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Chiral Salen−Aluminum Complex as a Catalyst for Enantioselective α-Addition of Isocyanides to Aldehydes: Asymmetric Synthesis of 2-(1-Hydroxyalkyl)-5-aminooxazoles

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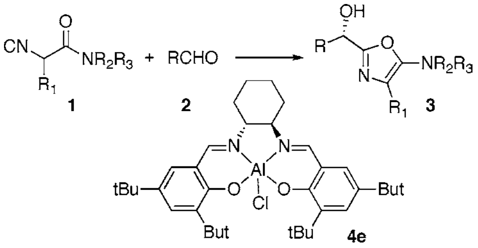
ABSTRACT



In the presence of a catalytic amount of (salen)Al(III)Cl complex (4e), reaction between α-isocyanoacetamides (1) and aldehydes (2) afforded the corresponding 5-aminooxazoles (3) in good yields and enantioselectivity.

The pronounced ability of α-isocyanide to undergo α-addition with both electrophiles and nucleophiles has been well-recognized ever since the discovery of the classic Passerini (P-3CR)[1] and the Ugi (U-4CR)[2] multicomponent reactions (MCRs). This dual reactivity has been extensively explored, in the past decade, for the development of novel domino and multicomponent synthesis of medicinally relevant heterocycles and for generating molecular diversity for drug discovery.[3] Although diastereoselective P-3CR[4] and U-4CR[5] using chiral substrate or chiral auxiliary have been reported,[6] the development of catalysts for enantioselective nucleophilic addition of the divalent isonitrile carbon to the polarized double bond (carbonyl group, imine, etc.) remains a significant challenge. Indeed, only very few examples are known in the literature in spite of the great efforts dedicated to these important reactions.[7] Denmark reported the first examples of the truncated enantioselective Passerini-type reaction by applying the elegant concept of Lewis base activation of

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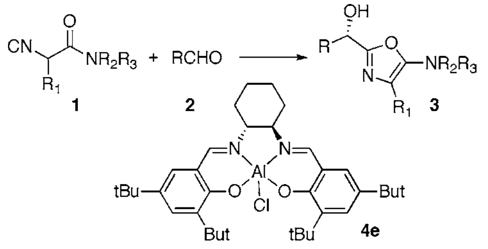
Lewis acid.[8] Dömling performed a massive parallel screening of a large number of metal−ligand combinations and found that a stoichiometric amount of Ti−Taddol complex was capable of promoting the P-3CR to afford the α-acyloxyamides in low to moderate enantioselectivity.[9] Schreiber demonstrated that an indan (PyBox)−Cu(II) complex was able to catalyze the P-3CR; however, the enantioenriched Passerini adduct was obtained only when the chelating aldehyde was used as a reaction partner.[10] We have recently documented a [Sn-(*R*)-Ph-PyBox]$(OTf)_2$-catalyzed enantioslective reaction between α-isocyanoacetamide (**1**) and benzyloxyacetaldehyde.[11]

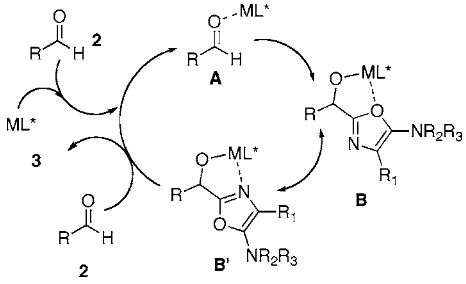
Contrary to the formidable progress achieved in the Lewis acid catalyzed asymmetric syntheses, it is interesting to note that there was no single example of metal-based catalytic system for the enantioselective α-addition of isocyanide to nonchelating aldehyde. We report herein an efficient chiral (salen)Al(III) complex catalyzed enantioselective addition of α-isocyanoacetamides to aldehydes. The catalyst tolerates a wide range of aldehydes to afford the diversely substituted 2-(1-hydroxyalkyl)-5-aminooxazoles **3** in good yields and enantioselectivity (Scheme 1).

Scheme 1. Chiral (salen)Al(III)Cl Complex Catalyzed Enantioselective Addition of α-Isocyanoacetamide to Aldehyde



The condensation of α-benzyl-α-isocyanoacetamide (**1a**)[12] and 2-methylpropanal (**2a**) leading to 5-aminooxazole[13] was used as a standard reaction for the screening of a suitable chiral Lewis acid catalyst (0.1 equiv). Besides the need to create a chiral environment to discriminate the two faces of the carbonyl function, several pitfalls exist that make this reaction particularly challenging: (a) As a strong Lewis base, isocyanide is known to be an excellent ligand for transition as well as main group metals.[14] If this coordination occurred, then other reaction manifolds such as aldol reaction could take place due to the increased acidity of the α-proton of isocyanoacetamide.[15] (b) Assuming that a Lewis acid coordinated preferentially to the aldehyde, the catalyst turnover would then be an important issue to be considered (Scheme 2). In fact, starting from a nonchelating aldehyde, the reaction produced a compound that contained two vicinal Lewis basic sites and consequently was able to chelate the metal center (**B** or **B′**). The transfer of catalyst ML_n from product (intermediate **B**/**B′**) to aldehyde leading to **A**, an essential step for the overall catalytic asymmetric induction, would thus be thermodynamically unfavorable.

Scheme 2. Enantioselective Addition of α-Isocyanoacetamide to Aldehyde: Problem of Catalyst Turnover



Based on these considerations, we hypothesized that any Lewis acid having two or more vacant coordinating sites would not be good candidate for the development of catalytic process. Indeed, the reaction between **1a** and **2a** catalyzed by [Sn-(*R*)-Ph-PyBox]$(OTf)_2$[11] wherein two-point binding model at the metal center is available, afforded the adduct **3a** without any detectable enantioselection (entry 1, Table 1). Parallel to this study, we have shown that aluminum chloride[11] is able to catalyze the condensation of **1a** and **2a** leading to the racemic oxazole **3a** in good yield. Consequently, we decided to examine the chiral aluminum complex with the hope to not only create the suitable chiral environment by ligand tuning but also reach the requisite catalyst turnover by using a catalyst having only one coordinating

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Table 1. Reaction of **1a** (R_1 = Bn, NR_2R_3 = Morpholinyl) and 2-Methylpropanal (R = *i*-C_3H_7), Survey of Enantioselective Catayst

entry	catalyst	solvent	yield,[b] (%)	ee,[c] (%)
1	**4a** + $Sn(OTf)_2$	CH_2Cl_2	74	0
2	**4b** + Et_2AlCl	toluene	40	0
3	**4c** + Et_2AlCl	toluene	54	9
4	**4d**	toluene	64	46
5	**4e**	toluene	76	80
6	**4e**	toluene	74	80[d]
7	**4e**	CH_2Cl_2	64	50
8	**4e**	THF	18	52
9	**4e**	MeCN	56	42

[a] General reaction conditions: 0.12 M solution of **1a**, 0.1 equiv/mol of catalyst, −20 °C, 24−48 h. [b] Yield of chromatographically pure material. [c] Determined by chiral HPLC analysis. [d] The reaction was performed at −40 °C for 2 days. Abbreviations: THF = tetrahydrofuran, MeCN = acetonitrile.

site available.[16] Initial experiments using catalysts derived from the combination of D-phenylglycinol or (*R*)-Binol with Et_2AlCl failed to provide the significant enantioselection (entries 2 and 3). Gratifyingly, the reaction catalyzed by the chiral (salen)Al(III) complex **4d**[17] afforded the oxazole **3a** in 64% yield and 46% enantiomeric excess. Switching the catalyst from **4d** to **4e** further increased the catalytic efficiency leading to the oxazole **3a** in 76% yield and 80% ee (entry 5). A simple recrystallization afforded the product **3a** with an ee of 90%. Lowering the reaction temperature to −40 °C slowed down significantly the reaction rate without noticeable beneficial effect on the enantioselectivity (entry 6). Solvent also played a key role in the enantioselectivity. The catalytic efficiency of **4e** decreased in terms of both yield and ee when the reaction was performed in dichloromethane (entry 7), THF (entry 8) or actetonitrile (entry 9) under otherwise identical conditions.[18] Control experiments indicated that the chirality of α-isocyanoacetamide (**1a**) exerted no influence on the stereoselectivity since both L-**1a** and DL-**1a** provided **3a** with identical ee (80%) and same sense of selectivity. Thus, chiral information was transmitted solely from the catalyst.

The scope of the reaction was explored using the optimized conditions (0.1 equiv of **4e**, toluene, −20 °C, 24 h) with representative aldehydes and α-isocyanoacetamides (Table 2). Aliphatic aldehydes, whether linear or α-branched, gave the corresponding oxazoles in good yield and good enantioselectivity (entries 1−6). It is worth noting that the reaction worked efficiently with sterically encumbered 2,2-dimethylpropanal to afford the corresponding adduct (**3e**) in 70% yield and 65% ee. The presence of a neighboring chelating group

Table 2. **4e**-Catalyzed Enantioselective Addition of Isocyanide to Aldehyde[a]

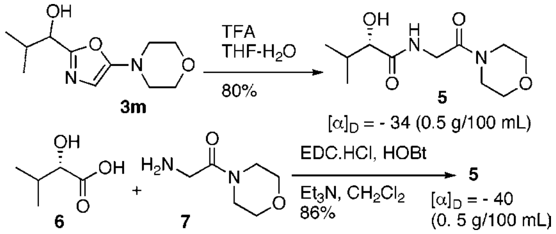
entry	isocyanide **1**	aldehyde **2**	product **3**	yield,[b] (%)	ee,[c] (%)
1	**1a**[f]	R = *i*-C_3H_7	**3a**	76	80[d]
2	**1a**	R = *n*-C_2H_5	**3b**	82	75
3	**1a**	R = $PhCH_2$	**3c**	57	50
4	**1a**	R = *c*-C_6H_{11}	**3d**	59	73
5	**1a**	R = *t*-C_4H_9	**3e**	70	65[e]
6	**1a**	R = $BnOCH_2$	**3f**	62	60
7	**1a**	R = phenyl	**3g**	30	53
8	**1a**	R = 2-MeO-C_6H_4	**3h**	53	61
9	**1a**	R = 4-Cl-C_6H_4	**3i**	41	54
10	**1a**	R = 4-NO_2-C_6H_4	**3j**	70	71
11	**1b**[f]	R = *i*-C_3H_7	**3k**	90	70
12	**1b**	R = *m*-Br-C_6H_4	**3l**	35	67
13	**1c**[f]	R = *i*-C_3H_7	**3m**	60	73

[a] General reaction conditions: 0.12 M solution of **1** in toluene, 0.1 equiv/mol of **4e**, −20 °C, 24−48 h. [b] Yield of chromatographically pure material. [c] Determined by chiral HPLC analysis. [d] After recrystallization, ee value ungraded to 90%. [e] The reaction was performed at −40 °C. [f] **1a**: R_1 = Bn, NR_2R_3 = morpholinyl. **1b**: R_1 = Bn, NR_2R_3 = NEt_2. **1c**: R_1 = H, NR_2R_3 = morpholinyl.

tends to reduce the enantioselectivity of the reaction in contrast to the [Sn-(*R*)-Ph-PyBox]$(OTf)_2$ catalyzed reaction (entries 2 vs 6). The benzaldehyde (entry 7) and other aromatic aldehydes with electron-donating (entry 8) and -withdrawing groups (entries 9 and 10) were suitable substrates to afford the corresponding oxazole with ee ranging from 53% to 71%. The *N*,*N*-diethyl-α-isocyano-*β*-phenylpropionamide **1b** reacted with aldehydes as efficiently as the morpholinyl counterpart (**1a**) (entries 11 and 12). The parent α-isocyanoacetamide **1c** participated well in this reaction to afford the expected adduct **3m** in 60% yield and 73% ee. In this latter case, neither the double condensation product[19] nor the oxazoline resulting from the Al-catalyzed [3 + 2] cycloaddition of the resulting oxazole with aldehyde[20] or from the aldol reaction between α-isocyanoacetamide and aldehyde was observed.[21]

The absolute configuration of oxazole **3m** was determined as shown in Scheme 3. Hydrolysis of **3m** under acidic

Scheme 3. Determination of Absolute Configuration of **3m**



conditions furnished amide **5**.[13c] Alternatively, the authentic amide (*S*)-**5** was synthesized by coupling of (*S*)-2-hydroxy-3-methylbutanoic acid (**6**) with the glycine amide **7** under classic conditions. Comparison of the sign of optical rotation

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allowed us to assign the (*S*)-configuration to the oxazole **3m**. Assuming that the (salen)Al(III)Cl complex **4e** (Figure 1) coordinates preferentially to the aldehyde, the observed (*S*)-enantioselectivity indicated a *Re*-face attack on the aldehyde by the isocyanide and can be accounted for on the basis of the simplified stereochemical model shown in Figure 2. The requisite catalyst turnover is ensured by the fact that only one coordination site is available at the aluminum center to reach the stable hexacoordinated intermediate. The one-point binding model facilitated the dissociation of the metal catalyst from the product, extending consequently the asymmetric catalytic cycle.

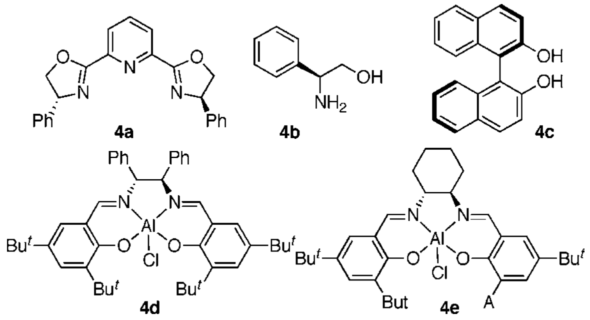

Figure 1. Structure of chiral ligands and catalysts.

In summary, we have reported an efficient chiral Lewis acid catalyzed α-addition of of α-isocyanoacetamides to aldehydes for the synthesis of enantioenriched 2-(1-hydroxyalkyl)-5-aminooxazoles. The conditions are applicable to both aliphatic and aromatic aldehydes, and in general, the ee is higher for aliphatic than for the aromatic ones. It is thus complementary to the Denmark protocol. We propose that the chiral catalyst with only one single coordination site available would be essential for the development of efficient enantioselective Passerini and Ugi-type reactions. This notion can also explain why the previously reported Cu-based[10] and Sn-based[11] catalyst worked only for the chelating aldehyde and the fact that stoichiometric amount of catalyst was necessary for the nonchelating aldehyde when Ti−Taddol[9,22] was used as a catalyst. Additionally, in view of the frequent occurrence of oxazole in natural products and medicinally relevant compounds, its unique reactivity for generating the molecular complexity and diversity,[23,24] we believe that the present protocol could be of high synthetic value.

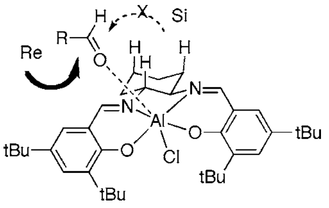

Figure 2. Stereochemical model.

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Note Added after ASAP Publication. The yields listed in Table 2 were incorrect in the version published ASAP August 8, 2007; the revised version was published ASAP August 14, 2007.

Supporting Information Available: Experimental procedures, product characterization, copies of ^{1}H NMR of **3a−m** and **5**, and chiral HPLC analysis of **3a−m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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