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COMMUNICATIONS

Published on Web 03/24/2006

Highly Enantioselective Addition of Me_2Zn to Aldehydes Catalyzed by ClCr(Salen)

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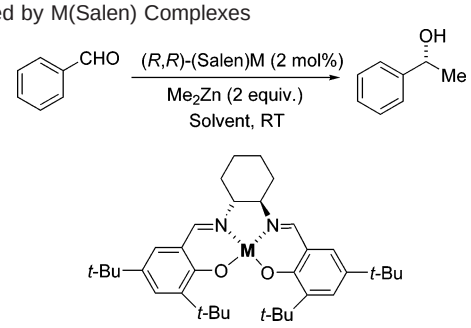
The addition of R_2Zn reagents to aldehydes represents a benchmark reaction in which new chiral ligands are evaluated. Hundreds of successful chiral ligands based on amino alcohols[2] or related SN,[3] SeN,[4] and NN[5] frameworks have been introduced in recent years.[6] Most of the ligands introduced are employed in the presence of Et_2Zn, while Me_2Zn was used in a few reports.[7] The small number of studies in the addition of Me_2Zn to aldehydes is in part determined by the lower reactivity of Me_2Zn, well documented in the literature.[8] However, the development of a highly enantioselective methodology for the addition of a methyl group is still a highly desirable process.

Herein we describe a highly efficient catalytic asymmetric addition of Me_2Zn to aldehydes promoted by a chiral Cr(Salen) metal complex.

Salen metal complexes are useful catalysts for a variety of asymmetric transformations.[9] The Schiff base framework, able to act as a bifunctional catalyst, is also well adapted to promoting the addition of organometallic reagents to aldehydes.[10] Recently, we reported that Zn(Salen) metal complexes are able to promote the addition of Et_2Zn to aldehydes[11] in moderate ee. Kozlowski and co-workers have exploited this concept through the tailored design of new Salen Schiff bases, able to coordinate electrophiles and nucleophiles in a close proximity.[12] On the other hand, ClCr(Salen) represents a privileged metal complex, able to transmit chiral information in a variety of processes.[13] Jacobsen has recently reported the activation of tin enolate[14] in a remarkable catalytic alkylation, expanding the scope of ClCr(Salen)-mediated processes. On the basis of this intriguing reactivity, we have explored the possibility of using ClCr(Salen) catalysts in the activation of other organometallic reagents. Particularly, we were interested in searching for new promoters for the addition of the stable and rather unreactive Me_2Zn.[15] Initial screens of different M(Salen) in the presence of Me_2Zn and benzaldehyde (Table 1) revealed the unique properties of Cr(Salen) in this transformation. While different metal Salen complexes did not produce a reaction after 24 h, 2% of commercially available ClCr(Salen) was able to promote the addition of Me_2Zn at room temperature, and a remarkable enantiomeric excess of 97% was obtained in this model reaction. Decreasing the reaction temperature makes no difference to the selectivity. Different solvents were employed and, in general, ethereal solvents, or toluene, gave high ee, while the reaction was not promoted in CH_2Cl_2. Levels of less than 1% of the catalyst can be employed at room temperature (Table 1, entries 16 and 17), but a lower enantiomeric excess was observed. However, in the presence of 0.5 mol % of the catalyst, in concentrated conditions, good yield and ee of 85% was obtained in the model reaction with benzaldehyde (Table 1, entry 17).[16] The more reactive Et_2Zn reacted smoothly with benzaldehyde at room temperature, but the product was isolated with low enantiomeric excess. The reaction was performed at 0 °C, but a decreasing enantiomeric excess was observed (Table 1, entry 19). This quite efficient and straightforward

Table 1. Enantioselective Addition of Me_2Zn to Benzaldehyde Promoted by M(Salen) Complexes



entry[a]	Salen	solvent	yield (%)[b]	ee (%)[c]	entry[a]	Salen	solvent	yield (%)[b]	ee (%)[c]
1	ClMn	^{t}BuOMe	0		11	CrCl	Et_2O	82	94(*R*)
2	Co	^{t}BuOMe	0		12	CrCl	CH_2Cl_2	0	
3	Co(OTs)	^{t}BuOMe	0		13[e]	CrCl	^{t}BuOMe	79	94(*R*)
4	Cu	^{t}BuOMe	0		14[f]	CrCl	^{t}BuOMe	12	11(*S*)
5	AlCl	^{t}BuOMe	10	*d*	15[g]	CrCl	^{t}BuOMe	35	8(*R*)
6	V(O)	^{t}BuOMe	0		16[h]	CrCl	^{t}BuOMe	70	55(*R*)
7	Zn	^{t}BuOMe	0		17[i]	CrCl	^{t}BuOMe	90	85(*R*)
8	Mn(N)	^{t}BuOMe	0		18[j]	CrCl	^{t}BuOMe	90	34(*R*)
9	CrCl	^{t}BuOMe	91	**97**(*R*)	19[i,e]	CrCl	^{t}BuOMe	83	29(*R*)
10	CrCl	toluene	90	95(*R*)					

[a] Reactions were carried out on a 0.2 mmol scale at RT for 24 h employing 2 equiv of Me_2Zn (2 M solution in toluene) and 2 mol % of ClCr(Salen). [b] Isolated yield after chromatographic purification. [c] Determined by chiral HPLC analysis. [d] Not determined. [e] Reaction was performed at 0 °C for 24 h. [f] The reaction was performed for 48 h on 0.5 mmol scale using 0.03 mol % of the catalyst in 1 mL of ^{t}BuOMe. [g] The reaction was performed for 48 h on a 0.5 mmol scale using 0.03 mol % without adding ^{t}BuOMe. [h] The reaction was performed on 0.3 mmol for 48 h using 0.2 mol % of the catalyst without adding ^{t}BuOMe. [i] The reaction was performed on 0.3 mmol for 48 h using 0.5 mol % of the catalyst without adding *t*BuOMe. [j] Et_2Zn (1.1 M in hexane, 2 equiv) was used as organometallic reagent in this reaction.

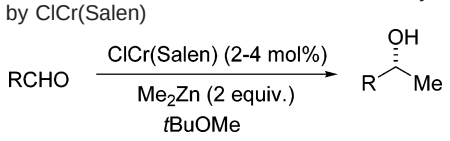
catalytic process was extended to other aldehydes (Table 2). As reported in Table 2, aliphatic, aromatic, α,β-unsaturated, and heterocyclic aldehydes are good substrates for this process.

It is particularly worth noting that in the case of aromatic aldehydes the enantiomeric excesses obtained are in the range of 92−99%. Yields are generally from good to excellent, and the purification of the reaction mixture consists of a rapid chromatography in order to eliminate the metal complex. Electron-rich aromatic substrates require 4 mol % of the catalyst to produce a good yield.

As increasing sterical hindrance in the proximity of the carbonyl group normally gives lower yield and lower enantiomeric excess in the catalytic addition of alkyl zinc reagents, we have studied our system using concentrated conditions with challenging hindered aldehydes (Table 2, entries 14−21), obtaining good results in terms of yield and enantiomeric excesses.[17] While with ClCr(Salen) it was possible to perform the reaction even with 1% of the catalyst (Table 1, entry 17), it is worth noting that the reported methodolo-

10.1021/ja057969d CCC: $33.50 **© 2006 American Chemical Society**

Table 2. Enantioselective Addition of Me_2Zn to Aldehydes Promoted by ClCr(Salen)



entry[a]	RCHO	yield[b]	ee (%)[c]
1	2-naphthylCHO	91	93
2	3-BrC_6H_4CHO	86	96
3	3-thiophenylCHO	86	99
4	4-$MeSC_6H_4CHO$	88	98
5	4-$CF_3C_6H_4CHO$	95	94
6	4-PhC_6H_4CHO	89	94
7	4-$^{i}PrC_6H_4CHO$	87	96
8[d]	3-benzo[*b*]thiophenylCHO	80	95
9	4-^{t}BuPhCHO	89	96
10[d]	4-MeOPhCHO	95	92
11[d]	(*E*)-PhCH=CHCHO	81	89
12[f]	$cC_6H_{11}CHO$	68	82
13[e,f]	^{i}PrCHO	82	80
14[e,f,g]	^{t}ButylCHO	75	97
15[g]	1-(3-phenyl-allyl)-cyclohexanecarbaldehyde	73	80
16[g]	2-methyl-2-phenyl-propionaldehyde	78	73
17[f,h]	2,2-dimethyl-pent-4-enal	57	76
18[f,g]	2,2-dimethyl-3-phenylpropionaldehyde	56	79
19[f,g]	2,2-dimethyl-4-phenyl-pent-4-enal	49	82
20[g]	1-benzyloxy-2-methyl-propanal	40	71
21[f,g]	1-^{t}Bu-dimethylsilyloxy-2-methyl-propanal	65	77

[a] Reactions were carried out on a 0.3 mmol scale at RT for 24 h employing 2 mol % of ClCr(Salen). [b] Isolated yield after chromatographic purification. [c] Determined by chiral HPLC analysis unless noted otherwise. Absolute configuration was established by comparison with the reported optical rotation for known alcohols. [d] Reaction carried out for 48 h using 4 mol % of catalyst. [e] Volatile product. Yield calculated on the corresponding 3,5-dinitrobenzoate prepared from the crude reaction mixture. [f] Determined by chiral HPLC analysis on the corresponding 3,5-dinitrobenzoate. [g] The 4% of ClCr(Salen) was dissolved in the 2 M toluene solution of Me_2Zn, then the aldehyde was added neat by syringe at 0 °C. The reaction was stirred 24 h at RT. [h] The 1% of ClCr(Salen) was dissolved in the 2 M toluene solution of Me_2Zn, then the aldehyde was added neat by syringe at 0 °C. The reaction was stirred 48 h at RT.

gies are often not reactive enough to hindered aliphatic aldehydes.[7b] Our procedure does not require the use of $Ti(O^{i}Pr)_4$[6b] and gives new perspective to the M(Salen)-catalyzed addition of organometallic reagents,[10,11] where Cr(Salen) metal complexes could be employed.[18] Possible mechanisms involving activation of aldehydes and/or activation of Me_2Zn by the chiral Cr complex will be evaluated in more comprehensive studies.

To summarize, we have developed a highly enantioselective addition of Me_2Zn to aldehydes employing the commercially available ClCr(Salen), which provides high selectivity for aromatic and hindered aliphatic aldehydes or α,β-unsaturated aldehydes with a simple reaction procedure. Further work in our laboratory will be directed toward exploiting the use of Cr(Salen) metal complexes in the catalytic addition of other organometallic reagents to aldehydes and ketones.[19]

Acknowledgment. Financial support from the European Community (IBAAC Project), MIUR (Progetto Nazionale Stereoselezioni in Chimica Organica: Metodologie ed Applicazioni), and FIRB (Progettazione, preparazione e valutazione biologicae farmacologica di nuove molecole organiche quali potenziali farmaci innovativi) are gratefully acknowledged.

Supporting Information Available: Representative experimental procedure, and details for ^{1}H and ^{13}C NMR and chiral HPLC analysis of enantiomerically enriched alcohols. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA057969D