Mild lanthanide(III) catalyzed formation of 4,5-diaminocyclopent-2-enones from 2-furaldehyde and secondary amines: a domino condensation/ring-opening/electrocyclization process†‡

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Lewis acid catalyzed reaction of 2-furaldehyde and secondary amines results in the formation of 4,5-diaminocyclopent-2-enones exclusively as the *trans* diastereomers: computational studies support the stereochemistry of the adducts as arising from a thermal conrotatory π4a electrocyclization of an initial ring-opened intermediate (a deprotonated Stenhouse salt).

First isolated in 1850, the highly coloured Stenhouse salts **1** (R^1 = Ar, R^2 = H, X = OH), form through a 2 : 1 condensation of anilines with furfuraldehyde **2** in the presence of protic acids (Fig. 1).[1] Similar polymethine salts **1** (R^1 = Ar, R^2 = H, X = H) are also known to be formed from glutoconaldehyde or Zincke salts.[2] Our attention became focussed upon these intriguingly functionalized intermediates following a synthetic analysis of the marine sponge bromopyrrole alkaloid agelastatin A **3**.[3] Embedded in the tetracyclic structure of **3** is a *trans* diaminocyclopentane motif **4**.[4] The formation of **4** had been demonstrated by the pioneering studies of Lewis and co-workers, who had shown that **4** can be formed in low yield from the reaction of **2** and anilines.[5,6] Heretofore this remarkable transformation has received little synthetic attention, presumably, because the formation of **4** occurs in poor yields, under harsh conditions (*i.e.* refluxing methanol in the presence of hydrochloric acid), or with reaction times as long as 80 days. One of the most serious problems with existing procedures is the concomitant formation of the more thermodynamically stable 2,4-diaminocyclopent-2-enones **5**.[5,7] Lewis has proposed a mechanism for the formation of both **4** and **5** from anilines and 2-furaldehyde, in which compound **5** is believed to result through further conjugate addition and elimination of aniline from **4**.[5,6b,6c] We now report a mild Lewis acid catalyzed protocol for the generation of **4**, which offers considerable potential as a densely functionalized intermediate.

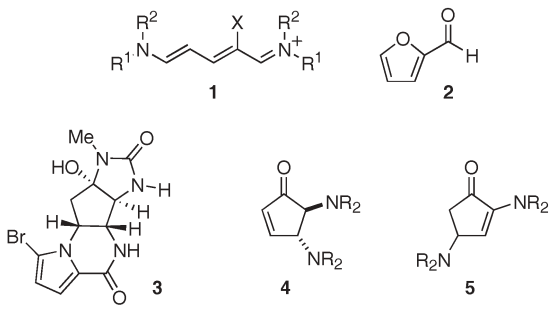

Fig. 1

Our initial studies focussed upon the formation of **4a** (NR_2 = morpholino) from 2-furaldehyde and morpholine using a variety of Lewis acids. Partial conversion to **4a** occurred in the presence of 1 equiv. of $BF_3{\cdot}OEt_2$ in THF at rt for 48 h. Lower conversions were obtained in the absence of a Lewis acid (*e.g.*, 38% at rt). Quantitative formation of **4a** was accomplished using $BF_3{\cdot}OEt_2$ and 4 Å molecular sieves with EtOH as the solvent. Other Lewis acids also accomplished this transformation, and in higher yields than under protic acid catalysis. Thus, formation of **4a** occurred in 95%, 71% and 60% yields respectively using 0.5 equivalents of $Ti(O^iPr)_4$, $Al(O^iPr)_3$ and $B(OMe)_3$ with 4 Å molecular sieves in EtOH, whereas 50% and 0% yields of **4a** were obtained using 2 and 4 equiv. of HCl, respectively. The use of lanthanide triflates with ethanol as the solvent did not yield **4a**, but instead resulted in the quantitative formation of the diethylacetal of 2-furaldehyde. However, use of catalytic amounts of either scandium or dysprosium triflate in acetonitrile with 4 Å molecular sieves for 16 h at room temperature, achieved quantitative formation of **4a**. Application of the protocol using a variety of secondary aliphatic amines and anilines resulted in the formation of the desired 4,5-diaminocyclopent-2-enones **4** in good to excellent yields (Table 1, Entries 1–8). $Dy(OTf)_3$ is preferred over $Sc(OTf)_3$ in these cases because of its lower cost. In every case examined only the *trans* diastereomer was observed (d.e. $\geqslant$ 95%), as revealed by NMR studies (a coupling constant of 3.0 Hz between H-4 and H-5 was observed for all adducts) and X-ray crystallographic analysis of **4d** (Fig. 2).§

Interestingly, the reaction of primary aliphatic amines such as benzylamine did not afford the product under the reaction conditions (Table 1, entry 9). However, primary anilines react to give the adducts **4** (Table 1, entries 10–12). In these cases use of $Sc(OTf)_3$ as the catalyst gives higher yields of the adducts **4** than were obtained using $Dy(OTf)_3$ (Table 1, entries 10 and 11).

The overall transformation to form **4**, an ABB′ type coupling,[8] must proceed through a pathway involving initial ring-opening of the furan ring, presumably from the iminium ion **6**, which would be activated toward nucleophilic attack at the 5-position (Scheme 1). The exact nature of this furan ring-opening step has yet to be established, but it is possible that addition reaction to give **7** is followed by ring-opening to give intermediate **8** (*i.e.*, the

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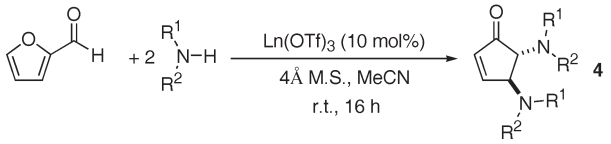
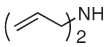
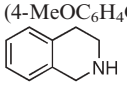
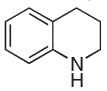
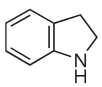
‡ In memory of Prof. Charles Rees and his contributions to the field of heterocyclic chemistry.

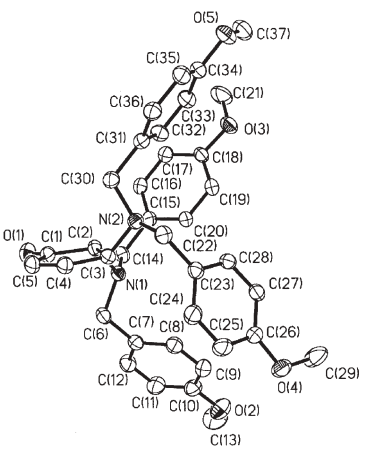
Table 1 Reaction of 2-furaldehyde with secondary amines catalyzed by lanthanide and scandium triflates



Entry	R^1R^2NH	Product	Yield[a](%)
1		**4a**	quantitative
2		**4b**	82
3	Bn_2NH	**4c**	98
4	$(4\text{-}MeOC_6H_4CH_2)_2NH$	**4d**	quantitative
5		**4e**	92
6	PhNHMe	**4f**	78
7		**4g**	81
8		**4h**	99
9	$BnNH_2$	—	0
10	$PhNH_2$	**4i**	17
11	$PhNH_2$	**4i**	78[b]
12	$2\text{-}MeOC_6H_4NH_2$	**4j**	52[b]

[a] Isolated yields using $Dy(OTf)_3$. [b] Isolated yields using $Sc(OTf)_3$. Traces of the corresponding 2,4-diaminocyclopent-2-enone **5** were also isolated.

deprotonated Stenhouse salt). Ring-closure of **8** then gives compound **4**. The zwitterion **8** can be independently generated by deprotonation of Stenhouse salts with base. A kinetic study using low temperature NMR for the ring closure of **8** (NR_2 = NHPh) by treatment of the corresponding Stenhouse salt (*i.e.*, the HCl salt of **1**, NR_2 = NHPh, X = OH) with EtN^iPr_2, revealed ring



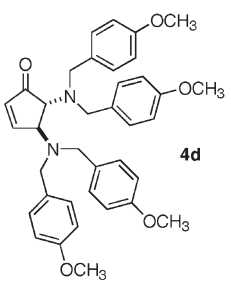


Fig. 2 X-Ray crystal structure of **4d**. Thermal ellipsoids are shown at 30% probability.

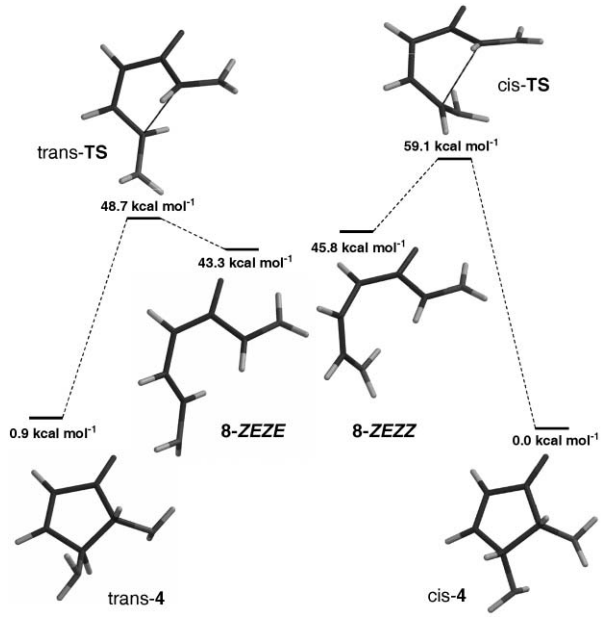
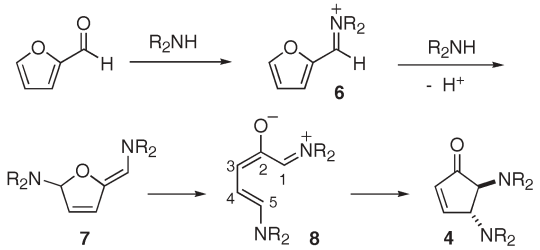


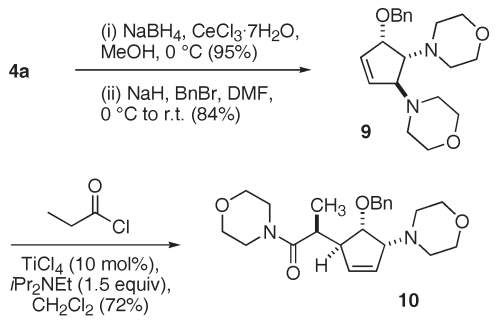
Fig. 3 6-31G** Energy profile (MacSpartan 02, version 1.0.4, Wavefunction, Irvine, CA) of electrocyclic formation of *trans*-**4** and *cis*-**4** (NR_2 = NH_2) from **8**. Relative energies include corrections (unscaled) for zero-point vibrational energies.



Scheme 1 Proposed overview of the mechanism of the reaction of 2-furaldehyde with secondary amines.

closure to be first order with respect to **1**, with an estimated activation barrier of 16.3 kcal mol^{-1} for the formation of **4** (NR_2 = NHPh). This fast ring-closure reaction supports the hypothesis that formation of **7** (or **8**) is rate-determining rather than ring-closure of **8** to **4**. In addition, and consistent with previous observations, this result demonstrates that lanthanide or Lewis acid catalysis is not required for the ring-closure step. In combination, these results suggest that it is likely that Ln(III) catalyzed formation of **7** (or **8**) is rate-determining, and that the Ln(III) salt is not involved in the ring-closure of **8** into **4**.

To understand the highly diastereoselective nature of this transformation, a computational study (UHF/6-31G**) on the ring-closure step of **8** (NR_2 = NH_2) into **4** was undertaken (Fig. 3). Examination of the transition states for formation of *trans*-**4** and *cis*-**4** clearly show that the ring-closure is consistent with a thermal conrotatory π4a electrocyclization. In the case of *trans*-**4** the calculated barrier for electrocyclic ring-closure from **8**-*ZEZE* (*i.e.*, the 1,2-*Z*, 2,3-*E*, 3,4-*Z*, 4,5-*E* stereoisomer)[9] is just 5.4 kcal mol^{-1}, although lower energy conformations of **8** exist, such as **8**-*ZZEE*, **8**-*ZZZE* and **8**-*ZZZZ* which are respectively a further 6.5, 8.8 and 12.8 kcal mol^{-1} lower in energy than **8**-*ZEZE*. The calculated



Scheme 2 Bellus ketene-Claisen type rearrangement of **9**.

transition state for the formation of *cis*-**4** from **8**-*ZEZZ* is disfavored by 10.4 kcal mol^{-1} over that for the *trans* closure. These computational results support a "Nazarov-like" mechanism, and the *trans*-stereochemistry of **4** is consistent with the Woodward–Hoffmann rules. Similar electrocyclization mechanisms have also been proposed for the acid promoted conversion of 2-furyl-carbinols into 4- hydroxycyclopentenones.[10] While the computational results provide insight into the stereodetermining step of the reaction, further mechanistic studies are necessary before a definitive mechanism for the overall reaction pathway can be established.

The 4,5-diaminocyclopent-2-enone products **4** are versatile synthetic equivalents for the formation of densely functionalized derivatives. For example, Luche reduction of **4a** followed by benzyl protection affords **9**, which was subjected to a Bellus ketene-Claisen type rearrangement using MacMillan's conditions,[11] to give **10** as a single diastereomer (Scheme 2).

In conclusion, the first practical preparation of 4,5-diamino-cyclopent-2-enones **4** from 2-furaldehyde and secondary amines by Ln(III) and Sc(III) catalysis has been developed. The products **4** are exclusively formed as the *trans*-diastereomers, consistent with a thermal conrotatory π4a electrocyclization, reminiscent of the Nazarov cyclization.[12] Further studies and applications on this remarkable domino ring-opening electrocyclization process of 2-furaldehyde to cyclopentanoid synthesis and manipulations of Stenhouse salts will be reported in due course.

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Notes and references

§ CCDC 651248. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b709337n

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9 Ring-opening of intermediate **7** would presumably lead to **8** as the *ZZZE* isomer. Isomerization of **8**-*ZZZE* to **8**-*ZEZE* (as depicted in Scheme 1) would be necessary before cyclization to **4** could occur.
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