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Catalytic enantioselective domino Michael/transannular aldol reaction under bifunctional catalysis

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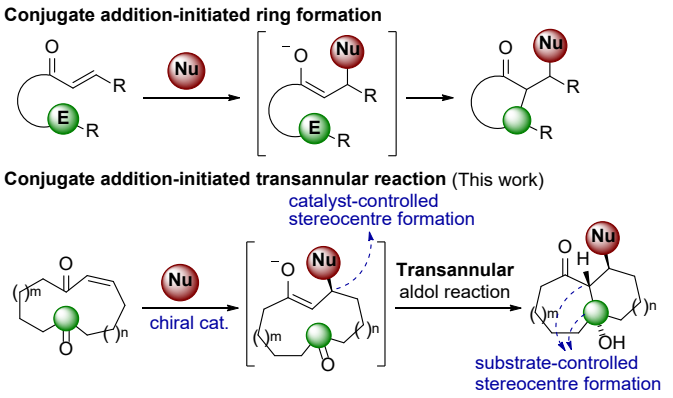
Raquel Mato,[a] Efraim Reyes,*[a] Luisa Carrillo,[a] Uxue Uria,[a] Liher Prieto,[a] Ruben Manzano[a] and Jose L. Vicario*[a]

The enantioselective Michael reaction catalyzed by a bifunctional tertiary amine/squaramide has been used to trigger a Michael/transannular aldol cascade process that leads to densely substituted bicyclo[5.4.0]undecanes and in which three contiguous stereogenic centres, one of them a tertiary alcohol moiety, have been formed in a fully stereocontrolled fashion.

Domino reactions enable the synthesis of complex molecular scaffolds from simple starting materials, minimizing the number of laboratory operations and the generation of waste.[1] In this context, the mechanistic profile of the Michael reaction stands as a very convenient platform to trigger cascade processes due to the formation of a nucleophilic enolate-type species after the conjugate addition step, which is ready to react with an external electrophile. In particular, the use of catalytic and enantioselective versions of Michael reaction-initiated domino processes[2] has become extremely useful, especially for the stereoselective construction of complex carbo- or heterocylcic scaffolds when one of the reactions participating in the domino sequence involves an intramolecular process (see Scheme 1, top).[3] As an alternative approach, we have been involved in the last years on the active development of catalytic and enantioselective transannular reactions[4] in which a polycyclic molecular framework is assembled through the reaction between two functionalities present within the annular structure of a medium- or large size cyclic starting material. In this context, while transannular reactivity has been widely used for the total synthesis of complex natural products,[5] almost all these cases involved diastereoselective reactions using a chiral enantioenriched substrate. In fact, only a small number of examples of catalytic and enantioselective transannular reactions that transform an achiral substrate into an enantioenriched product have been described in the literature up to date,[6] which also include a couple of examples from our group that make use of related ketoenone substrates that have shown to perform excellently in transannular Morita-Baylis-Hillman[7] and in borylative transannular reactions[8] under chiral phosphine and copper catalysis respectively.



Scheme 1 Methods for the sterecontrolled formation of complex cyclic frameworks.

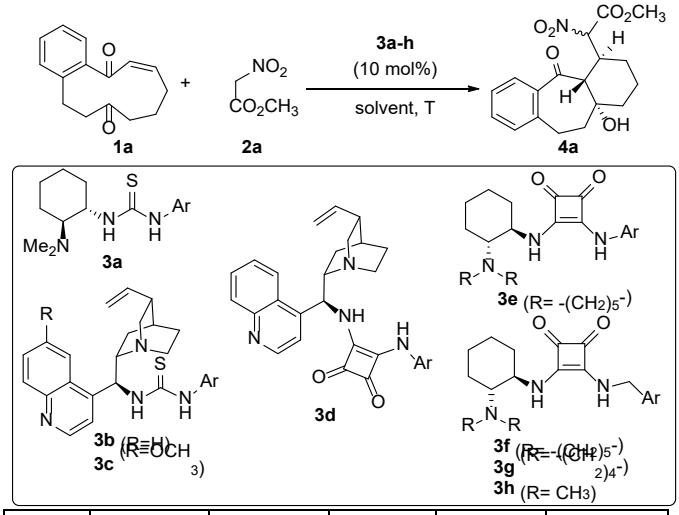
We wish to report herein the potential of the Michael reaction to trigger a transannular cascade conjugate addition/transannular aldol reaction to form complex bicyclic scaffolds in a single step from a conveniently functionalized ketoenone (Scheme 1, bottom). In addition, we envisaged that if a chiral catalyst would be able to control the stereochemical outcome of the initial conjugate addition step, the possibility for full stereochemical control of the three contiguous stereocentres formed in the overall process could be achieved assuming a highly diastereoselective transannular aldol reaction under substrate control assisted by the conformational restraints associated with this type of medium-sized cyclic structures.

We started to study this transformation using ketoenone **1a** as model substrate to optimize the projected Michael-initiated transannular aldol reaction (Table 1) and using methyl nitroacetate as a convenient Michael donor, which has been reported to be a suitable pronucleophile in a wide number of examples of Michael reactions under bifunctional tertiary amine/H-bond donor catalysis.[9] The initial results showed that bifunctional thiourea **3a**[10] was indeed able to promote the projected reaction yielding tricyclic product **4a** in an excellent

[a] *Department of Organic Chemistry II, University of the Basque Country. P. O. Box 644, 48080 Bilbao (Spain). E-mail: joseluis.vicario@ehu.es; efraim.reyes@ehu.es*
Electronic Supplementary Information (ESI) available: Characterization of all new compounds, copies of ^{1}H and ^{13}C NMR spectra, HPLC traces of all adducts prepared (PDF). Crystallographic data CCDC 2010938 (**6i**) and CCDC 2010939 (**7a**). See DOI: 10.1039/x0xx00000x

yield and with a promising 70% e.e. (entry 1). This adduct was isolated as a mixture of two epimers due to the configurational lability of the stereocentre between the nitro and the ester moieties, but with a complete control on the relative configuration of the other three contiguous stereocentres. Thioureas derived from cinchonidine (**3b**) and quinine (**3c**) performed similarly (entries 2 and 3), but modifying the hydrogen bond donor moiety of the catalyst from thiourea to squaramide[11] had a remarkably positive influence on the enantiocontrol of the reaction (entry 4). These results prompted us to evaluate the performance of a series of bifunctional tertiary amine/squaramide catalysts. For instance, benzylamine-derived squaramide **3f** turned out to be more efficient compared to the analogous aniline **3e** (entry 6 vs 5 in table 1), providing **4a** with an excellent yield and e.e.

Table 1 Optimization of the reaction (Ar=3,5-$(CF_3)_2C_6H_3$).[a]



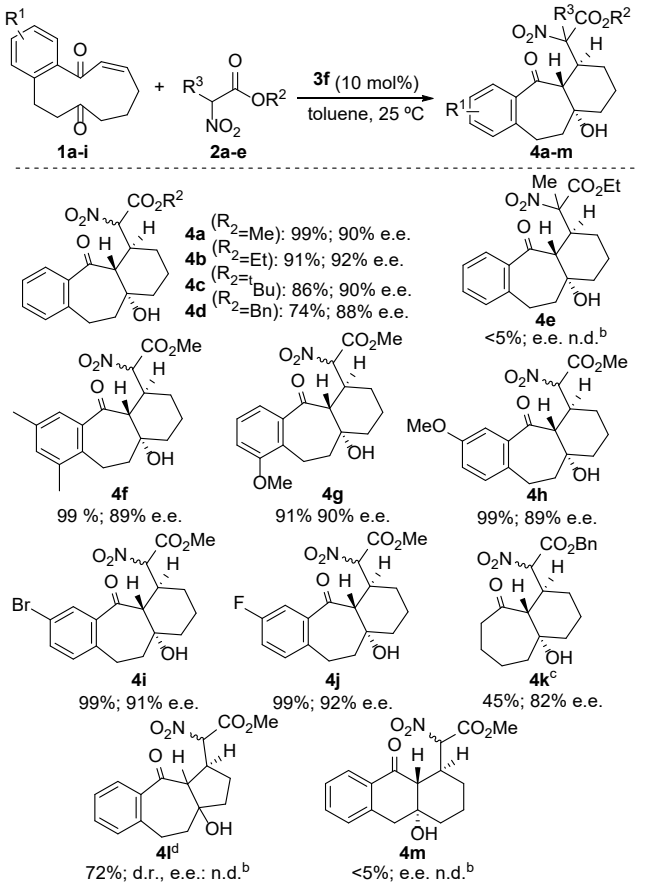
Entry	Catalyst	Solvent	T	Yield (%)[b]	e.e. (%)[c]
1	**3a**	Toluene	r.t.	90	70
2	**3b**	Toluene	r.t.	91	62
3	**3c**	Toluene	r.t.	93	68
4	**3d**	Toluene	r.t.	64	82
5	**3e**	Toluene	r.t.	70	82
6	**3f**	Toluene	r.t.	94	90
7	**3g**	Toluene	r.t.	92	84
8	**3h**	Toluene	r.t.	99	78
9	**3f**	CH_2Cl_2	r.t.	87	88
10	**3f**	THF	r.t.	86	88
11	**3f**	EtOH	r.t.	88	75
12[d]	**3f**	Toluene	0°C	90	88
13	**3f**	Toluene	40°C	90	84

[a] Reaction carried out in a 0.15 mmol scale of **1a,** employing a 10 mol% of catalyst and 3 eq. of **2a** in the indicated solvent (0.6 mL) until complete consumption of **1a** (TLC analysis, typically 48-72h). [b] Yield of pure product isolated as c.a. 2:1 mixture of epimers. [c] Determined by HPLC analysis on a chiral stationary phase for both epimers separated under conditions optimized for a racemic standard (see Supporting Information). The e.e. of both epimers was the same in all cases within experimental error. [d] Reaction run for 7 days

The influence of the substituents in the tertiary amine site of the catalysts was also evaluated by surveying catalysts **3g** and **3h** (entries 7 and 8), which also provided adduct **4a** in high yield although with a slightly inferior e.e. Finally, other experimental parameters such as the solvent or the temperature of the reaction were evaluated (entries 9-13) but without improving the initial results obtained with the conditions shown in entry 6.

Once the optimal experimental conditions were defined, we proceeded to study the scope and limitations of this process with respect to the structure of the reagents participating in the reaction (table 2). First of all, the influence of the alkoxy group on the nitroacetate reagent was evaluated. As it can be observed in table 2, the reaction proceeded well in all cases, only observing a slightly lower yield when a bulky *tert*-butyl ester was employed. Benzyl nitroacetate **2d** (R^2=Bn, R^3=H) could also be satisfactorily used, although the yield of **4d** was slightly lower. We also evaluated an α-substituted nitroacetate such as ethyl 2-nitropropionate (**2e**) as potential pro-nucleophile which would lead to a quaternary stereocentre but the expected adduct **4e** was not formed.

Table 2. Scope of the reaction



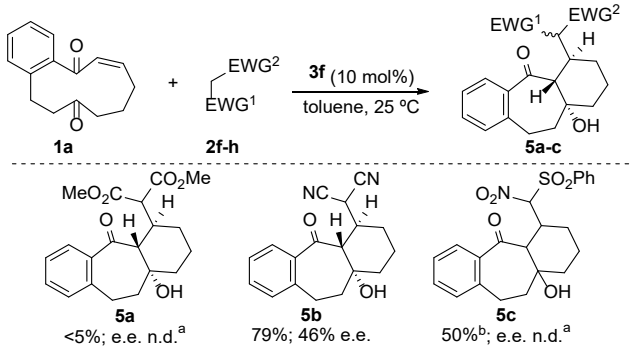
[a] Reaction carried out in a 0.15 mmol scale of **1,** with 10 mol% of **3f** and 3 eq. of **2** in toluene (0.6 mL) at r.t. until complete consumption of **1** (TLC analysis). Yields refer to pure products isolated as c.a. 2:1 mixture of epimers and e.e. was determined by HPLC analysis. The e.e. of both epimers was the same in all cases within experimental error. [b] n.d. Not determined. [c] 20 mol% of **3f** was used. [d] Adduct **4m** was isolated as a complex mixture of diastereoisomers.

Regarding the substitution in the aromatic ring of the keto-enone substrate, both electron-donating and electron-withdrawing groups at different positions were well tolerated, isolating the tricyclic adducts **4f-j** in excellent yields and

enantioselectivities. On the other hand, we also surveyed the performance of keto-enone **1d**, which does not contain a fused arene moiety. In this case, the reaction was much slower and required a higher 20 mol% catalyst loading to provide the adduct **4k** in moderate yield and 82% e.e. Finally, the possibility of generating products with different ring sizes was evaluated. The reaction using a 10-membered ketoenone substrate (**1h**) led to **4l** in good yield, but as a complex mixture of several diastereoisomers that could not be separated. When we attempted the reaction leading to benzodecalone adduct **4m**, only starting material was recovered.

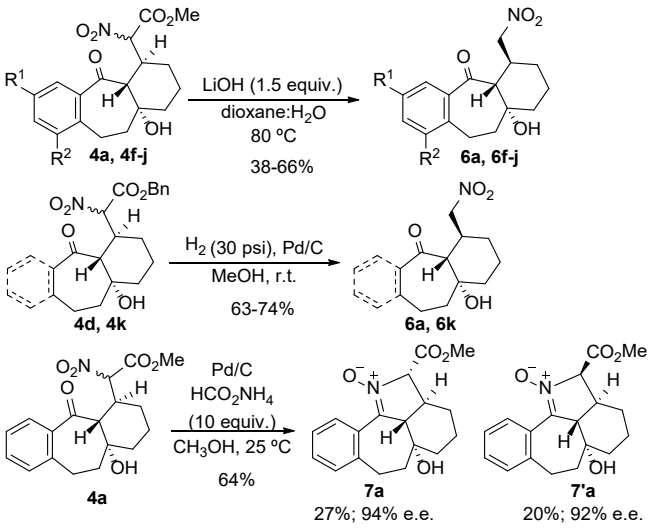
On the other hand, we also decided to evaluate the performance of other active methylene compounds as pronucleophiles under the optimized reaction conditions (Table 3). Dimethylmalonate **2f** did not lead to the formation of the desired product **5a** but when malononitrile was subjected to the optimized conditions, adduct **5b** was isolated in 79% yield as a single diastereoisomer, although with moderate e.e. In the same way, nitromethyl phenyl sulfone **2h** exhibited the desired reactivity leading to the formation of **5c** in 50% yield, although as a complex mixture of diastereoisomers.

Table 3. Cascade Michael reaction/transannular aldol using other pronucleophiles.



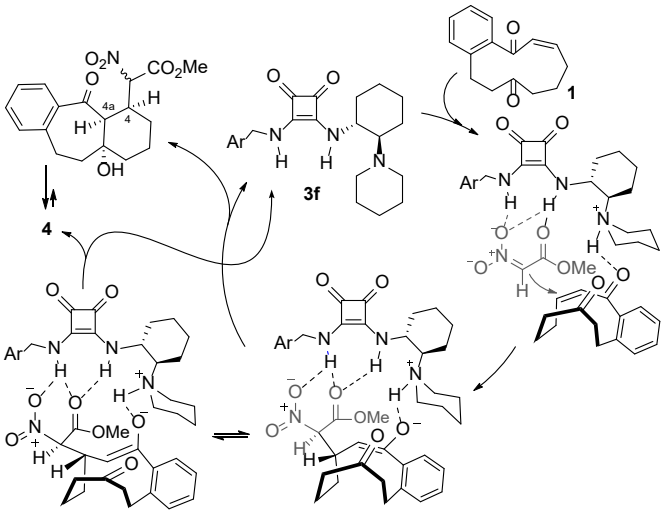
[a] n.d. Not determined. [b] Adduct **5c** was isolated as a complex mixture of diastereoisomers.

We also explored the potential of the obtained adducts to be modified into other useful building blocks. Base hydrolysis followed by thermal decarboxylation delivered compounds **6a** and **6f-j** as single diastereoisomers in good yields.[12] Compound **6a** could also be obtained by hydrogenolysis of the corresponding benzylic ester **4d** which underwent spontaneous decarboxylation[13] and the same conditions could be successfully applied to adduct **4k**. On the other hand, reduction of substrate **4a** using ammonium formate and Pd/C led to the formation of epimeric nitrones **7a** and **7'a** after partial reduction of the nitro moiety followed by intramolecular condensation, which could be isolated separately as highly enantioenriched compounds.[14]



Scheme 2. Chemical modifications carried out on adducts **4**.

A plausible mechanistic pathway for the reaction is depicted in Scheme 3. We propose that the initial Michael reaction catalyzed by **3f** takes place following the generally accepted model described in the literature.[15] Considering this reaction as the stereodefining step of the process, we propose that the subsequent formation of the other two stereocentres takes place under substrate control. However, it is noteworthy that the experimentally observed diastereoselectivity shows a *trans* relative orientation between hydrogen atoms at positions C4 and C4a in the final product. Considering the initial *cis* configuration of α,β-unsaturated system, two plausible scenarios have been contemplated in order to explain this fact: (a) *Z*/*E* isomerization of the generated enolate (either by direct isomerization and/or by retro-aldol process) and (b) epimerization of the proton at position C4a under the reaction conditions.



Scheme 3. Proposed mechanism and model for the stereochemical outome of the reaction

In conclusion, keto/enones of the general structure shown for compounds **1** are outstanding substrates to undergo a cascade process initiated by a Michael reaction and followed by

a transannular reaction that enables the formation of complex polycyclic scaffolds in a direct and straightforward way. Bifunctional tertiary amine/squaramide catalyst **3f** ensures that the initial Michael reaction step of the cascade proceeds with high enantiocontrol, which is subsequently transferred to the subsequent transannular reaction, in which the conformational restraints associated to the 11-membered medium-sized enolate intermediate also contribute to the excellent diestereoselectivity observed for the overall cascade process. This reaction consists on an excellent synthetic approach to stereodefined bicyclo[5.4.0]undecanes containing three contiguous stereogenic centres, one of them a tertiary alcohol moiety with high diastereo- and enantioselectivity.

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Conflicts of interest

There are no conflicts to declare.

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