Favouring Trienamine Activation through Unconjugated Dienals: Organocatalytic

Enantioselective Remote Functionalization of Alkenes

Liher Prieto, Garazi Talavera, Uxue Uria, Efraim Reyes,* Jose L. Vicario* and Luisa

Carrillo[a]

[a] L. Prieto, Dr. G. Talavera, Dr. U. Uria, Prof. E. Reyes, Prof. J. L. Vicario, and Prof.

 L. Carrillo

Departamento de Química Orgánica II

Facultad de Ciencia y Tecnología

Universidad del País Vasco/Euskal Herriko Unibertsitatea UPV/EHU

P.O. Box 644, 48080 Bilbao (Spain)

e-mail: efraim.reyes@ehu.es; joseluis.vicario@ehu.es

Abstract

Unconjugated 2,5-dienals are proposed to constitute more reactive substrates than the corresponding fully conjugated $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes towards organocatalytic activation through trienamine intermediates. This has been demonstrated in the Diels-Alder reaction with nitroalkenes, which proceeds with clean β,ε-selectivity to afford the final products in high yields and stereoselectivities, while the related polyconjugated 2,4-dienals were found to be completely unreactive.

Main text

The discovery of the proline-catalyzed cross-aldol reaction in 2000 by List, Barbas and Lerner[1] and of the iminium activation concept by MacMillan in the same year[2] established the beginning of one of the most active research fields in chemistry that has revolutioned the area of asymmetric catalysis in the last decade. The possibility for primary or secondary amines to activate enolizable aldehydes or ketones towards a variety of reactions opened the way for their α-functionalization in a catalytic and enantioselective fashion by means of the reversible formation of an enamine[3] or an iminium radical-cation intermediate.[4] In the same line, the β-functionalization of enones and enals is possible through the catalytic formation of an α,β-unsaturated iminium ion.[5] More recently, the combination of these two activation manifolds along with the principle of vinylogy[6] has opened the possibility for the remote functionalization of unsaturated aldehydes and ketones, allowing the γ- and the δ-functionalization through dienamine catalysis[7] and vinylogous iminium ion activation[8] respectively. Much more recently, Jørgensen and Chen have also shown that even a more remote ε-functionalization is also possible by the formation of trienamine intermediates which, if conformationally locked, also allow the selective installation of ε-stereocentres with high degree of stereochemical control.[9].

In addition to the different issues that have to be controlled when a stereocentre is generated so far away from the chirality-inducing element, the application of the vinylogy concept in enamine and iminium ion activation also suffers from an additional reactivity problem, which is associated to the covalent nature of the catalyst-substrate interaction. In this sense, the implementation of a reaction through dienamine or

trienamine intermediates entails that the conjugation level of the starting material has to increase from a simple aldehyde or ketone to an α,β-unsaturated or α,β,γ,δ-polyunsaturated aldehyde or ketone respectively and this involves a progressive depletion of its reactivity towards condensation with the aminocatalyst. In this context, we wish to introduce herein the use of non-conjugated polyunsaturated aldehydes as more reactive starting materials that have an enhanced tendency to undergo this initial activation step by condensation with the chiral secondary amine catalyst and which also end up in the formation of the same conjugated trienamine intermediate as the one generated with a fully conjugated 2,4-dienal (see scheme 1). Importantly, this alternative unconjugated dienal substrate has also to be able to generate the trienamine intermediate as a single diastereoisomer and with a well defined geometry for the subsequent reaction to proceed with high stereocontrol, which means that all the dynamic equilibria participating in the formation of this intermediate have to end up in a trienamine showing preferential reactivity through one single reactive configuration and/or conformation.[10] In this manuscript, we wish to present our first results regarding the application of this approach to a Diels-Alder reaction[11] in which the trienamine intermediate is participating as the diene reagent and nitroalkenes are used as the dienophile counterparts.[12].

<INSERT SCHEME 1 HERE>

In order to test our hypothesis, we reacted 2,5-dienal **1** with nitrostyrene (**2a**) in the presence of 20 mol% of *O*-TMS diphenylprolinol **3**, which is a privileged chiral secondary amine catalyst that has shown its excellent performance in promoting reactions

under enamine, iminium or dienamine activation and also incorporating benzoic acid as Brønsted acid co-catalyst. This reaction furnished Diels-Alder cycloadduct **4a** in a promising 47% yield and as a single diastereoisomer with 92% ee. At the same time, when we carried out the reaction using conjugated dienal **5** under the same conditions, only the starting materials were recovered after prolonged reaction time, without any evidence of the formation of product **4a**.[13].

<INSERT SCHEME 2 HERE>

These two experiments confirmed our initial proposal and led us to further investigate this enhanced reactivity showed by unconjugated dienal **1**. Assuming the excellent performance of catalyst **3** in terms of almost perfect stereocontrol, we therefore focused our efforts on increasing the chemical yield of the process, working with the same set of model reagents (Table 1). We started our studies testing different solvents observing that, while the use of CH_2Cl_2 (entry 2) or a more polar solvent like THF (entry 3) led to an important decrease in the yield of the process, changing to toluene was found to have a positive effect, obtaining **4a** in a better 66% yield (entry 4). We next surveyed the influence of the acid co-catalyst, testing a set of different Brønsted acids (entries 5-7). Surprisingly, using additives of either more or less acidic character resulted in poorer conversions, which led us to consider the use of Brønsted bases as co-catalysts (entries 8-10). In this case, the incorporation of NaOAc resulted in an important increase in the chemical yield of the reaction, mantaining the high level of diastereo- and enantioselection (entry 8). When other bases such as DABCO or DBU were used (entries

9 and 10), no formation of **4a** was detected, only observing the complete conversion of **1** into conjugated dienal **5**, which has been shown to be unreactive towards condensation with the catalyst as demonstrated with the preliminary experiment shown in Scheme 2. On the other hand, the reaction without including any additive was also found to be very effective, leading to the formation of **4a** in excellent yield and stereocontrol (entry 11). Finally, we also evaluated the effect of the temperature in the reaction, observing that this was indeed a crucial parameter to be controlled. In fact, while carrying out the reaction at lower temperature led to a decrease in the yield of the reaction without any noticeable improvement in the enantioselectivity (entry 12), performing the reaction in a slightly higher temperature resulted into the formation of important amounts of conjugated dienal byproduct **5**, which turned into a poorer yield of **4a** and also resulted into lower enantiocontrol (entry 13).

<INSERT TABLE 1 HERE>

Having established the best protocol for the reaction, we decided to extend this methodology to nitroalkenes with different substituents (Table 2). Under the optimized conditions, a wide variety of differently substituted cyclohexenes **4a-n** were obtained with excellent yields and as single diastereoisomers. In this sense, the reaction performed equally well when nitrostyrene derivatives containing either more electron-rich or electron-deficient β-aryl moieties (entries 7-11). In the same line, the reaction proceeded satisfactorily without showing important influence with respect to the substitution pattern on the aryl group, maintaining excellent yields and stereoselectivities even if the

substituent is located at *ortho, meta* or *para* position (see for example entries 2-4 and entries 7-9). Moreover, heteroaryl substituents were also well tolerated (entries 12 and 13). For all the cases tested the reaction proceeded with excellent enantioselectivity, furnishing the final adducts **4a-n** as highly enantioenriched compounds. Remarkably, α,β-disubstituted nitroalkene **2n** was also found to perform excellently in the reaction (entry 14), this example showing the potential of this methodology for the generation of cyclohexenes with a quaternary stereocentre. It has to be pointed out that, as previously mentioned, the temperature of the reaction had to be carefully kept at 20ºC during all the process by using thermostatized baths, observing that when carrying out the reaction at a higher room temperature yields were significantly affected by the presence of important amounts of the corresponding fully conjugated dienal, whose formation is presumably also catalyzed by **3** through trienamine formation/hydrolysis.

<INSERT TABLE 2 HERE>

The absolute configuration was assigned by single-crystal X-ray analysis of adduct **4e** (Figure 1).[14] Accordingly to the stereostructure obtained for this compound, the configuration of all other adducts **4a-n** was established by analogy. This structure is also consistent with the one previously observed in other [4+2] reactions in which trienamine intermediates derived from linear fully conjugated dienals are participating.[11a-e]

<INSERT FIGURE 1 HERE>

In conclusion, we have demonstrated that unconjugated dienals in reactions under trienamine activation can be used as alternative substrates to the related fully conjugated α,β,γ,δ-unsaturated aldehydes in those reactions in which the later fail to react. The effect of breaking the conjugated system translates into better ability to condense with the chiral secondary amine catalyst, therefore leading to the same vinylogous trienamine intermediate which is able to react subsequently in a very efficient manner. In this report we have illustrated the potential of this new methodological approach by implementing a Diels-Alder reaction between these unconjugated dienals and nitroalkenes in which the former ones act as the electron-rich diene counterparts, leading to the formation of cyclohexene adducts resulting from the formal ε-activation of the unconjugated olefin moiety. Moreover, we have also demonstrated the ability of the catalyst to induce remote stereoinduction with the same high level of efficiency as for those cases in which fully conjugated dienals are employed.[15]

Experimental Section

General procedure for the cycloaddition reaction. Synthesis of 4a-n. The starting nitroolefin **2a-n** (0.20 mmol) was added to a solution of **3** (0.04 mmol) and **1** (0.26 mmol) in toluene (2 mL) in an ordinary vial equipped with a magnetic stirring bar. The reaction mixture was stirred at 20 ºC for 12 hours, after which the crude reaction mixture was concentrated, directly charged onto silica gel and subjected to flash chromatography (hexane/AcOEt gradient from 19:1 to 9:1) affording the corresponding tetrasubstituted cyclohexenyl adduct **4a-n.**.

Acknowledgements

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[13]   Other conditions and catalysts were also tested but in all cases unreactive starting materials were recovered.

[14]   CCDC 971642 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[15]   During the submission process of this manuscript a recent paper appeared detailing the use of unconjugated dienones as active substrates in trienamine catalysis in one example of a hetero Diels-Alder reaction under inverse electron demand: X. Feng, Z. Zhou, C. Ma, X. Yin, R. Li, L. Dong, Y.-C. Chen. *Angew. Chem. Int. Ed.* **2013**, DOI: 10.1002/anie.201307460
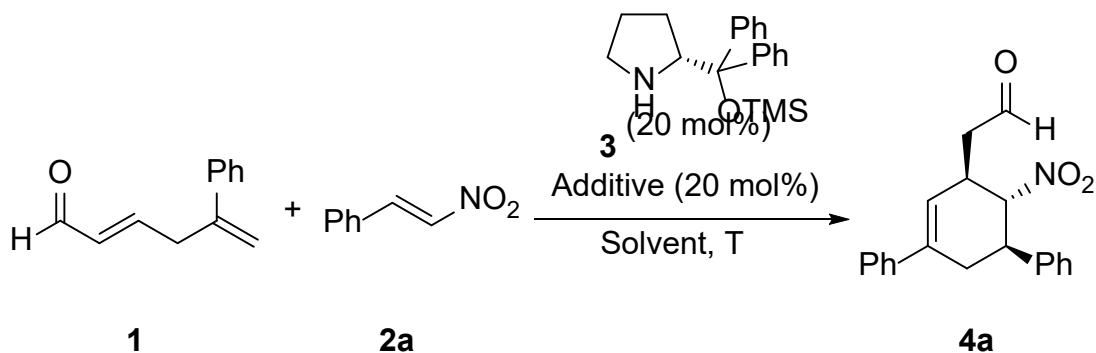
Legends

Scheme 1. Conjugated *vs* unconjugated dienals as substrates for organocatalytic reactions *via* trienamine intermediates.

Scheme 2. Proof of concept experiments.

Figure 1. X-ray structure of **4e**.

Tables

Table 1. Optimization of experimental conditions using the reaction between **1** and **2a** as model system.[a]

Entry	Solvent	Additive	T [ºC]	Yield [%][b]	dr[c]	ee [%][d]
1	CHCl3	PhCO2H	20	47	>10:1	92
2	CH2Cl2	PhCO2H	20	20	>10:1	93
3	THF	PhCO2H	20	8	n.d. [e]	n.d. [e]
4	Toluene	PhCO2H	20	66	>10:1	93
5	Toluene	4-NO2C6H4CO2H	20	27	n.d. [e]	n.d. [e]
6	Toluene	4-MeOC6H4CO2H	20	41	n.d. [e]	n.d. [e]
7	Toluene	4-FC6H4CO2H	20	53	n.d. [e]	n.d. [e]
8	Toluene	NaOAc	20	96	>10:1	90
9	Toluene	DBU	20	<5	-	-
10	Toluene	DABCO	20	<5	-	-
11	Toluene	none	20	99	>10:1	94
12	Toluene	none	4	67	>10:1	91
13	Toluene	none	30	61	>10:1	64

[a] Reactions were carried out in a 0.2 mmol scale of **1** and **2a** using 20 mol% of catalyst **3** in 2.0 mL of solvent at the specified temperature for 12h. [b] Yield of isolated product **4a** after flash column chromatography purification. [c] Determined by ^{1}H-NMR spectroscopy of crude reaction mixture. [d] Determined by HPLC (see supporting information). [e] n.d.: not determined.

Table 2. Scope of the reaction.[a]

Entry	Product	R^1	R^2	Yield (%)[b]	dr[c]	ee (%)[d]
1	**4a**	Ph	H	99	13:1	94
2	**4b**	4-MeOC$_6$H$_4$	H	93	>20:1	93
3	**4c**	3-MeOC$_6$H$_4$	H	91	16:1	90
4	**4d**	2-MeOC$_6$H$_4$	H	92	12:1	97
5	**4e**	4-MeC$_6$H$_4$	H	85	19:1	92
6	**4f**	4-BnOC$_6$H$_4$	H	98	16:1	96
7	**4g**	4-ClC$_6$H$_4$	H	99	14:1	90
8	**4h**	3-ClC$_6$H$_4$	H	94	12:1	93
9	**4i**	2-ClC$_6$H$_4$	H	88	14:1	96
10	**4j**	4-BrC$_6$H$_4$	H	92	13:1	96
11	**4k**	2-BrC$_6$H$_4$	H	81	13:1	92
12	**4l**	2-thienyl	H	87	13:1	97
13	**4m**	2-furyl	H	80	>20:1	89
14	**4n**	Ph	Me	64	16:1	96

[a] Reactions were carried out in a 0.2 mmol scale of **1** and **2a-n** using 20 mol% of catalyst **3** in 2.0 mL of toluene at 20ºC for 12h. [b] Yield of pure isolated product. [c] Determined by ^{1}H-NMR spectroscopy on crude reaction mixture. [d] Determined by HPLC (see supporting information).

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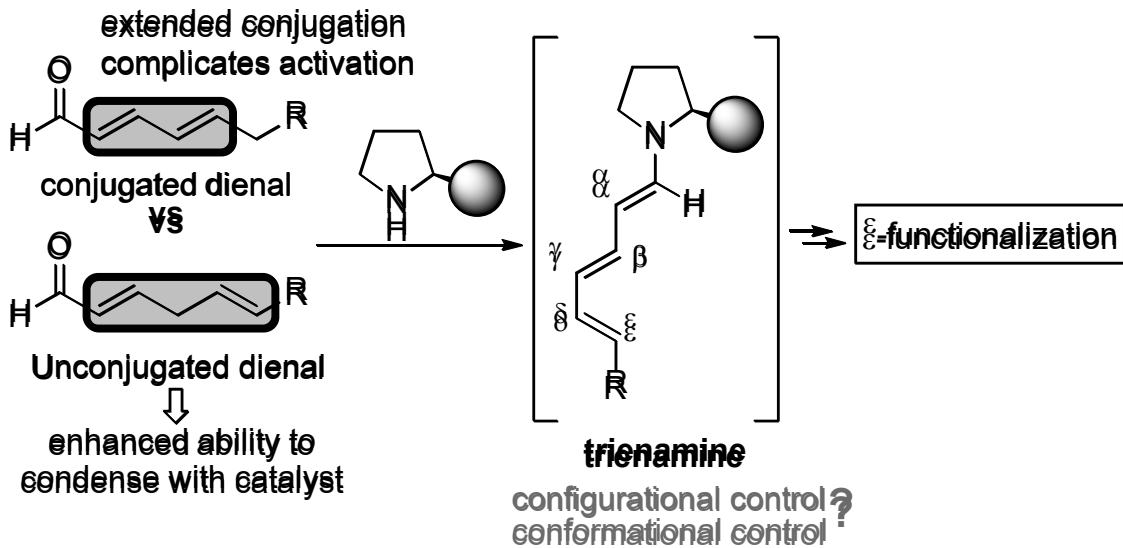
Trienaminocatalysis

Break it up!. Unconjugated 2,5-dienals are proposed to constitute more reactive substrates than the corresponding fully conjugated $\alpha,\beta,\gamma,\delta$-unsaturated aldehydes towards organocatalytic activation through trienamine intermediates. This has been demonstrated in the Diels-Alder reaction with nitroalkenes, which proceeds with clean β,ϵ-selectivity to afford the final products in high yields and stereoselectivities, while the related polyconjugated dienals were found to be completely unreactive.
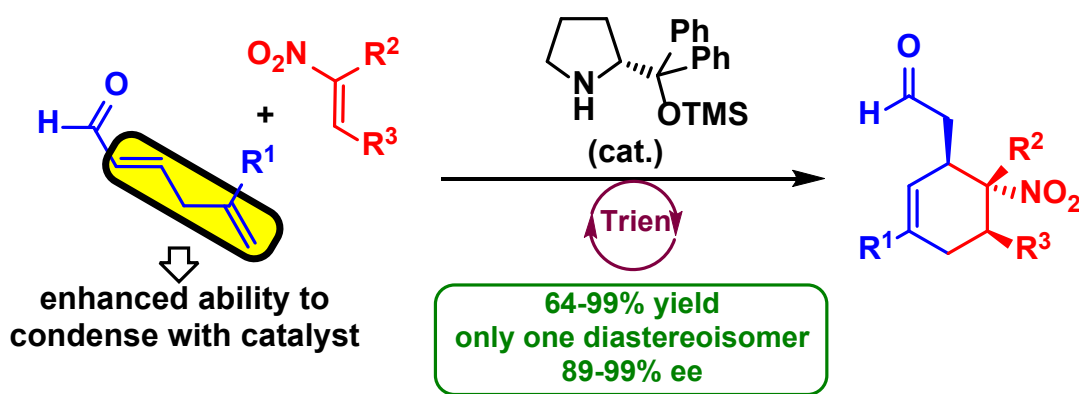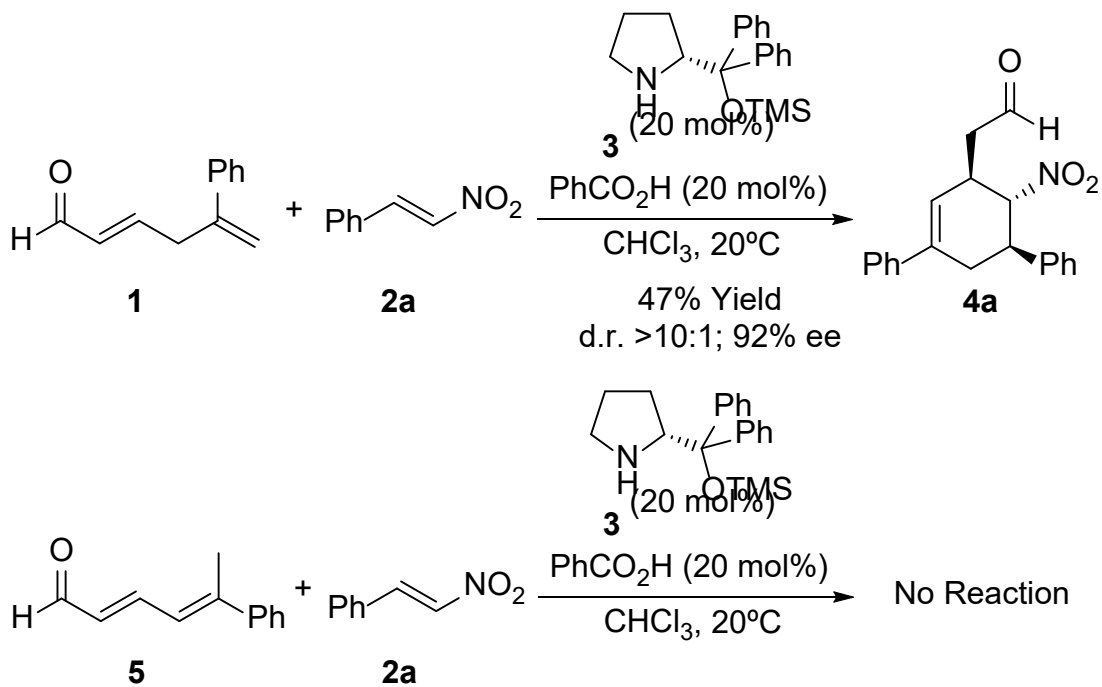

Keywords:

Asymmetric catalysis · Cycloaddition · Trienamine · Organocatalysis · Vinylogy
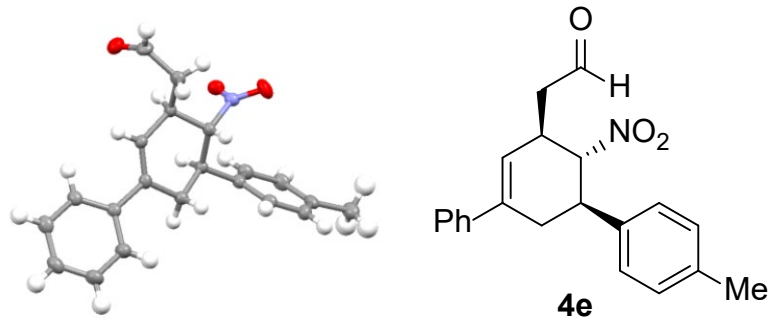
Figures and Schemes

extended conjugation
complicates activation

conjugated dienal
vs

Unconjugated dienal

⇩

enhanced ability to
condense with catalyst

trienamine

configurational control?
conformational control

ε-functionalization

<SCHEME 1>

1 + **2a**

3 (20 mol%)

PhCO$_2$H (20 mol%)

CHCl$_3$, 20°C

47% Yield
d.r. >10:1; 92% ee

4a

5 + **2a**

3 (20 mol%)

PhCO$_2$H (20 mol%)

CHCl$_3$, 20°C

No Reaction

<SCHEME 2>

<FIGURE 1>