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Trienamines derived from 5-substituted furfurals: remote ε-functionalization of 2,4-dienals

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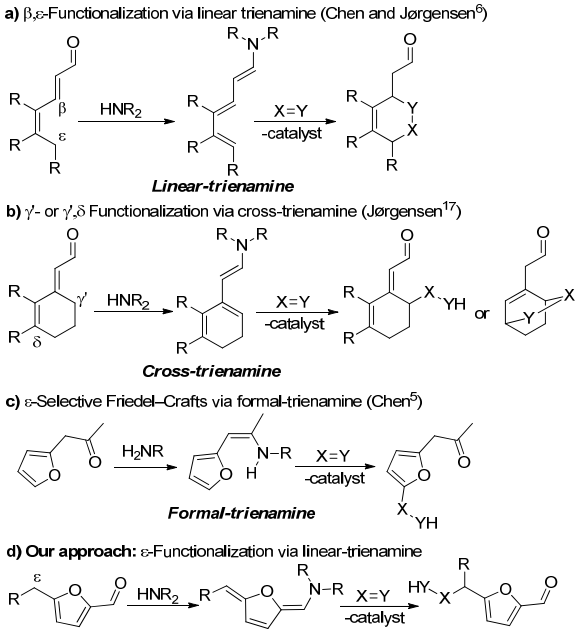
The selective ε-functionalization of 5-substituted furfurals via trienamine intermediates is reported herein. This methodology was successfully applied to several 5-substituted furfurals with different amines via formation of a trienamine through the furan ring. The rationalized reaction mechanism involves the addition of the trienamine intermediate to its corresponding iminium-ion producing new furan-containing scaffolds.

Vinylogous Mannich addition reaction is a powerful synthetic methodology for carbon-carbon bond formation that produces useful synthons for the synthesis of a variety of molecules from simple pyrrolidine and piperidine heterocycles to complex naturally occurring alkaloidal compounds.[1, 2] Extension to the bisvinylogous version seems to be much more challenging, and to the best of our knowledge has not been described to date. Nevertheless, very limited attempts in bisvinylogous additions were reported in Mukayama aldol reaction, Friedel-Crafts alkylation and Michael addition.[3-5]

Firstly reported in 2011 by Chen, Jorgensen and their coworkers,[6] trienamine catalysis has emerged by means of a new activation mode as an extension of the enamine catalysis[7-16]. Both vinylogous iminium-ion activation by LUMO-lowering and trienamine activation by HOMO-raising have been demonstrated as powerful strategies for modifications of 2,4-dienals.[6, 14-19] Linear trienamine intermediates effectively react with dienophiles yielding formal cycloadducts products having up to four contiguous stereocenters through direct β,ε-functionalization of 2,4-dienals (Scheme 1a).[6] Moreover, cross-trienamines intermediates can undergo γ',δ-functionalization by reaction with dienophiles or γ'-functionalization by selective additions to polarized olefins (Scheme 1b).[17] Very recently Chen *et al.*, reported the remote Friedel–Crafts Alkylation of furans through a formal-trienamine catalysis using a primary amine (Scheme 1c).[5] Noteworthy, specific substitution patterns of the starting carbonyl compounds are usually required to achieve high regioselectivity in these transformations.[16] Despite the fact that functionalization of the γ'-position of 2,4-dienals have been achieved by reaction with highly reactive Michael acceptors, ε-functionalization was not observed,[20] which is believed to be a result of kinetic control. The cross-conjugated trienamine is preferred compared to the thermodynamically linear-trienamine as proposed independently by the groups of Jørgensen and Houk.[17, 21]

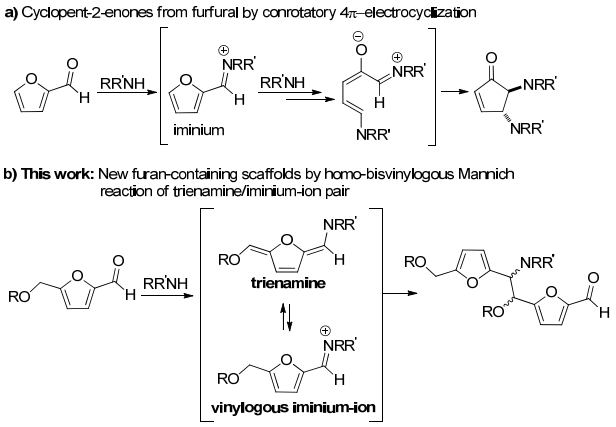
To the best of our knowledge, linear-trienamine catalysis derived from 2,4-dienals has been limited to Diels-Alder reactions, and ε-functionalization is not reported. Herein, we report the exclusive ε-functionalization of 5-substituted furfurals via trienamine intermediate (Scheme 1d).



Scheme 1. Functionalizations via trienamine catalysis.

As part of our on-going studies towards furfurals modifications,[22-24] an unprecedented reactivity of *O*-protected 5-hydroxymethyl furfurals was discovered. Unsuccessful attempts to use this type of compounds as starting material for the synthesis of cyclopent-2-enones via Nazarov type reaction (Scheme 2a)[25, 26] led to the isolation of a unexpected product[27], as depicted in Scheme 2b.

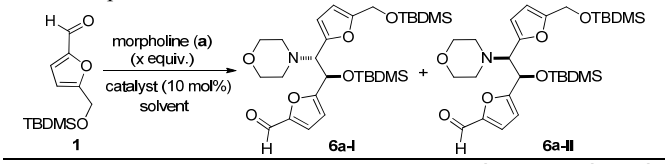
Remarkably the new scaffold contains two furan units linked by a new formed C-C bond and a C-N bond bearing the secondary amine. This change in reactivity is believed to be a result of increased steric effects at the 5-position of the furan moiety. Thus, we propose that a reaction between the linear-trienamine intermediate and its corresponding iminium-ion pair is taking place (homo-Mannich type reaction) to afford the product bearing two stereocenters.



Scheme 2. Furfural vs 5-substituted furfural reactivity.

We continued our study by screening different acid catalysts for the homo-bisvinylogous Mannich reaction between **1** and morpholine (Table 1).[28] Despite the fact that Brønsted acids are known catalysts for amine catalysis, no reaction was observed when TFA or PTSA were used at 50ºC (entry 1).[29] When Lewis acids were employed as catalyst moderate to very good conversions were obtained together with low yields of **6a** at 50ºC (entries 2-4[28]). Dysprosium triflate was identified as the most reactive catalyst, leading to full conversion of aldehyde **1** at 50ºC. Despite the high conversion, product **6a** was only isolated in low yields, which led us to hypothesize that **6a** product may not be stable under the reaction conditions. Gratifyingly, decreasing the temperature and increasing the reaction time improved the yield to 73% (entry 6 *vs* entries 4-5). Optimization of the amine stoichiometry allowed to decrease its quantity from 2 to 1 equivalents without changing both conversion and yield (entry 7). No improvement in the yield was observed when other solvents were screened (entry 8[28]). Finally, increasing the reaction concentration further increased the combined overall yield to 88% for the two diastereoisomers (entry 9).

Table 1. Optimization of the Reaction Conditions[a]



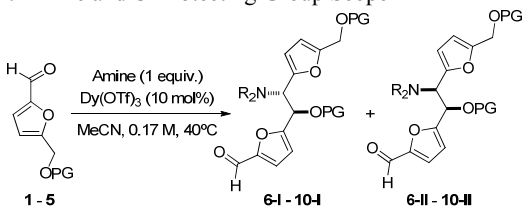
Entry	cat.	x	t (h)	T (ºC)	Conv. (%)[b]	Yield (%)[b]	d.r.[b]
1	Brønsted acids[c]	2	16	50	-	NR	-
2	$GdCl_3$	2	16	50	51	18	1:0.8
3	$ZrCl_4$	2	16	50	47	23	1:0.8
4	$Dy(OTf)_3$	2	16	50	93	42	1:1.5
5	$Dy(OTf)_3$	2	16	40	47	47	1:0.9
6	$Dy(OTf)_3$	2	48	40	73	73	1:1.0
7	$Dy(OTf)_3$	1	48	40	74	74	1:1.0
8[d]	$Dy(OTf)_3$	1	48	40	77	59	1:0.9
9[e]	$Dy(OTf)_3$	1	48	40	88	88	1:1.1

[a]Reaction conditions: 10 mol % of catalyst, 0.125 mmol of **1**, 1.5 mL of acetonitrile. [b]Determined by HPLC of the crude reaction mixture, ratio **6a-II**:**6a-I**. NR - No reaction was observed by TLC. [c]Sulfuric acid, trifluoroacetic acid, *p*-toluenesulfonic acid (PTSA), formic acid were tested. [d]Dichloromethane was used as solvent. [e]0.25 mmol of **1** in 1.5 mL of solvent was used.

Secondary amines were screened under the optimized reaction conditions until full conversion of starting material is reached. Using **1** as formal 2,4-dienal several amines were successful applied in this transformation in moderate to good yields (entries 1-5). From this study it was found that the reaction outcome depends strongly on the nucleophilicity of the nitrogen atom. Steric hindered amines such as 2,2,6,6-tetramethylpiperidine and *N*-benzyl-2-methylpropan-2-amine did not react even in refluxing acetonitrile.[28] Highly reactive amines such as pyrrolidine and piperidine, that led to full conversion of **1**, but furnished only traces or moderate yields of the respective products, respectively. These results can be explained by the stability of the product under the reaction conditions. In fact, for extended reaction times the yield of product **6f** decreases (entry 5, 24h *vs* 48 h). Furthermore it was observed that product **6a** is not stable in the presence of pyrrolidine (leading to a complex mixture), but is stable in the presence of morpholine.[28]

The effect of the alcohol protection group was also investigated (entries 6-9). When the protection group (PG) is Bz or Bn moderate yields are obtained (full conversion was not achieved using non-optimized conditions[28]). When acetate was employed as PG the observed yield drops to 29%, while 5-(hydroxymethyl) furfural gave 44%. These results highlights the importance of the protection group in the reaction efficiency, most probably by offering additional steric stabilization to the trienamine. Remarkably when 5-(cloromethyl) furfural was used instead of **1**, no reaction took place under the optimized reaction conditions.

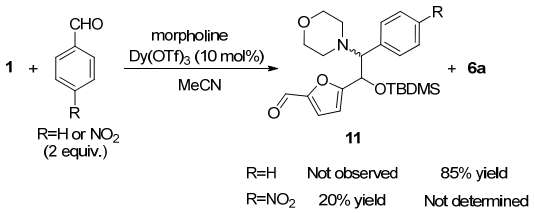
Table 2. Amine and *O*-Protecting Group Scope[a]



Entry	Amine	1-5 PG	t (h)	Yield (%)[b]	Product	d.r.[c]
1	dibenzylamine(**b**)	TBDMS(**1**)	41	86	**6b**	ND
2	diethylamine(**c**)	TBDMS(**1**)	24	78	**6c**	ND
3	1-methylpiperazine(**d**)	TBDMS(**1**)	24	37	**6d**	1:1.0
4	*N*-ethylbutylamine(**e**)	TBDMS(**1**)	20	60	**6e**	1:0.25
5	piperidine(**f**)	TBDMS(**1**)	24 [48]	48 [38]	**6f**	ND
6	morpholine(**a**)	Bz(**2**)	54	58	**7a**	1:1.0
7	morpholine(**a**)	Bn(**3**)	54	58	**8a**	1:0.8
8	morpholine(**a**)	H(**4**)	54	44	**9a**	1:1.1
9	morpholine(**a**)	Ac(**5**)	54	29	**10a**	1:1.0

[a]Reaction conditions: 10 mol % of catalyst, 0.125 mmol of aldehyde, 0.125 mmol of amine, 1.5 mL of acetonitrile. [b]Isolated yield after column chromatography. [c]Determined by ^{1}H NMR. ND – not determined.

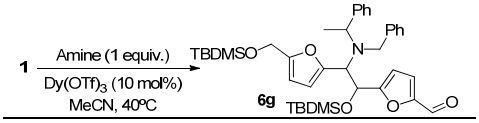
Next we aimed to achieve a cross reaction by intersecting the trienamine intermediate with other electrophiles (Scheme 3). Several electrophiles such as substituted benzaldehydes, chalcone, *N*-protected isatine and acrylonitrile were tested using different ratios of **1**/susbtrate/amine. 4-Nitro benzaldehyde was found to react with this intermediate to give the cross-product **11** (Scheme 3). It is noteworthy the great selectivity relatively to the homo-reaction as **6a** was isolated as the major product using other electrophiles[28] (for the reaction in presence of benzaldehyde, **6a** was isolated in 85% yield).

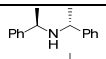
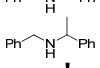
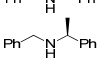
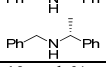


Scheme 3. Cross-reaction experiments.

The possibility to perform the asymmetric reaction was also examined. Both Brønsted (e.g., Chiral phosphoric acids) and Lewis (e.g., $Sc(OTf_3)$/chiral BOX ligands system) acid catalysts were explored.[28] In all cases the reaction did not display significant diasterio- and enantio- selectivities.[28] Encouraged by the reported asymmetric trienamine reaction using chiral amines,[6] we were please to observe a great selectivity of 1:1:0:0 when a chiral amine is employing *vs* 1:1:0.4:0.3 for the reaction with racemic amine (Table 3). These results suggest the existence of an interaction between the amine moieties from the iminium-ion and the trienamine, resulting in a chiral induction from a very remote position.

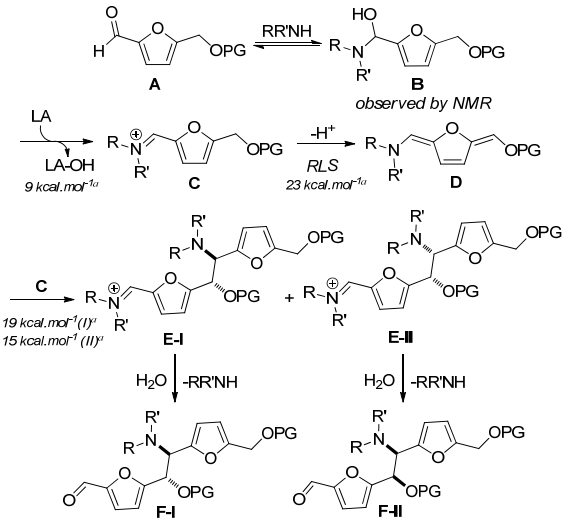
Table 3. Asymmetric induction by chiral amines[a]



Entry	Amine	*d.r.*[b]
1		NR
2		1:1:0.4:0.3[c]
3		1:1:0:0[d]
4		1:1:0:0[e]

[a]Reaction conditions: 10 mol % of catalyst, 0.125 mmol of aldehyde, 0.125 mmol of amine, 1.5 mL of solvent. [b]Determined by ^{1}H NMR. [c]*15%* isolated yield after column chromatography. [d]Yield not determined. [e]*13%* isolated yield after column chromatography. NR – No reaction was observed by ^{1}H NMR.

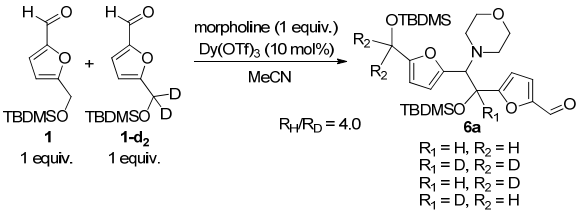
To gain insights into the mechanism of the transformation, the reaction of **1** with secondary amines was followed by ^{1}H NMR. To our surprise, formation of aminal **B** (Scheme 4) was observed as the only intermediate of the reaction. The formation of **B** immediately occurs even at room temperature and in absence of the catalyst (an equimolar amount of **1** and **B** is reached after 4 h when morpholine is used as amine). For the unreactive amines, such as bis(1-phenylethyl)amine, **B** was not observed, explaining why no reaction took place. Noteworthy is the fact that no further reaction takes place if catalyst is not added, even at 80ºC. Following the reaction catalyzed by $Sc(OTf)_3$ in acetonitrile-d_3 at 40ºC, did not led to the identification of other intermediates, apart from the aminal **B** and product **F** as diastereoisomers **F-I** and **F-II**.[28] We were particularly interested to identify the proposed trienamine intermediate **D**. With this goal in mind, we performed the optimized reaction in the presence of D_2O or using *N*-deuterated morpholine, however no incorporation of deuterium into the final product was found. These observations led us to hypothesize that formation of **D** is the rate-limiting step (RLS). In fact, by preparing the bisdeuterated derivative **1-d$_2$** (Scheme 5) and submitting a 1:1 mixture of **1** and **1-d$_2$** to optimized conditions, primary hydrogen kinetic isotope effect was observed (K_H/K_D = 4.0,[28] Scheme 5). The existence of this substantial isotope effect is a strong evidence that the carbon-hydrogen/deuterium bond is being broken in the RLS. Taking in consideration these observations we propose the mechanism depicted in Scheme 4. The great ε-selectivity of this transformation can be explained by the rearomatization of the furan ring of **D**.



[a]Energies (kcal.mol^{-1}) calculated for the reaction of substrate **1** and morpholine producing **6a**.

Scheme 4. Proposed mechanism.

In addition, Density Functional Theory (DFT)[30] studies also corroborate the proposed mechanism. The conversion of iminium-ion C into trienamine **D** exhibited the highest energy barrier (23 kcal.mol^{-1}), which is in agreement with this being the RLS. On the other hand, conversion of aminal **B** into iminium-ion **C** displayed the lowest energy barrier (9 kcal.mol^{-1}). Finally, reaction of **D** with **C** to give the two iminium-ions products **E-I** and **E-II** exhibited energy barriers of 19 and 15 kcal.mol^{-1}, respectively.[28]



Scheme 5. Kinetic isotope effect experiment.

Conclusions

In conclusion, we have reported the exclusive ε-functionalization of 2,4-dienals via trienamine intermediates. Several amines were successful applied producing a new highly functionalized skeleton. Specific patterns in 5-substituted furfural showed to be important to achieve good yields. Mechanistic studies suggested that formation of vinylogous iminium-ion is the rate limiting step, which is different from the known amine catalysis.

Notes

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Electronic Supplementary Information (ESI) available: Characterization data; copies of NMR; complete details of screening experiments, DFT details and atomic coordinates of all optimized species. See DOI: 10.1039/c000000x/

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27. Further modification of one of the diastereoisomers allowed us to confirm the structure by X-ray analysis. See supporting information for more details.
28. See supporting information for complete details of screening experiments or further details.
29. However, increasing the temperature afforded complex mixtures with a moderate yields of **6a**.
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