Pergamon

Tetrahedron Letters 39 (1998) 8905–8908

TETRAHEDRON LETTERS

A Parallel Combinatorial Approach to Locating Homochiral Lewis acid Catalysts for the Asymmetric Aza-Diels-Alder Reaction of an Imino Dienophile.

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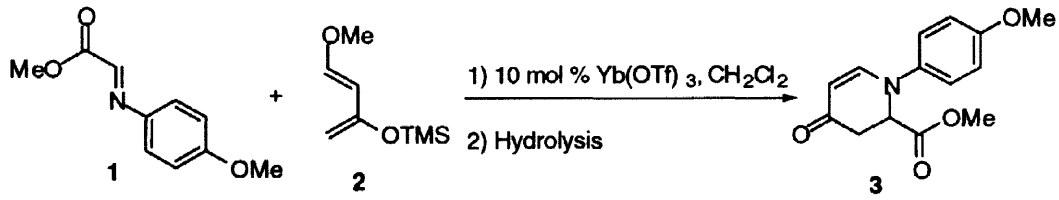
Received 4 August 1998; accepted 14 September 1998

Abstract *New catalytic asymmetric Lewis acids have been developed for the aza-Diels-Alder reaction of a methyl glyoxalate and p-anisidine derived imine with Danishefsky's diene. The catalysts were developed using parallel combinatorial methods, with the highest e.e. being 97 % using (1S, 2S)-1,2-diphenylethylenediamine and magnesium iodide in acetonitrile.*

There are myriad examples of catalytic asymmetric induction in Diels-Alder reactions, involving homochiral Lewis acid catalysts and olefinic dienophiles.[1] Similarly, hetero-Diels-Alder reactions involving aldehyde dienophiles have also succumbed to catalysis using homochiral Lewis acids,[2] however similar asymmetric catalysis of imine dienophiles has remained elusive. Successful asymmetric induction in the aza-Diels-Alder reaction has relied almost entirely upon auxiliary-based methodology,[3] with the exception of Yamamoto's stoichiometric homochiral triarylborate Lewis acids.[4] Recent results from Kobayashi's laboratory has shown however that asymmetric induction is possible with an aza-diene using catalytic ytterbium-based Lewis acids, which has been followed by imine cycloaddition using an asymmetric zirconium catalyst.[5] We are therefore prompted to report[6] our own work on the catalytic asymmetric induction in an aza-Diels-Alder reaction, using a homochiral Lewis acid catalyst and an imino dienophile.

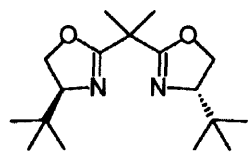
Our approach to finding a solution to the problem of asymmetric induction in aza-Diels-Alder reaction of imino dienophiles was to examine a range of likely candidate reactions which were susceptible to achiral Lewis catalysis. Of many reactions examined over several years, the reaction of N-aryl imines of type **1** appeared to be an ideal candidate for the development of an asymmetric catalyst, since it was found that such imines do not undergo thermal cycloaddition with Danishefsky's diene.[7]

Equation 1.



PII: S0040-4039(98)01947-9

However, the addition of a catalytic amount of ytterbium(III) triflate[8] did catalyse the reaction shown in **Equation 1**,[9] when harder Lewis acids failed to accomplish the same reaction (*e.g.* BF_3, $TiCl_4$ and $EtAlCl_2$). Thus formal cycloadduct **3** was isolated in 76 % yield after silica gel chromatography. These findings led us to explore the potential of asymmetric Lewis acids for catalysing the reaction shown in **Equation 1** using a combinatorial approach to catalyst selection.[10]



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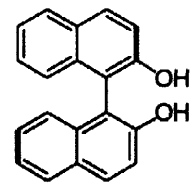

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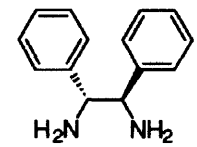

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Table 1.

Lewis acid	Ligand	Additive	Solvent	e.e./%
$Yb(OTf)_3$	**5**	2,6-lutidine	MeCN	41
$Yb(OTf)_3$	**6**	2,6-lutidine	MeCN	77
$Yb(OTf)_3$	**6**	4 Å MS	CH_2Cl_2	72
$Yb(OTf)_3$	**6**	2,6-lutidine	CH_2Cl_2	81
$Yb(OTf)_3$	**6**	4 Å MS	PhMe	64
$Yb(OTf)_3$	**6**	2,6-lutidine	PhMe	87
$Cu(OTf)_2$	**6**	4 Å MS	MeCN	51
$Cu(OTf)_2$	**6**	2,6-lutidine	MeCN	64
$Cu(OTf)_2$	**6**	-	MeCN	88
$Cu(OTf)_2$	**6**	-	CH_2Cl_2	72
$Cu(OTf)_2$	**6**	4 Å MS	PhMe	60
$Cu(OTf)_2$	**6**	-	PhMe	56
MgI_2	**5**	-	PhMe	64
MgI_2	**6**	4 Å MS	MeCN	79
MgI_2	**6**	2,6-lutidine	MeCN	97
MgI_2	**6**	-	MeCN	83
MgI_2	**6**	4 Å MS	CH_2Cl_2	65
MgI_2	**6**	2,6-lutidine	CH_2Cl_2	54
MgI_2	**6**	-	CH_2Cl_2	94
MgI_2	**6**	4 Å MS	PhMe	90
MgI_2	**6**	2,6-lutidine	PhMe	91
$FeCl_3$	**4**	-	MeCN	57
$FeCl_3$	**4**	4 Å MS	CH_2Cl_2	92
$FeCl_3$	**4**	2,6-lutidine	CH_2Cl_2	70

[a] All e.e.'s unoptimised.

The approach adopted involved library generation using single ligand synthesis, *i.e.* discrete homochiral Lewis acid complexes were generated individually, in solution, using multiple well plates. This parallel screening approach for chiral catalyst discovery, involved initial examination of four different metal salts [$Yb(OTf)_3$, MgI_2, $Cu(OTf)_2$, and $FeCl_3$], three different homochiral ligands (**4**-**6**), three different solvents (dichloromethane, toluene and acetonitrile), and two different additives (2,6-lutidine and 4 Å molecular sieves) with the total amount of Lewis-acid being calculated to be approximately 10 mol % relative to imine **1**. Enantiomeric excesses (e.e.'s) were measured using chiral h.p.l.c. with a Chiralcel OJ column and autosampler, allowing 144 sets of approximate yields and e.e.'s to be obtained in approximately one week. Active catalyst

combinations were subsequently identified using the positional identification method.[11] The combinations which produced e.e.'s greater than 40 % are shown in **Table 1**.

This preliminary screening process rapidly showed that all four metal salts chosen were capable of catalysing the aza-Diels-Alder reaction giving products in >80 % e.e. with certain ligand, additive and solvent combinations (see **Table 1**). In fact, 70 % of the combinations tried showed some level of asymmetric induction and catalysis. Additionally, and by coincidence, the sense of asymmetric induction produced for all the combinations shown in **Table 1** are the same (*vide infra*)! Hence, under the different reaction conditions chosen, all three ligands **4**, **5**, and **6** produce the same enantiomer in excess when combined with any of the four metal salts used for the small scale screens.

The most promising leads from each of the metal salts tested were then selected for reinvestigation on a preparative scale (1 mmol), using 10 mol % of Lewis acid, in order to determine accurate yields and e.e.'s for the isolated product **3** (after silica gel chromatography) (**Table 2**). In all cases, the small scale reactions (5 mg scale) were all completely reproducible in terms of e.e. and produced yields which clearly exceeded the amount of catalyst added, confirming true catalytic activity of the Lewis acid complexes generated in each case.

Table 2.

Lewis acid	Ligand	Additive	Solvent	Yield[a]/%	e.e./%
MgI_2	**6**	2,6-lutidine	MeCN	64	97[b]
$Yb(OTf)_3$	**6**	2,6-lutidine	PhMe	60	87
$Cu(OTf)_2$	**6**	none	MeCN	58	86
$FeCl_3$	**4**	4 Å M.S.	CH_2Cl_2	67	92

[a]All yields unoptimised, after silica gel chromatography. [b]For procedure and characterisation, see reference 12.

Clearly, the fact that the three homochiral ligands chosen for the study produce the same sense of absolute stereochemical control has mechanistic implications for the entire asymmetric induction process and attempts to determine the actual sense of asymmetric induction are underway. However, this study does show the power of high throughput screening coupled with combinatorial methods for the discovery of new asymmetric, catalytic processes. Further studies to prove the absolute stereochemistry of the adducts, and mode of action and structure of the active catalysts are underway.

Acknowledgements.

We thank the EPSRC for an industrial CASE studentship award (to PCW) (95700486) and Peter Lovell (SmithKline Beecham, Harlow, UK) for helpful advice and discussion.

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12. *General procedure: using magnesium(II) iodide and diamine 6.* To a solution of magnesium(II) iodide (29 mg, 0.10 mmol) and (1*R*, 2*R*)-diphenylethylene diamine **6** (24 mg, 0.11 mmol) in acetonitrile (5 ml) was added 2,6-lutidine (0.01 ml, 0.11 mmol). After 30 mins, imine **1** (200 mg, 1.04 mmol) was added in dry acetonitrile (10 ml), followed by diene **2** (0.25 ml, 1.29 mmol) after a further 30 mins. The reaction mixture was stirred for 18 h, mixed with silica gel (2 g) and the solvent evaporated. The resulting solid was loaded onto a silica gel column and eluted with petroleum ether : ethyl acetate (1 : 2) to give enone **3** as a yellow solid (174 mg, 64 %); $[\alpha]_D^{23}$ -2.9° (c. 0.1 $CHCl_3$); υ_{max} (film, *inter alia*) 1740 (ester CO) and 1650 (ketone CO) cm^{-1}; λ_{max} (EtOH) 203 (ε 12,000), 239 (ε 7,520) and 341 (ε 15,100) nm; δ (^{1}H, $CDCl_3$, 400 MHz) 2.97 (1H, ddd, J 17, 2 and 1 Hz, C<u>H</u>H), 3.11 (1H, dd, J 17 and 7.5 Hz, CH<u>H</u>), 3.79 and 8.84 (each 3H, s, 2 x OCH_3), 4.72 (1H, ddd, J 7.5, 2 and 1 Hz, N.C<u>H</u>.CH_2), 5.24 (1H, dd, J 17.5 and 1 Hz, N.CH:C<u>H</u>), 6.93 and 7.12 (each 2H, d, J 8 Hz, 2 x ArCH), 7.43 (1H, dd, J 17.5 and 1 Hz, N.C<u>H</u>:CH); δ (^{13}C, $CDCl_3$, 100.7 MHz) 38.8 (CH_2), 53.4 (ArO<u>C</u>H_3), 56.0 (CO.O<u>C</u>H_3), 61.7 (N.CH), 102.3 (ArCH), 115.2 (ArCH), 122.3 (N.CH:<u>C</u>H), 138.6 (Ar<u>C</u>.N), 150.5 (N.<u>C</u>H:CH), 170.8 (<u>C</u>O.OCH_3), 189.5 (<u>C</u>O.CH_2); m/z (c.i., NH_3) 262.3 ($M+H^+$, base peak); Anal. $C_{14}H_{15}NO_4$ requires C, 64.1; H, 5.8; H, 5.3; found C, 64.2; H, 5.7; N, 5.6 %.