also demonstrated this methodology by a recent asymmetric total synthesis of (-)-podophyllotoxin,[3] (+)-phyltetralin,[2c] and the AB-ring of aklavinone.[4] In the above sequence, **3** was formed almost exclusively as the *trans* addition

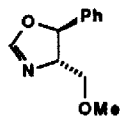


3

4, X = CO_2H
5, X = CHO
6, X = CH_2OH

1, OXZ =

2, OXZ* =

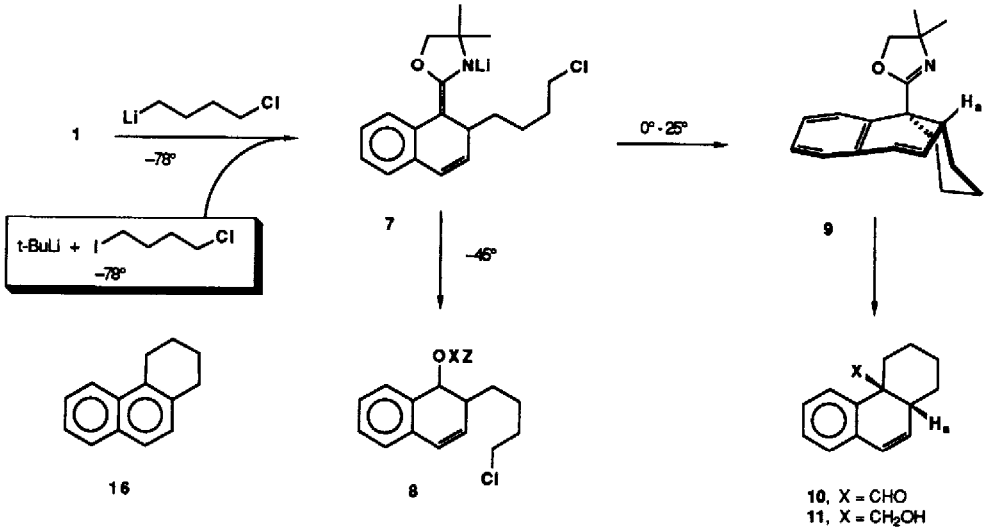


product (>98%) as the electrophile always preferred entry from the face *anti* to that occupied by the alkyl addition. In the chiral examples derived from **2**, the products were also those derived from *trans* addition and the only impurity was the diastereomer resulting from lack of facial selectivity.

We have now extended this tandem addition to an intramolecular variation and we found that the process appears to be equally efficient and affords a stereoselective annulation of the dihydronaphthalene nucleus.

The first experiments that were performed involved the simple, achiral naphthyl oxazoline **1** prepared as described earlier.[1] It was our intention to introduce a bifunctional moiety such as a haloalkyl lithium species although these were known to readily form cyclic alkanes from the studies of Bailey.[5]

However, since it was necessary to avoid cycloalkane formation, studies were carried out to optimize the chloroalkyl lithium intermediate. When an ether-pentane solution (2:3) was made 0.1M in 1-chloro-4-iodobutane and cooled to -78°C and treated dropwise with 2.12 eq of *t*-butyl lithium (2.3M, pentane), the desired 1-chloro-4-lithiobutane was obtained. Addition of the latter (cannula) to a solution of 0.66 eq naphthalene **1** in THF(-78°C) was followed by slow warming to -45°C. After stirring for 3 h and warming to room temperature overnight, the reaction mixture was quenched (NH_4Cl), extracted (CH_2Cl_2), and dried to afford, after chromatography (Silica, Hex-EtOAC, 9:1) an 84% yield of the annulated product **9**.[6] When the reaction was quenched at -45°C, the chloroalkyl adduct **8** was isolated indicating that although the addition to the naphthalene nucleus had occurred, cyclization required higher temperatures (ca 0° C). The stereochemical outcome of this process, e.g. *cis* or *trans* ring fusion, could not be assessed on the oxazoline **9** but was readily determined when the oxazoline was removed[1] furnishing the aldehyde **10** (82%) or the alcohol **11**[7] ($NaBH_4$,80%). The latter two derivatives showed distinct NOE between H_a and the formyl proton (3.1%) in **10** and Ha and the carbinol protons in



11 (4.2%,1.1%). This confirms that the cyclization of the intermediate azaenolate **7** proceeds from the same face as the carbanionic lithio portion and is contrary to that observed in the intermolecular process, leading to **3**. It is noteworthy that the formyl derivative **10** on standing, loses CO and readily aromatizes to the naphthalene, **16**.

We next addressed the chiral nonracemic analog (+)-**2** and subjected it to the same conditions as above using 1-chloro-4-iodobutane and *tert*-butyllithium. After workup, the annulated product **13** was obtained in 75% yield and from the nmr spectrum appeared to be mainly a single diastereoisomer. To assess the stereochemical selectivity it was necessary to remove the chiral oxazoline moiety.[3] This was accomplished using Na_2SO_4-CF_3COOH -Ac_2O-Pyr to give the ester **14** (oil, $[\alpha]_D$ +94)[6] in 76% yield which was subsequently treated with lithium aluminum hydride affording the carbinol **15** in 86% yield.[7] The enantiomeric excess of the carbinol was determined as 96% using 10%Eu(hfc)$_3$ in C_6D_6 (Fig. 1) on both the racemic and the enantiomerically enriched version. The stereochemical assignment of this material was also found to be *cis* at the ring fusion *via* NOE while the absolute configuration of **15** may be assumed to be as drawn (R,R). This is based on the absolute configuration of a number of earlier examples which were known[2c] to arise from attack of the organolithium onto the β-face of the naphthalene.

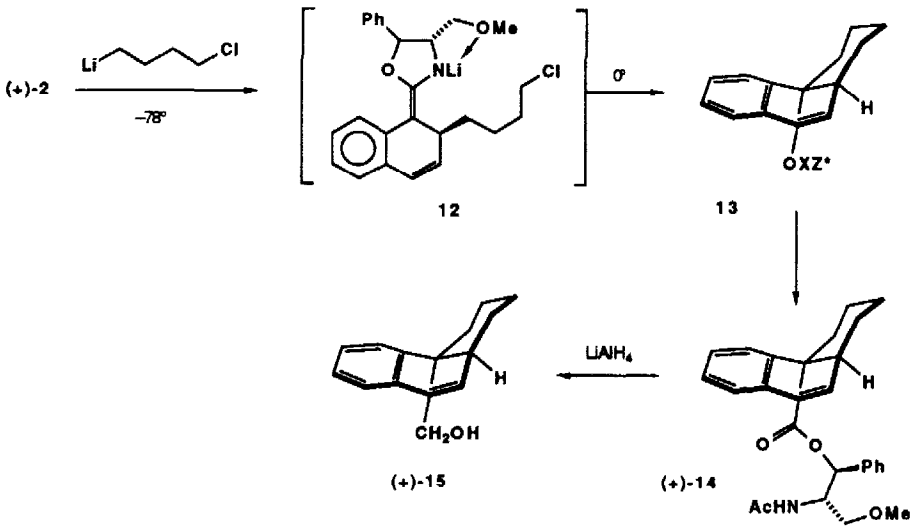
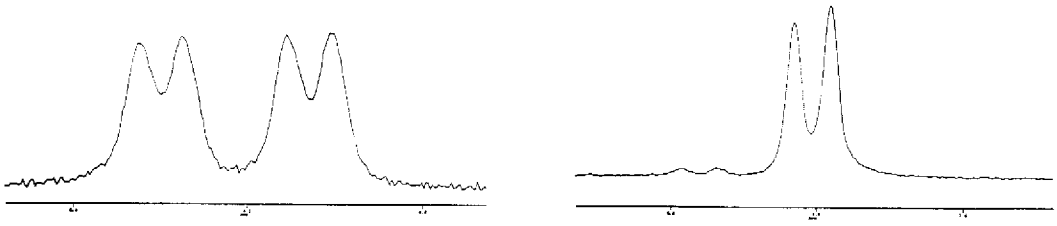


Figure 1. Enantiomeric Determination of Carbinols **11** and **15** in C_6D_6.



Eu(hfc)$_3$ + **11**

Eu(hfc)$_3$ + **15**

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(6) All products were totally consistent with IR, ^{1}H-NMR, CMR spectroscopic data.

(7) Physical data for (±)-**11** and (+)-**15**.

(±)-11: ^{1}H-NMR ($CDCl_3$) δ 7.34-7.15 (m, 3 H), 7.10-7.04 (m, 1 H), 6.36 (d, 1 H, J = 9.5 Hz), 5.95 (dd, 1 H, J = 9.5, 6.2 H), 3.56 (d, 1 H, J = 10.6 Hz), 3.37 (d, 1 H, J = 10.6 Hz), 2.49 (m, 1 H), 2.19 (ddd, 1 H, J = 11.7, 6.2, 3.6 Hz), 1.70-0.89 (m, 8 H), mp 106-107.5°C.

(+)-15: ^{1}H NMR identical to above, mp 140-141.5°C: $[\alpha]_D^{25}$ +267.7° (c, 0.99, EtOH).

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