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High stereocontrol in the allylation of chiral non-racemic α-alkoxy and α-amino nitrones

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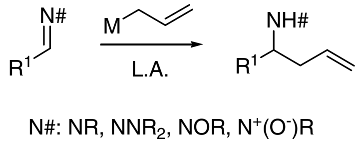
Dedicated to the memory of Professor Marcial Moreno-Mañas

Abstract—The stereocontrolled addition of allylic metals to chiral non-racemic nitrones promoted by the addition of Lewis acids is described. Whereas for α-alkoxy nitrones the stereocontrol depends on the Lewis acid used as an activator, for α-amino nitrones the diastereofacial course of the reaction depends on the protection of the α-amino group. The successful implementation of the methodology is represented by the enantiodivergent synthesis of D- and L-allylglycine.

The reaction of allylic organometallics with imines and related compounds is a useful method for preparing synthetically important nitrogen-containing compounds.[1,2] Despite numerous studies of imine additions,[3] the most significant ones reported by Yamamoto and co-workers,[4] other substrates such as oximes, nitrones or hydrazones have not received much attention.[2] The use of a nitrone as the electrophile in the allylation reaction is an attractive approach because (i) the product of the reaction, a hydroxylamine, contains a nitrogen in an intermediate oxidation state, (ii) the presence of the nitrone oxygen atom can facilitate the use of Lewis acids to modulate both reactivity and selectivity and (iii) if necessary, it is easy to transform the hydroxyamino group into the corresponding homoallylamine by reductive methods (Scheme 1).



N#: NR, NNR_2, NOR, $N^+(O^-)R$

Scheme 1.

In the course of our research, we need to prepare highly functionalized homoallylic hydroxylamines in an enantiomerically pure form. The trimethylsilyltriflate catalyzed addition of allylsilane to nitrones was first described by Wuts and Jung.[5] This reaction as well as the addition of allylmagnesium chloride have successfully been applied by Trombini et al.[6] towards the synthesis of 3,5-substituted isoxazolines. However, with chiral non-racemic α-alkoxy nitrones derived from sugars, such as *N*-benzyl-D-glyceraldehyde nitrone **1a** the reaction took place only with moderate selectivity.[7] In spite of a further report in which the use of Lewis acids enhanced the reactivity of the nitrones,[8] a synthetically viable acyclic stereocontrol of allylation of α-alkoxy nitrones has not yet been reported. In our continuing efforts to develop stereocontrolled additions to nitrones, we have found that the addition of several nucleophiles to α-alkoxy and α-amino nitrones can be stereodirected by the use of appropriate substrates and additives.[9] Prompted by these results and the desirable synthetic properties of homoallyl hydroxylamines, herein we report our exploration on the addition of several allylic organometals to α-alkoxy and α-amino nitrones **1a–f**. These nitrones were readily prepared from the corresponding aldehyde and *N*-benzylhydroxylamine.[10] All these compounds are stable solid products that can be stored for long time.

The allylation of nitrone **1a** was investigated first (Scheme 2). We exhaustively examined the dependence

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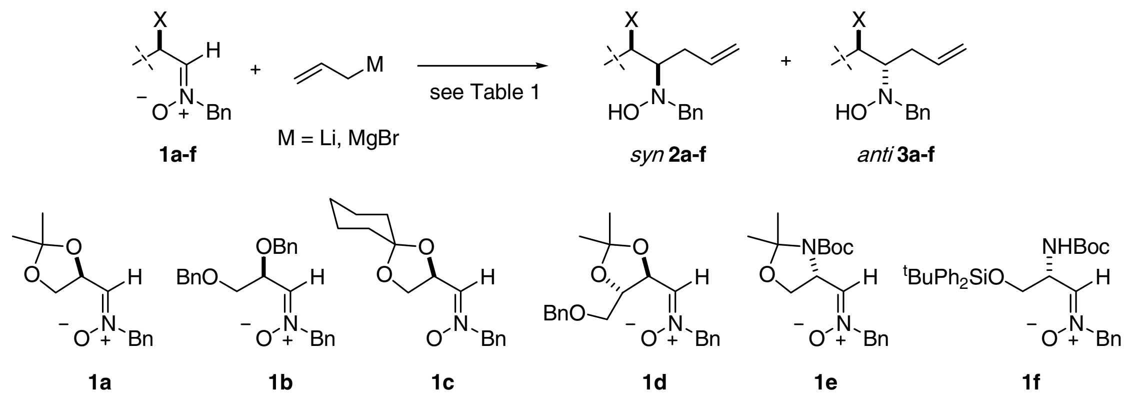


Scheme 2. Allylation of nitrones **1a**–**f** (enantiomers are shown for **2e**–**f** and **3e**–**f**).

Table 1. Allylation of nitrones **1** produced via Scheme 1

Entry	Nitrone	M[a]	Additive[b]	Solvent	*T* (°C)	Time (h)	*syn*:*anti*	Yield[c] (%)
1	**1a**	Li	None	THF	−80	1	55:45	86
3	**1a**	Li	TMEDA	Et_2O	−80	1	71:29	90
4	**1a**	Li	$ZnBr_2$	Et_2O	−80	1	90:10	75
5	**1a**	Li	$TiCl_4$	Et_2O	−80	1	37:63	43
6	**1a**	Li	Et_2AlCl	Et_2O	−80	1	52:48	64
7	**1a**	Li	$BF_3{\cdot}Et_2O$	Et_2O	−80	1	44:56	69
8	**1a**	Li	TMSOTf	Et_2O	−80	1	81:19	50
9	**1a**	$SnBu_3$	$BF_3{\cdot}Et_2O$	CH_2Cl_2	25	72	>5:95	90
10	**1a**	$SnBu_3$	TMSOTf	CH_2Cl_2	25	72	31:69	92
11	**1a**	MgBr	None	THF	0	2	53:47	100
12	**1a**	MgBr	None	Et_2O	−50	8	76:24	100
13	**1a**	MgBr	$ZnBr_2$	Et_2O	0	2	88:12	100
14	**1a**	MgBr	$ZnBr_2$	Et_2O	−50	8	>96:4	100
15	**1a**	MgBr	$TiCl_4$	Et_2O	0	3	17:83	43
16	**1a**	MgBr	$Ti(^iPrO)_2Cl_2$	Et_2O	−50	8	45:55	78
17	**1a**	MgBr	$Ti(^iPrO)_4$	Et_2O	−50	8	55:45	80
18	**1a**	MgBr	Et_2AlCl	Et_2O	0	3	32:68	86
19	**1a**	MgBr	Et_2AlCl	Et_2O	−50	8	35:65	90
20	**1a**	MgBr	$BF_3{\cdot}Et_2O$	Et_2O	0	3	30:70	35
21	**1a**	MgBr	$BF_3{\cdot}Et_2O$	THF	0	3	17:83	40
22	**1a**	MgBr	$BF_3{\cdot}Et_2O$	THF	−50	10	5:95	90
23	**1a**	MgBr	TMSOTf	Et_2O	0	2	45:55	70
24	**1b**	Li	None	THF	−80	1	60:40	90
25	**1b**	Li	$ZnBr_2$	Et_2O	−80	1	61:39	80
26	**1b**	Li	Et_2AlCl	Et_2O	−80	1	37:63	86
27	**1b**	MgBr	None	Et_2O	0	2	62:38	100
28	**1b**	MgBr	$ZnBr_2$	Et_2O	−50	8	69:31	90
29	**1b**	MgBr	Et_2AlCl	Et_2O	0	2	48:52	90
30	**1b**	MgBr	$BF_3{\cdot}OEt_2$	THF	−50	8	29:71	90
31	**1c**	Li	None	Et_2O	−80	1	72:28	86
32	**1c**	Li	$ZnBr_2$	Et_2O	−80	1	76:24	87
33	**1c**	Li	Et_2AlCl	Et_2O	−80	1	64:36	80
34	**1c**	MgBr	None	Et_2O	0	2	74:26	78
35	**1c**	MgBr	$ZnBr_2$	Et_2O	−50	8	91:9	93
36	**1c**	MgBr	$BF_3{\cdot}OEt_2$	THF	−50	8	8:92	85
37	**1d**	MgBr	None	THF	0	2	38:62	100
38	**1d**	MgBr	$ZnBr_2$	Et_2O	−50	4	92:8	100
39	**1d**	MgBr	$BF_3{\cdot}OEt_2$	THF	0	2	10:90	100
40	**1e**	Li	None	Et_2O	−80	1	>95:5	89
41	**1e**	MgBr	None	Et_2O	0	2	>95:5	100
42	**1e**	MgBr	$ZnBr_2$	Et_2O	−50	8	>95:5	94
43	**1e**	MgBr	$BF_3{\cdot}OEt_2$	THF	−50	8	>95:5	92
44	**1f**	Li (3.0)	None	Et_2O	−80	1	20:80	75
45	**1f**	MgBr (3.0)	None	Et_2O	0	2	10:90	81

[a] An excess of 2.0 equiv was used.
[b] 1.0 equiv was used in all cases.
[c] Isolated yield after purification of the mixture of adducts.

of both the diastereoselectivity and the yield of the reaction, on the temperature, solvent, allylic reagent and Lewis acid.[11] The results are collected in Table 1.

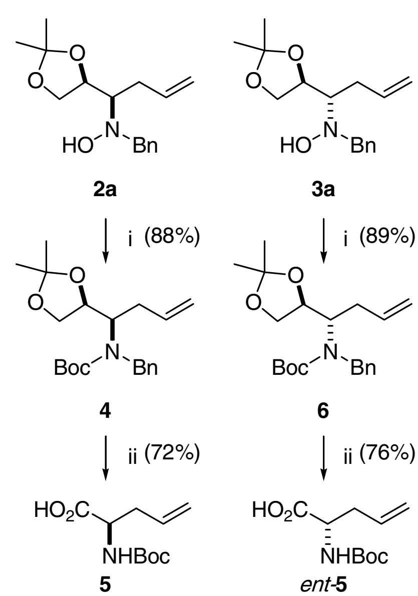
With allyllithium (prepared from allyltriphenyltin and phenyllithium[12]) mixtures of *syn* and *anti* compounds were formed (entries 1–8). Only when $ZnBr_2$ was used as an additive the *syn* hydroxylamine was obtained preferentially. On the other hand, by changing the Lewis acids only a slight reversal of selectivity could be obtained. When using allyltributyltin, the reaction only worked if activated with $BF_3{\cdot}OEt_2$ and trimethylsilyltriflate (entries 9 and 10) and needed 3 days to go on completion. In both cases, the *anti* adduct was obtained preferentially, the best results being observed with the former; in that case the *anti* isomer was obtained as the only product of the reaction in an excellent chemical yield. For the reactions with commercially available allylmagnesium bromide the diastereomeric ratio of the products **2a**–**3a** depended more strongly on the reaction conditions (entries 11–23). Thus, in the absence of any additive (entries 11 and 12), the reaction proceeded smoothly to give mixtures of adducts in which the *syn* isomer was the major component. The addition of zinc(II) bromide as a promoter of the reaction notably increased the amount of the *syn* isomer and at low temperature (entry 14) an almost total *syn* selectivity was obtained in quantitative yield after 8 h. The question as to whether a reversal of the stereochemistry could be achieved, as in other nucleophilic additions developed in our laboratory,[9] was examined by using titanium, boron and aluminium derived Lewis acids. With titanium additives (entries 15–17) only moderate *anti* selectivities were obtained. In the case of titanium(IV) chloride, which afforded the best result the chemical yield dropped to 45%, probably due to the competitive acetonide hydrolysis promoted by the Lewis acid. Similar results were obtained with diethyl aluminium chloride (entries 18 and 19), which afforded moderate values of *anti* selectivity even at low temperature. On the other hand, by using boron trifluoride etherate as an additive (entries 20–22) a complete reversal of the diastereofacial selectivity was observed, and at −50 °C in THF as a solvent, an excellent ds value was obtained. The low chemical yield observed at 0 °C might be due to the acetonide hydrolysis. The use of a TMSOTF as a promoter (entry 23) did not improve these results. Thus it seems that the diastereofacial selectivity observed strongly depends not only on the Lewis acid but also on the allylic organometallic reagent. To evaluate the influence of the protecting groups in the substrate we took our best systems and applied them to acyclic nitrone **1b** (entries 24–30). In this case, although a trend in stereocontrol is observed, the results are rather moderate and they cannot be considered as synthetically useful. On the other hand, with nitrone **1c**, which possess a cyclic system vicinal to the nitrone functionality, excellent values of stereocontrol were obtained. Whereas the addition in the presence of zinc(II) bromide (entry 35) afforded the *syn* isomer in 91% dr, the same reaction carried out in the presence of boron trifluoride etherate (entry 36) furnished the *anti* isomer in 92% dr. We then extended the study to nitrone **1d**, derived from Mukaiyama's aldehyde. Good ds values and chemical yields again were found for this nitrone (entries 37–39) and a complete stereocontrol was obtained by moving from zinc(II) bromide to boron trifluoride etherate.

Attempts to extend this methodology to α-amino nitrones led to completely different results. As outlined in previous papers,[13] the selectivity of nucleophilic additions to α-amino nitrones are not influenced by Lewis acids but by the protection of the α-amino group. As expected, allylation of nitrone **1e** furnished the *syn* isomer in excellent yields, whatever the Lewis acid is used (entries 40–43).[14] However, switching to monoprotected nitrone **1f** proved beneficial since this afforded a mixture of adducts with a dr of 9:1, the *anti* adduct being the major isomer.

We also attempted the addition of samarium and indium allyl derivatives following the reported procedures by Prajapati[15] and Kumar,[16] respectively. Unfortunately, we did not observe any reaction after several days. This behaviour might be due to the less reactivity generally observed for alkyl nitrones with respect to aryl nitrones like those used in the cited reports.

The dr's were determined by both NMR spectroscopy and HPLC. The configuration of the obtained isomers was unambiguously assigned by comparison with literature data for **2a** and **3a**,[7a] and following our previously published rule[17] for hydroxylamine **2e**. Assignment of the other hydroxylamines was made by chemical correlation through their conversion into known compounds.[18] In addition, the configurations for all compounds were in good agreement with COSY, NOESY and HMQC experimental data.

Further demonstration of the diastereodivergency of the process was achieved by the transformation of



Scheme 3. Reagents and conditions: (i) Zn, AcOH, 70 °C; then Boc_2O, dioxane, rt. (ii) Li, NH_3 (liq); then *p*-TosOH, MeOH; then $NaIO_4$, SiO_2, CH_2Cl_2; then TEMPO, [bis(acetoxy)iodo]benzene, MeCN–H_2O.

diastereomeric hydroxylamines **2a** and **3a** into enantiomeric protected derivatives of allylglycine (Scheme 3). Deoxygenation of the hydroxyamino function, N-protection and further transformation of the dioxolane ring into a carboxyl group,[19] afforded **5** and *ent*-**5** in good overall yields.

In this letter we have described the successful application of Lewis acids to control the diastereofacial selectivity in allylation reactions of chiral non-racemic α-alkoxy nitrones. We have also demonstrated the utility of the methodology by preparing *N*-Boc-L-allylglycine and its enantiomer. The effect of the Lewis acid in the stereochemical course of the allylation reaction is a matter of interest, and further studies are in progress.

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