Tetrahedron Letters, Vol.31, No.45, pp 6569-6572, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

METAL ION CATALYSED ASYMMETRIC 1,3-DIPOLAR CYCLOADDITION REACTIONS OF IMINES OF α-AMINO ESTERS

Darrin A Barr,[a] Michael J Dorrity,[a] Ronald Grigg,[#b] John F Malone,[a]
John Montgomery,[b] Shuleewan Rajviroongit[c] and Paul Stevenson.[a]

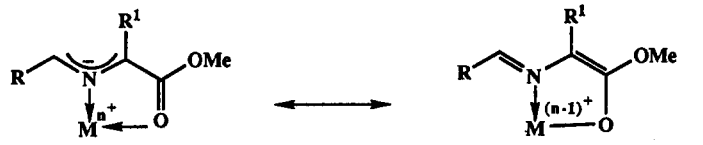
a. Chemistry Department, Queens University, Belfast, Northern Ireland BT9 5AG
b. School of Chemistry, Leeds University, Leeds LS2 9JT.
c. Chemistry Department, Mahidol University, Bangkok, Thailand.

Summary Cycloaddition of a range of imines of α-amino esters to homochiral menthyl acrylate proceeds with complete asymmetric induction at room temperature in the presence of silver(I), lithium(I) and thallium(I) salts. The imine of 2-aminomethylpyridine reacts similarly. Reversal of cycloaddition regiochemistry, together with complete asymmetric induction, occurs when titanium (IV) complexes are used as catalysts. The absolute configuration of one of the cycloadducts has been established by X-ray crystallography.

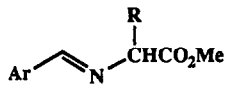
We recently reported a mild (room temperature), rapid, regio- and stereo-specific cycloaddition of imines of α-amino esters to electronegative olefins to give polysubstituted pyrrolidines in excellent yield.[1-3] These cycloadditions are catalysed by a wide range of metal ions [Ag(I), Li(I), Zn(II), Mg(II), Co(II), Mn(II) and Ti(IV)] and in some cases proceed via the metallo-dipole (1) whilst in other cases Bronsted acid catalysis may be involved.[2]

Unsuccessful attempts were made to achieve asymmetric cycloadditions by employing metal salts with homochiral anions or by addition of homochiral amines.[1-3] Recently Kanemasa et al[4] have described a a single example of a lithium bromide catalysed cycloaddition of a chiral dipolarophile to an imine of glycine methyl ester. We now report our related studies of an efficient asymmetric cycloaddition using a homochiral dipolarophile (menthyl acrylate). A range of metal salts have proved effective in achieving complete asymmetric induction as deduced by examination of the ^{1}H n.m.r. spectra of the crude reaction mixtures.

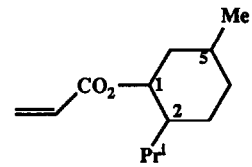
In previous studies[1,2,5] we have shown that silver salts in combination with triethylamine promote clean cycloaddition whilst lithium salts due to their greater oxophilicity frequently give mixtures of cycloadduct and Michael adduct. Initially we therefore studied the cycloaddition (MeCN, 25°C) of (2a) with (3a) and (3b) in the presence of silver acetate (1.5 mol) and triethylamine (1 mol).[6,7] In each case a single



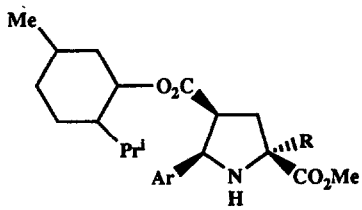
(1)



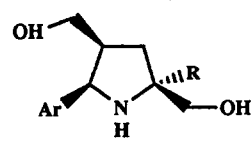
(2) a. Ar = 2- naphthyl, R = H
b. Ar = Ph, R = Me
c. Ar = R = Ph



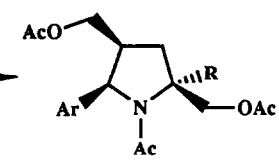
(3) a. (1R,2S,5R) - (-)-menthyl
b. (1S,2R,5S) - (+)-menthyl



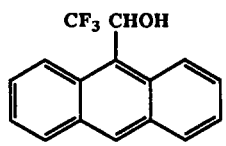
(4) a. Ar = 2- naphthyl, R = H
b. Ar = Ph, R = Me
c. Ar = R = Ph



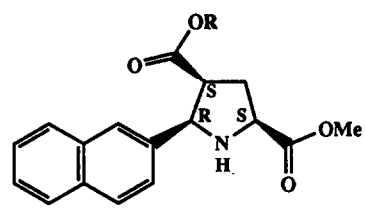
(5)



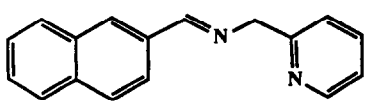
(6)



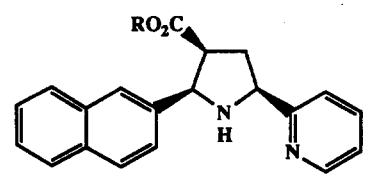
(7)



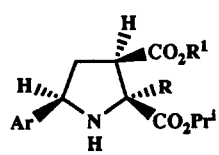
(8)



(9)



(10) R = (-)-menthyl



(11) Ar = 2- naphthyl, R = H, R^1 = menthyl

diastereomer of (4a) was obtained in ca 50% yield, $[\alpha]_D^{20}$ ($CHCl_3$) - 31.6° and + 30.8° respectively, and no Michael adduct was detected. These reactions can also be carried out (MeCN, 25°C, 18h) using silver acetate (0.1mol) and triethylamine (1mol) or with lithium bromide (1.5mol), tetramethylethylene diamine (1mol) (THF, 25°C, 16h). In the latter case the product comprises a 10:1 mixture of (4a) and the corresponding Michael adduct. The homochiral integrity of the product was established in each case by reduction ($LiAlH_4$) to the diol (5,R=H), conversion to the triacetate (6,R=H), and comparison of the ^1H n.m.r. of the homochiral triacetates, in the presence of a mixture of the (+) Pirkle reagent (7) and $Eu(hfc)_3$, with that of racemic triacetate. Absolute stereochemistry was established by a single crystal X-ray structure of the cycloadduct from (2a) and (3a) which showed it to be the (2S, 4S, 5R) - diasteromer (8, R=1R, 2S, 5R - menthyl). Analogous cycloadditions of (2b) with (3a) and (3b) (MeCN, 25°C, 48h) furnished a single diastereomer of (4b) in each case $[\alpha]_D^{20}$ ($CHCl_3$) - 16.9° and +15.8° respectively]. Stereochemical integrity of the cycloadducts was again established by conversion, via (5, R=Me), to the triacetates (6, R=Me).

Previous work[1] had shown that the lithium bromide catalysed cycloaddition of the phenylglycine imine (2c) to methyl acrylate occurs in quantitative yield. In this case the bulkyl phenyl substituent (2, R=Ph) disfavours Michael addition. When (2c) was reacted with (3a) (MeCN, 25°C, 4h) in the presence of lithium bromide (1.5 mol) and triethylamine (1 mol) clean cycloaddition occurred to give (4c) (>90%) as a single diastereomer $[\alpha]_D^{20}$ ($CHCl_3$)-4.5°]. We have also explored the use of Tl(I) salts as potential catalysts for this type of cycloaddition. Thallium(I) nitrate, carbonate, and acetate (1.5 mol) all catalyse the cycloadditon of (2a) and methyl acrylate (MeCN, 25°C, 1-18h) in the presence of triethylamine (1 mol) to give (8, R=Me, racemic) in essentially quantitative yield. Similarly (2a) and (3a) (DMSO, 25°C)[8] in the presence of $TlNO_3$(1.5 mol)/NEt_3(1 mol) react to give the homochiral cycloadduct (4a) in essentially quantitative yield. Imine (9) reacts with (3a) [AgOAc (1mol), NEt_3(1mol), 25°C] in either acetonitrile (12h) or DMSO (6h) to give the homochiral cycloadduct (10), $[\alpha]_D$($CHCl_3$)-39.5°, in ca. 70% yield showing that other potentially chelating imines undergo the asymmetric cycloaddition reaction.

We previously reported an intriguing and synthetically useful reversal of regiochemistry in the cycloaddition of (2a-c) with methyl acrylate to give the corresponding cycloadducts (11, R=H, Me or Ph, R^1=Me) in the presence of $Ti(OPr^i)_3Cl$ and $Ti(OPr^i)_2Cl_2$. The transesterification occurs on the imine (2) prior to cycloaddition.[3] When (2a) and (3a) or (3b) were allowed to react (THF, 25°C, 10h) in the presence of $Ti(OPr^i)_3Cl$(1.5 mol) and triethylamine (1 mol) the homochiral cycloadducts (11) ($[\alpha]_D^{20}$ -41° and +43°) were isolated in ca. 75% yield.[6]

Further studies on these and related cycloadditions are in progress.

We thank the SERC, Organon Laboratories, and Leeds and Queen's Universities for support.

References

1. Barr, D.A., Grigg, R., Gunaratne, H.Q.N., Kemp, J., McMeekin, P., and Sridharan, V., *Tetrahedron*, 1988, 44, 557-570.
2. Amornraksa, K., Donegan, G., Grigg, R., Ratananukul, P., and Sridharan, V., *Tetrahedron*, 1989, 45, 4649-4668.
3. Barr, D.A., Grigg, R., and Sridharan, V., *Tetrahedron Letters*, 1989, 30, 4727-4730.
4. Kanemasa, S., Yamamoto, H., *Tetrahedron Letters*, 1990, 31, 3633-3636.
5. Barr, D.A., Donegan, G., and Grigg, R., *J. Chem. Soc., Perkin Trans 1*, 1989, 1550-1551.
6. All yields refer to isolated material and have not been optimised. However, the reactions are essentially quantitative in most cases with isolated yields reflecting loss of starting imine due to hydrolysis.
7. Careful examination of mother liquors together with ^{13}C n.m.r. studies failed to reveal the presence of another diastereomer. The stereospecificity observed in these cases compared to variable stereoselectivity in related Diels-Alder reactions is a consequence of the accentuated steric interactions in the 5-membered transition state of the 1,3-dipolar cycloaddition compared to the 6-membered transition state in the Diels-Alder reaction.
8. Tl(I) catalysed reactions occur faster in DMSO.

(Received in UK 9 August 1990)