ENANTIOSELECTIVE ADDITION OF THIAZOLYLLITHIUM TO ALDIMINES WITH THE AID OF CHIRAL LIGAND. ASYMMETRIC SYNTHESIS OF (*S*)-DOE, A COMPONENT OF MARINE NATURAL PRODUCT, DOLASTATIN 10[1]

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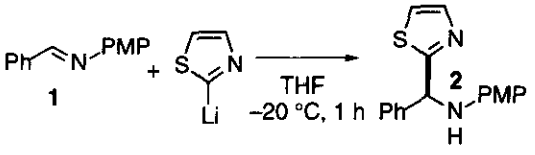
Abstract - The external chiral ligand mediated asymmetric reaction of thiazolyllithium with aldimines was examined. The amino ether (**5**) gave rise to relatively high selectivity in the reaction of phenylimine, and sparteine (**6**) provided high selectivity in the reaction of imines bearing an α-methylene group. The reaction was applied to the synthesis of (*S*)-Doe, a component of antileukemic marine natural product, dolastatin 10.

We have been engaged in the development of external chiral ligand mediated asymmetric reaction of organometallic carbonucleophiles such as organolithiums,[2] lithium ester enolates,[3] and Grignard reagents.[4] Highly enantioselective, stoichiometric and catalytic reactions of organolithiums with eneimines, imines, and enoates, giving the corresponding 1,4- and 1,2-addition products, have been developed.[5,6] Our strategy relies on activation and subsequent control of stereochemistry of organometallic species by the formation of a ligand-organometallics complex. Since heteroatoms in heterocyclic carbonucleophiles are of coordinating ability with metal of organometallic species, it is interesting to examine the reactions of lithiated heterocyclic carbonucleophiles with imines. We describe herein the asymmetric reactions of thiazolyllithium with imines and the synthetic application to (*S*)-Doe, a component of antileukemic marine natural product, dolastatin 10.[7]

Table 1. Yield Dependence on Workup Conditions

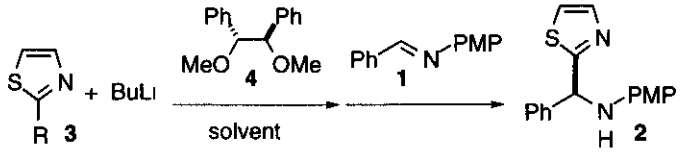


quench	yield %	recovered **1** %
brine	59	24
TMSCl	74	16
1M $KHSO_4$	92	trace

The reaction of thiazolyllithium, generated from 2-bromothiazole and butyllithium in THF, with benzaldehyde 4-anisidine imine (**1**: PMP=4-MeOPh) in

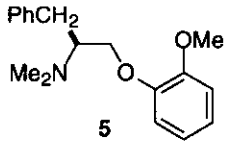
THF at –20 °C for 1 h gave the corresponding racemic amine (**2**) in 59% yield and **1** in 24% recovery yield when the reaction was quenched with brine (Table 1).[8] However, TLC monitoring indicated the reaction completed after 1 h at –20 °C. Sensitivity of **2** toward basic conditions was confirmed by observing retro-reaction to the starting **1** and thiazole by treating **2** with aqueous NaOH. The quench with TMSCl improved yield to 74%, but still recovered **1** in 16%. Finally we found that quench with aqueous $KHSO_4$ provided **2** in 92% without recovery of **1**.

Table 2. Yield Dependence on Thiazolyllithium Generation Method



		lithiation		addition			
solvent	R	temp °C	time h	temp °C	time h	yield %	ee %
Et_2O	H	–40	1	–40	1	82	28
Et_2O	Br	–40	2	–20	1.5	53	30
toluene	H	–40	1	–40	1	86	20
toluene	Br	–78	2	–78	0.5	71	24

We examined a couple of methods to generate thiazolyllithium through bromine-lithium exchange of 2-bromothiazole (**3**) (R=Br) in which butyl bromide is produced,[9] and direct lithiation from thiazole (**3**) (R=H).[10] Treatment of 2 eq of **3** (R=Br) with 2 eq of butyllithium in the presence of 2.6 eq of the ligand (**4**) in ether at –40 °C for 2 h and following addition of **1** afforded **2** in 53% yield and 30% ee, after –20 °C for 1.5 h (Table 2).[11] In a toluene solvent, the same sequential treatment afforded **2** in 71% yield and 24% ee. On the other hand, direct lithiation of **3** (R=H) with butyl–lithium gave **2** in the improved yields of 82 and 86% in ether and toluene, respectively. The ees of **2** were nearly the same, 28 and 20%, respectively. Thiazolyllithium prepared through direct lithiation is superior to that of bromine-lithium exchange with respect to a chemical yield. Since **5** has been shown to be a more satisfactory ligand,[5] then we examined the reaction of thiazolyllithium prepared through direct lithiation by using other ligands (**5**) and (**6**).



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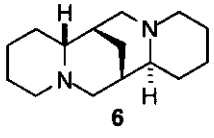


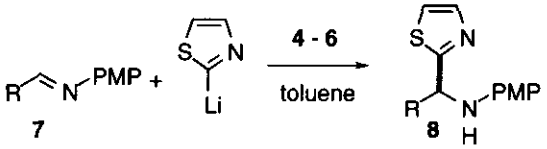
6

A chiral natural diamine, sparteine (**6**),[4] showed a very poor enantioselectivity to afford **8** (R=Ph) in only 9% ee and 82% yield. Fortunately, the amino ether ligand (**5**) exhibited an improved mediation to afford **8** (R=Ph) in 56% ee and 95% yield in toluene at –78 °C for 3 h. As shown in Table 3, the enantioselectivity is highly dependent on the imine and ligand structures. For example, **4** gave relatively poor ees regardless to the imine structures. The ligand (**5**) is a better ligand than **4** for phenylimine. Sparteine (**6**) is a good ligand for **7** bearing an α-CH_2 group, giving **8** (R=$PhCH_2$, $Ph(CH_2)_2$) in 85 and 81% ees from benzyl and phenylethylimines (**7**).

The ligand (**4**) mediated the reaction of thiazolyllithium with *t*-butylimine and gave **8** (R=Ph) in 26% ee, whereas the reaction of phenyllithium gave the amine in 87% ee.[5] These differences in enantioselection

may come from the nature of heterocyclic nucleophile. Since the lithiated heterocycles have a heteroatom available for coordination to the lithium cation, competitive coordination to the lithium cation may occur and leads to poor stereoselectivity. The ligands (**5** and **6**) involve the nitrogen atom with higher coordinating ability to the lithium cation than oxygen, and subsequently works as a better ligand than **4**.

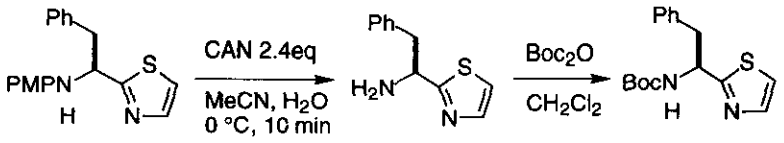
Table 3. Asymmetric Addition of Thiazolyllithium to Imines



	4		5		6	
R	yield %	ee %	yield %	ee %	yield %	ee %
Ph	86	20	95	56	82	9
$PhCH_2$	21	30	19	25	19	81
$Ph(CH_2)_2$	71	32	98	35	80	85
t-Bu	88	26			14	30

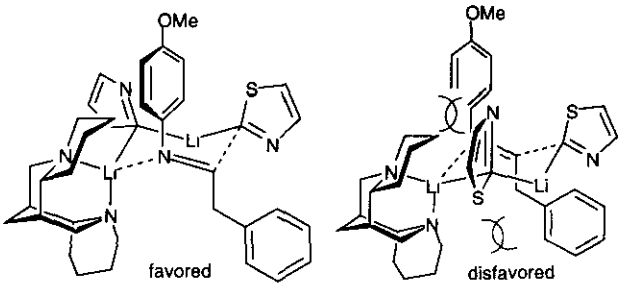
The process is applied to an asymmetric synthesis of (*S*)-Doe, a component of antileukemic marine natural product, dolastatin 10.[12] Treatment of phenylacetaldehyde with 4-anisidine in the presence of molecular sieves 4A in benzene at 0 °C for 15 min provided labile benzylimine (**7**) (R=$PhCH_2$) in quantative yield. The asymmetric reaction of the imine with thiazolyllithium in the presence of **6** provided **8** (R=$PhCH_2$) in 81% ee and 19% yield (Table 3). Deprotonation of the imine by thiazolyllithium is attributable to the poor yield.

The amine of 81% ee ((+)-**8** (R=$PhCH_2$)) was treated with CAN to (*S*)-Doe which was then treated with Boc_2O to give (+)-(*S*)-Boc-Doe of 82% optical purity in 25% overall yield without any racemization.[10]



(+)-**8** (R=$PhCH_2$) (*S*)-Doe (+)-(*S*)-Boc-Doe

The stereochemistry in the addition of thiazolyllithium complexed with sparteine (**6**) is predictable based on the model shown. The model in the right is endowed with severe steric repulsion between sparteine and imine moieties, hence this is disfavored. On the other hand, the model shown left is reasonably free from such steric repulsion, and predicts the formation of (*S*)-amine having the absolute configuration observed.[13]



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