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Chiral Co(II) and Mn(II) Catalysts for the 1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides Derived from Arylidene Imines of Glycine

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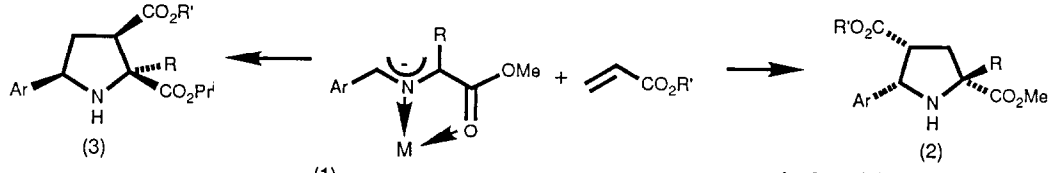
Key Words: Catalysis, cycloaddition, chiral, azomethine ylides.

Abstract: Anhydrous $MnBr_2$ and $CoCl_2$ in conjunction with chiral ephedrine ligands effect substantial asymmetric induction in cycloadducts derived from methyl acrylate and imines of glycine methyl ester. $CoCl_2$ is most effective and gives 96% e.e.

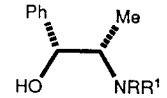
We have shown that imines of α-amino esters undergo rapid regio- and stereo-specific cycloaddition reactions with electronegative olefins (1) → (2) at room temperature in the presence of a range of metal salts [Ag(I), Tl(I), Li(I), Mn(II), Mg(II)] and a tertiary amine.[1,2] These processes are believed to involve metallodipoles. When Ti(IV) complexes are used [e.g. $Ti(OPr^i)_2Cl_2$] the regiochemistry of the cycloaddition is reversed and, in addition, regiospecific transesterification (1) → (3) occurs.[3] Certain metal salts [Co(II), Zn(II), Mg(II)][4] give imine* dimers (1) → (4) in which the imine functions as both dipole precursor and dipolarophile.[5] In at least some cases the imidazolidines, which are obtained as a mixture of cis- and trans-



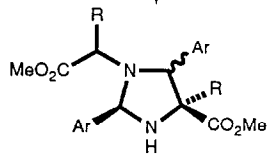
(3)

(1) a. Ar=2-naphthyl, R=H
b. Ar=4-BrC_6H_4, R=H
c. Ar=4-$MeOC_6H_4$, R=H

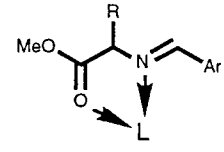
(2)
a. Ar=2-naphthyl, R=H, R'=Me
b. Ar=4-BrC_6H_4, R=H, R'=Me
c. Ar=4-$MeOC_6H_4$, R=H, R'=Me



(6)a. R=R^1=Me
b. R,R^1=$(CH_2)_4$
c. R=Me, R^1=Pr^i



(4)



(5)

isomers, are believed to arise via Bronsted acid catalysed processes.[1,5] Thus the "dipolarophile" in these cases is (5) ($L=M^+$ or M^{n+}) and the cycloaddition is probably a non-concerted addition to the iminium species (5). More recently we have achieved excellent asymmetric induction in the processes (1) → (2) and (1) → (3) using menthyl acrylate as the dipolarophile.[2,6]

We now report the development of the first chiral catalysts for 1,3-dipolar cycloaddition reactions. Initially we explored the use of anhydrous $MnBr_2$ in the presence of (1R, 2S)-N-methylephedrine (6a) for the reaction of (1a) with methyl acrylate to give (2a). The best results (64% yield, 60% ee)[7] were obtained with a mole equivalent of $MnBr_2$ and a 1:4 metal salt to ligand ratio. Reduced amounts of the ligand (6a) resulted in a lower e.e. whilst increased amounts slowed the reaction dramatically. Using a molar equivalent of anhydrous $CoCl_2$ in the presence of 2 mole of (6a) gave (2a) (45%, 80%ee) accompanied by a substantial amount of imine hydrolysis. The time required for the reaction to go to completion and the ee of the product (2a) were little changed in a variety of solvents (CH_2Cl_2, MeCN, PhCN, THF) although using the dipolarophile as solvent had a marked effect on both ee and rate of reaction (Table). The choice of cobalt salt had a marked effect on the reaction. Using $CoBr_2$ resulted in a faster reaction (8h) but a low ee (45%), whilst CoF_2 gave a very slow reaction (384h) and little chiral induction. Formation of dimer (4, Ar=2-naphthyl, R=H) is completely suppressed in the presence of (6a). A number of variations of the ligand were evaluated e.g. (6b), (6c), (7)-(9), with (6b)[8] proving the most effective (Table).

Table. Cycloaddition of (1a-c) with Methyl Acrylate Catalysed by $CoCl_2$ and (6b)[a].

Imine	Solvent	Time(h)	% e.e.	Yield(%)
1a	MeCN	16	84	55
1a	MA[b]	0.75	96	84
1b	MeCN	24	80	45
1b	MA	0.5	96	67
1c	MeCN	24	c	
1c	MA	0.75	96	83

a. $CoCl_2$(1 mole), ligand(6b)(2 mole), reactions carried out at 25°C

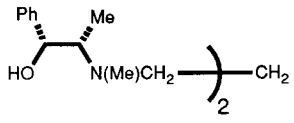
b. MA=methyl acrylate

c. Complex mixture of products

The increased yield of (2a-c) observed in methyl acrylate as solvent reflects the reduction in hydrolysis of the imine (1a-c) consequent on the faster cycloaddition. N-Methylephedrine (6a) is a less efficient catalyst

ligand for cobalt than (6b) in both acetonitrile (80% ee) and methyl acrylate (80% ee) and similar results were obtained with (6c) and were accompanied by lower chemical yields. Use of ligands (7) and (8) with cobalt failed to give any pyrrolidine products. Amino alcohol (8) in a 2:1 ratio with $MnBr_2$ gave (2a) with only 10% ee and a similar low ee (15%) was obtained when $CoCl_2$ and (9) were used to generate the catalyst.

Our working model for the asymmetric induction is shown in the figure. The cis-arrangement of the methyl and phenyl groups of the ligand results in a pseudo equatorial conformation for the phenyl group and effective blockade of one face of the imine/dipole.



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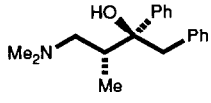

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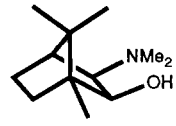

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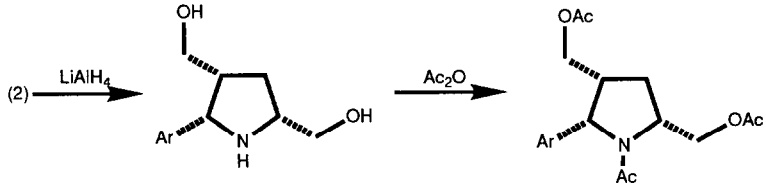
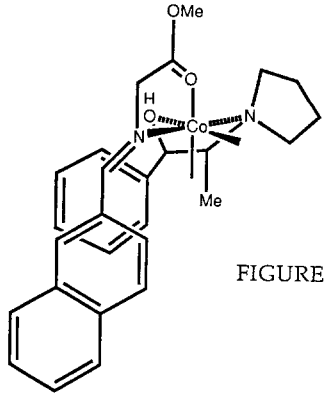


(10) (11)

The absolute stereochemistry of the cycloadduct (2a) was established by reduction to (10) and acetylation to give (11). The triacetate (11) was identical to that obtained previously from the cycloadduct (2a, R^1=1S, 2R, 5S-menthyl)[2] thus establishing the stereochemistry of (2a) as the 2R, 4R, 5S-compound.



FIGURE

Further work on these processes is in hand.

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2 Barr, D.A.; Dorrity, M.J., Grigg, R., Malone, J.F., Montgomery, J., Rajviroongit, S., and Stevenson, P., *Tetrahedron Letters,* 1990, **31**, 6569-6572.

3 Barr, D.A.; Grigg, R., and Sridharan, V., *Tetrahedron Letters,* 1989, **30**, 4727-4730.

4 Note that the chemoselectivity is a function of the metal counterion for certain metals e.g. $MgBr_2$ gives (2) whilst $Mg(ClO_4)_2$ gives (4). A correlation with single ion hydration enthalpies has been noted.[5]

5 Amornraksa, K.; Barr, D.A., Donegan, G., Grigg, R., Ratananukul, P., and Sridharan, V., *Tetrahedron,* 1989, **45**, 4649-4668.

6 For related work involving azomethine ylides generated by decarboxylation see: Coulter, T.; Grigg, R., Malone, J.F., and Sridharan, V., *Tetrahedron Letters.,* submitted.

7 In the initial phase of the work the % e.e. was determined by integration of the signals for the methyl protons of the ester in the p.m.r. spectra in the presence of a chiral lanthanide shift reagent. Subsequently a chiral hplc method was developed.

8 Prepared from (1R, 2S)-norephedrine and 1,4-dibromobutane in boiling ethanol over 16h; $[\alpha]_D$ + 13.6^0.

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