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Enantioselective Addition of Grignard Reagents to a 2-Thiazolyl Nitrone

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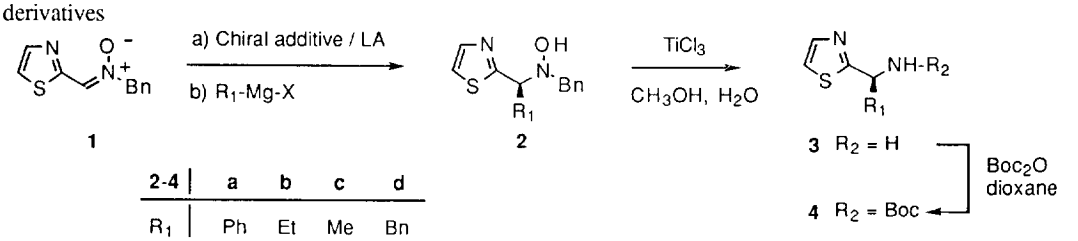
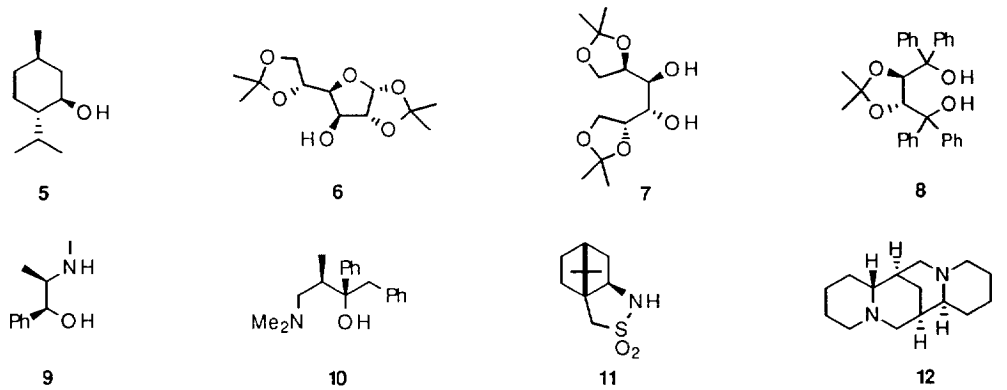
Abstract: The addition of organomagnesium compounds to the *N*-benzyl 2-thiazolyl nitrone **1** in the presence of various chiral additives and Lewis acids leads to hydroxylamines **2** in moderate to good enantiomeric excess (up to 74%); the reductive dehydroxylation of these compounds affords enantioenriched α-amino 2-alkylthiazoles **3** in good yields (76-66%) Copyright © 1996 Elsevier Science Ltd

The enantioselective addition of organometallic reagents, mainly Grignard reagents and organozinc compounds, to aldehydes and ketones promoted by various chiral catalysts has received considerable attention over the years and is now a well-established method for the synthesis of enantiopure or enantioenriched alcohols.[1] The same reactions with the nitrogen derivatives of carbonyls to give amines have been mainly applied to imines or iminium salts.[1a,2] Nevertheless, the addition of organometallic reagents to nitrones as iminium derivatives of aldehydes is attracting an increasing interest in synthetic methodologies of nitrogen containing compounds. For example, diastereoselective additions to chiral cyclic nitrones[3] and to nitrones bearing a chiral group either at the nitrogen[4] or at the carbon atom,[5] have been described in recent years. On the other hand, to the best of our knowledge, there is only one report concerning the enantioselective addition of alkyl magnesium halides and dialky zinc compounds to an achiral cylic nitrone, i.e. 3,4-dihydroisoquinoline N-oxide, in the presence of external catalysts.[6] In this report we wish to present our results on the enantioselective alkylation of the readily available *N*-benzyl-α-(2-thiazolyl)nitrone[7] **1** by Grignard reagents and its implementation for the synthesis of chiral α-amino-2-alkylthiazoles **3**. The occurrence of these compounds as molecular fragments in some natural products[8] and their potential use as precursors to α-aminoaldehydes through the thiazole to formyl conversion,[9] concur to the importance of the synthesis of this class of thiazole derivatives



The model addition reaction of phenylmagnesium bromide to the nitrone **1** was generated in THF at -80 °C in the presence of the various chiral ligands **5-12** (Fig. 1) and $ZnBr_2$ as a Lewis acid (LA). In all cases the resulting *N*-benzyl hydroxylamine **2a** which formed in variable yields (Table 1) was conveniently converted into the amine **3a** (76% yield) by reduction and debenzylation with aqueous titanium(III) chloride.[5a] The enantiomeric excess and the absolute configuration of this compound (see below) were assumed also for its percursor **2a**. Reactions carried out in the presence of $ZnBr_2$ invariably showed some increasing of the enantioselectivity which however remained in most of the cases at moderate values (Table 1). The use of other Lewis acids ($MgBr_2$, Et_2AlCl, $EtAlCl_2$, $TiCl_4$) proved to be less effective than $ZnBr_2$. Hence, the highest ee value (74%) was obtained with the use of 0.5 equivalents of $ZnBr_2$ and D-glucose diacetonide **6** (entry 18).[10] The effect of the LA can be rationalized by assuming the formation of [nitrone-LA-chiral additive] aggregates which react with the organometallic reagents. Some evidence for the presence of aggregates were provided by NMR and Mass spectroscopy.[11] The conditions in entry 18 were applied to the reactions of **1** with other Grignard reagents (entries 21, 23, and 24) to give also in these cases the corresponding hydroxylamines **2b-d** in good yields but modest ee values. The conversion of these compounds into the amines **3b-d** (yields: 74% **3b**, 70% **3c**, 66% **3d**) was equally carried out by the $TiCl_3$ based procedure.[5a]



5 6 7 8 9 10 11 12

Figure 1: Chiral additives used in the asymmetric alkylation of the nitrone **1**

The enantioselectivities of these alkylation reactions were determined on the (*R*)-α-methoxy-α-trifluoromethylphenylacetic amides (MTPA) derived from the amines **3**. The ratio of diastereoisomer MTPA amides was determined by integration of the corresponding peaks in the ^{19}F-NMR spectra.[12] The same type of analysis could not be applied to the MTPA esters derived from hydroxylamines **2** since their ^{19}F-NMR spectra did not show any signal splitting.

The absolute configuration of the major enantiomer hydroxylamine **2** obtained in the alkylation reaction, was tentatively assigned by the CD spectra of *N*-tert-butoxycarbonyl (N-Boc) derivatives **4** of amines **3**. Recently, we have reported that the sign of the Cotton effect (CE) in the range 217-230 nm in the CD spectra of *N*-protected α-amino-2-alkylthiazoles correlates with the absolute configuration at the α-carbon to the thiazole ring[13] Compounds with *R* configuration showed a positive CE, while those with *S* configuration exhibited a negative CE. Hence, since all the scalemic compounds **4** showed a negative CE, the *S*-configuration was provisionally assigned. Consistent with this assignment is the sign of the optical rotation of **4d**, $[\alpha]_D$ = - 16.7

(c 0.2, $CHCl_3$) matching the negative value reported for the *N*-Boc derivative of the natural product (*S*)-Dolaphenin,$[\alpha]_D$ = - 25.5 (c 0.6, $CHCl_3$).[14]

Table 1. Asymmetric alkylation of nitrone **1**[a]

Entry	R_1	Chiral Additive	eq. $ZnBr_2$	Product[b]	Yield[c] (%)	ee[d] (%)
1	Ph	**5**	---	**2a**	80	15
2	Ph	**5**	1.0	**2a**	74	33
3	Ph	**6**	---	**2a**	93	17
4	Ph	**6**	1.0	**2a**	75	68
5	Ph	**7**	---	**2a**	83	8
6	Ph	**7**	1.0	**2a**	74	11
7	Ph	**8**	---	**2a**	41	12
8	Ph	**8**	1.0	**2a**	40	37
9	Ph	**9**	---	**2a**	77	11
10	Ph	**9**	1.0	**2a**	67	35
11	Ph	**10**	---	**2a**	69	11
12	Ph	**10**	1.0	**2a**	73	12
13	Ph	**11**	---	**2a**	76	22
14	Ph	**11**	1.0	**2a**	68	49
15	Ph	**12**	---	**2a**	79	31
16	Ph	**12**	1.0	**2a**	69	45
17	Ph	**6**[e]	0.7	**2a**	74	71
18	Ph	**6**[f]	0.5	**2a**	71	74
19	Ph	**6**[g]	0.2	**2a**	73	57
20	Et	**6**	---	**2b**	78	13
21	Et	**6**[f]	0.5	**2b**	73	46
22	Et	**10**	---	**2b**	72	9
23	Me	**6**[f]	0.5	**2c**	77	41
24	Bn	**6**[f]	0.5	**2d**	69	67

a) Reactions were carried out by adding the Lewis acid to the mixture of **1** and chiral catalyst in THF at room temperature, then cooling to -80 °C and treating under stirring with 3 eq. of Grignard reagent; stirring at -80 °C was continued for an additional 1 h. b) All compounds showed consistent ^1H and ^{13}C-NMR spectra. c) Isolated yield. d) Determined in the ^{19}F-NMR spectra of the MTPA derivatives of compounds **3**. e) 0.7 eq. . f) 0.5 eq. . g) 0.2 eq.

The above synthesis of α-amino-2-alkylthiazoles via enantioselective nucleophilic addition to an imminium equivalent should be complementary to that involving the electrophilic substitution on α-aminocarbanions.[15] Studies directed to improving the enantioselectivity of both methods by the use of more efficient chiral auxiliaries and additives as well as Lewis acids are currently in progress in our laboratories.

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