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Enantioselective Radical Allylation of α-Iodoamides Using Chiral Aluminum Based Lewis Acids

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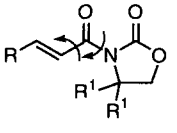
Abstract: We report here the first examples of enantioselective radical alkylations directed by chiral Lewis acids where complexated radicals are directly generated by a carbon-halogen bond homolysis. N-(2-Iodopropionyl)oxazolidinones are allylated with allylstannane in the presence of chiral aluminum based Lewis acids prepared from Me_3Al and chiral diols/diamides ligands. The observed enantioselectivities are still modest (≤ 34% ee). By analogy to cycloaddition reactions, a model is proposed to rationalize the sense of the enantioselectivity. © 1997 Elsevier Science Ltd.

Chiral Lewis acids have been used for highly enantioselective Diels-Alder reactions using for instance 3-acryloyl-1,3-oxazolidin-2-one **1** as dienophile.[1,2] In order to control the stereoselectivity, the Lewis acids should favor one geometry of the dienophile **1** (see possible rotation indicated by arrows) and mask one face of the alkene moiety. In our approach to devise enantioselective radical reactions,[3] we decided, by analogy of cycloaddition reactions, to investigate radicals of type **2**.



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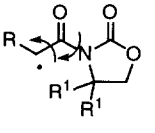

2

The *s-cis/s-trans* isomerism of these radicals and the stereofacial approach are expected to be also controlled by Lewis acids. During our previous work, we have observed that aluminum derivatives are particularly efficient in radical reactions.[4] Thus, we decided to focus first on chiral Lewis acids containing aluminum as metal center. Very high level of stereoselectivity have been observed in Diels-Alder reactions with this particular type of Lewis acids[5,6] and a model based on complexation of a single carbonyl group has been proposed.[5c]

The radical precursors **3** and **4** have been prepared from 1,3-oxazolidin-2-one and 4,4-dimethyl-1,3-oxazolidin-2-one by acylation ($BuLi/CH_3CHBrCOCl$) and subsequent Finkelstein reaction (NaI/acetone). Different chiral Lewis acids of general formula $MeAl[R^*(X)_2]$ ($R^*(XH)_2$ = chiral diol or chiral diamide) have been prepared by mixing Me_3Al with the ligands **5**-**7**.

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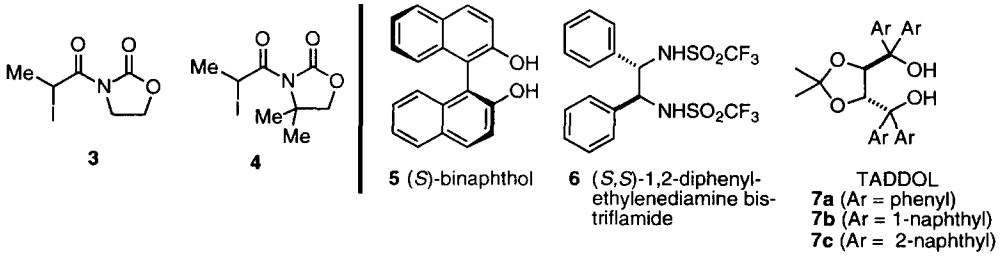
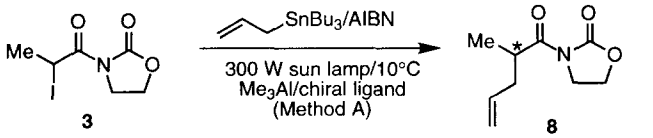


3 **4** **5** (*S*)-binaphthol **6** (*S,S*)-1,2-diphenyl-ethylenediamine bis-triflamide TADDOL **7a** (Ar = phenyl) **7b** (Ar = 1-naphthyl) **7c** (Ar = 2-naphthyl)

The first series of experiments was based on the allylation of **3** (CH_2=$CHCH_2SnBu_3$/AIBN/300 W sun lamp irradiation at 10 °C (method A)) according to Equation 1. (*S*)-Binaphthol **5** gave no asymmetric induction, however, the allylation yields was excellent (90%, Table 1, entry 1). Reaction with the (*S,S*)-bistriflamide **6** gave the allylated compound **8** in good yield and 20% ee (entry 2). The absolute *S* configuration of the newly formed center was assessed by hydrolysis of **8** to the known (*S*)-2-methyl-4-pentenoic acid using $LiOH/H_2O_2$ in THF/H_2O.[7] A very similar level of induction was obtained with the TADDOL **7b** (entry 3, 15% ee).[8]

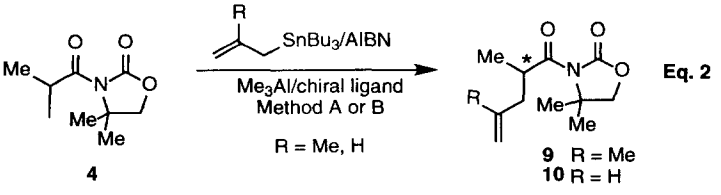


3 **8** **Eq. 1**

Table 1. Radical allylation of **3** in the presence of $MeAl[R^*(X)_2]$ (prepared by mixing 1 equiv. Me_3Al and 1 equiv. of $R^*(XH)_2$ according to Equation 1 (Method A).[9]

Entry	Ligand	Yield [%]	ee [%][a]	Abs. conf.
1	**5**	90	0	-
2	**6**	89	20	*S*
3	**7b**	88	15	*S*

Next, we decided to investigate reactions of oxazilidinone **4** (Equation 2). It was expected that the *gem*-dimethyl substituent would favor the *s-cis* conformation of the intermediate radicals relatively to the *s-trans* and therefore enhance the stereoselectivity. The (2-methylpropen-3-yl)tributylstannane (R = Me) was used as an allylating agent for the screening experiments because it was found slightly more efficient than the simple allyl derivative (R = H).



4 **9** R = Me **10** R = H **Eq. 2**

Table 2. Radical allylation of **4** in the presence of MeAl[R*$(X)_2$] according to Equation 2. Method A: 300 W sun lamp, 10 °C; method B: Et_3B/O_2, -78 °C.[9]

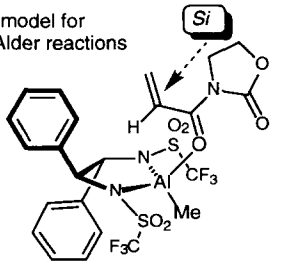
Entry	R	Product	Ligand	Method	Yield [%]	ee [%][a]	Abs. conf.[b]
1	Me	**13**	**5**	A	92	4	(-)-*R*
2	Me	**13**	**5**	B	93	8	(-)-*R*
3	Me	**13**	**6**	A	93	8	(+)-*S*
4	Me	**13**	**6**	B	80	8	(+)-*S*
5	Me	**13**	**7a**	A	80	0	-
6	Me	**13**	**7b**	A	95	24	(-)-*R*
7	Me	**13**	**7b**	B	93	34	(-)-*R*
8	H	**14**	**7b**	B	90	32	(-)-*R*
9	Me	**13**	**7c**	B	93	0	-
10	Me	**13**	**7c**[c]	B	90	10 (*R*)	(-)-*R*

a. Determined by GC analysis on chiral column (FS 320x, β-cyclodextrine, 100% diacetoxy).
b. The absolute configuration was proved for compound **14** by hydrolysis to the known (*S*)-2-methylpent-4-en-1-oic acid using $LiOH/H_2O_2$ in THF/H_2O, the absolute configuration of **13** was made based by comparison with **14** (sign of $[\alpha]_D^{20}$ and order of elution during the GC analysis).
c. Et_2AlCl was used instead of Me_3Al

Modest but reproducible enantioselectivities were obtained, the results are summarized in Table 2. The best selectivity has been observed with MeAl-TADDOLate **7b** (24% ee method A and 34% ee method B). In all cases, the yields are excellent even when the reaction were run at -78 °C (method B). The absolute configuration of the products is opposite when using the bistriflamide **6** relatively to the TADDOL **7b**. Interestingly, the introduction of the *gem*-dimethyl group causes an inversion of the sense of stereoselectivity with the TADDOL **7b**.

These enantioselectivities, although modest, represent the first enantioselective alkylations of a radical directly generated by homolysis of a carbon-halogen bond.[10] At the moment, the enantioselectivities are too low for a detailed discussion of the models which rationalize the results, however, the following points which are useful for the optimization of the enantioselectivities can be noted: 1) Preliminary ^{13}C-NMR study with Me_3Al and N-propionyl-1,3-oxazolidin-2-one confirms the observation of Corey, i.e. complexation is occuring exclusively at the external (= propionyl) carbonyl group. 2). In case of Corey's bistriflamide **6**, the model **11** initially developed for the Diels-Alder reactions[5c] can be applied to radical precursor **3**. The main isomer being formed via a radical lying in the *s-trans* conformation and attack is occuring from the less hindered *Re* face (model **12**). 3). For all the other systems investigated, several models affording the observed stereoselection can be proposed. More information is needed in order to fully understand these systems.

Corey model for Diels-Alder reactions
11



Model for radical reactions
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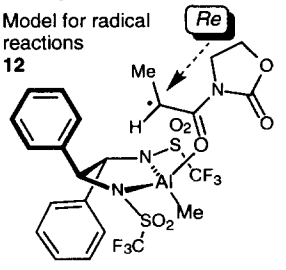

In conclusion, we have shown that aluminum-based Lewis acids can be used for enantioselective radical reactions. Although the level of inductions is still modest (≤ 34% ee), they may serve as a starting point for the development of highly enanantioselective reactions. These first results confirm also the validity of the analogy between radical reactions and cycloaddition reactions. Optimization of the reaction conditions (ligand and substrates) is actually under investigation.

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7. For a similar hydrolysis experiment, see: Sibi, M. P.; Ji, J. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 190-192. For the absolute configuration of (*S*)-2-methyl-4-pentenoic acid, see: Riley, R. G.; Silverstein, R. M. *Tetrahedron* **1974**, *30*, 1171-1174.
8. For a leading reference on the use of metal-TADDOLate in Diels-Alder reactions, see: Seebach, D.; Dahinden, R.; Marti, R. E.; Beck, A. K.; Plattner, D. A.; Kuhnle, N. M. *J. Org. Chem.* **1995**, *60*, 1788-1799.
9. *Method A*: a soln. of the chiral ligand **5-7** (3.3 mmol) in CH_2Cl_2 (4 ml) was treated with a 1M soln. of $AlMe_3$ in hexane (3.3 ml, 3.3 mmol) and stirred at r.t. during 1 h. A soln. of **3** or **4** (3.0 mmol) in CH_2Cl_2 (1 ml) was then added and the soln. was stirred for 20 min at r.t. before addition of AIBN (10 mg) and (2-methylpropen-3-yl)tributylstannane or allyltributylstannane (5.0 mmol). The solution was irradiated (300 W, sun lamp) at 10 °C for 9 h. A 1M NaOH soln. (15 ml) was added followed by CH_2Cl_2 (7 ml) and the heterogeneous soln. was stirred for 20 min. The organic layer was washed with H_2O, dried ($MgSO_4$) and treated with KF (0.75 g, 13 mmol). The suspension was stirred at r.t. overnight and filtered. The filtrate was evaporated and the residue was filtered through silica gel (hexane/EtOAc, 9:1) to afford crude **8-10**.
Method B: a soln. of the chiral ligand **5-7** (3.3 mmol) in CH_2Cl_2 (4 ml) was treated with a 1M soln. of $AlMe_3$ in hexane (3.3 ml, 3.3 mmol) and stirred at r.t. during 1 h. A soln. of **4** (890 mg, 3.0 mmol) in CH_2Cl_2 (1 ml) was then added and the soln. was stirred for 20 min at r.t.. The soln. was cooled to -78 °C and (2-methylpropen-3-yl)tributylstannane or allyltributylstannane (5.0 mmol) was added followed by an oxygen saturated soln. of CH_2Cl_2 (2 ml). After addition of a 1M soln. of Et_3B in hexane (1.0 ml), dry oxygen was bubbled for 20 min. The reaction mixture was then treated with 1M NaOH according to procedure A.
10. Enantioselective direct reduction of complexed radicals has been reported, see ref. **3a**. For examples dealing with radical additions to complexed activated alkenes, see ref. **3b-3e**.

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