

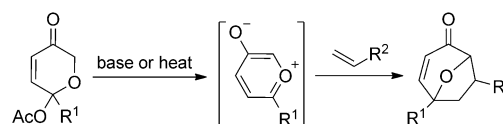
Catalytic Enantioselective [5+2] Cycloaddition between Oxidopyrylium Ylides and Enals under Dienamine Activation**

Ane Orue, Uxue Uria, Efraim Reyes,* Luisa Carrillo, and Jose L. Vicario*

Abstract: Benzopyrylium ylides generated in situ from 1-acetoxyisochroman-4-ones reacted with α,β -unsaturated aldehydes in the presence of a bifunctional secondary-amine/squaramide catalyst to furnish [5+2] cycloaddition products in good yield with high diastereo- and enantioselectivity. The reaction proceeds by dienamine activation and involves β,γ -functionalization of the enal. The dienamine intermediates showed exclusive β,γ -reactivity and provided direct access to compounds with the 8-oxabicyclo[3.2.1]octane framework. The ability of the bifunctional secondary-amine/squaramide catalyst to engage in hydrogen-bonding interactions with the ylide made it particularly effective in terms of both the yield and the stereoselectivity of the transformation.

Cycloaddition reactions are among the most important transformations in synthetic organic chemistry, as they constitute a direct approach to complex (poly)cyclic architectures from conveniently designed starting materials.^[1] Moreover, the stereospecificity associated with reactions of this type makes them appropriate candidates for stereocontrolled processes. Whereas the archetypal Diels–Alder reaction^[2] and some particular 1,3-dipolar cycloaddition reactions^[3] have been studied extensively, other less common reactions have been investigated to a far lesser extent, as in the case of the [5+2] cycloaddition between oxidopyrylium ylides and alkenes,^[4] which is one of the best synthetic approaches to the 8-oxabicyclo[3.2.1]octane scaffold, a key structural feature of a variety of natural products and bioactive compounds. The method used for the generation of the oxidopyrylium ylide is crucial for the success of this reaction. Typically, the ylide is formed by thermal or base-promoted elimination from a 6-acetoxy-2H-pyran-3(6H)-one precursor (Scheme 1).^[5]

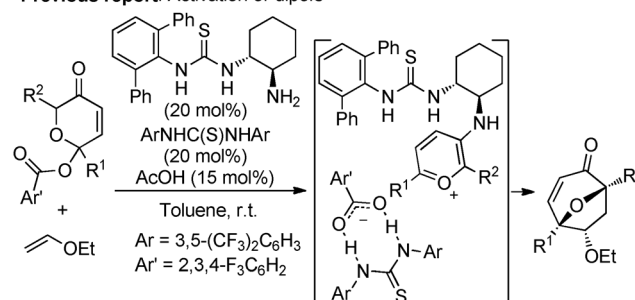
However, despite the potential of such transformations, methods reported for the asymmetric [5+2] cycloaddition of oxidopyrylium ylides are limited to diastereoselective variants: either reactions of substrates with backbone chirality^[6] or reactions involving the use of chiral auxiliaries.^[7] More-



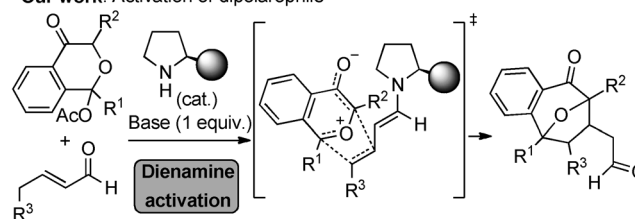
Scheme 1. Generation of oxidopyrylium ylides from 6-acetoxy-2H-pyran-3(6H)-ones and their [5+2] cycloaddition with alkenes.

over, most reported studies have dealt with intramolecular reactions and very few have been focused on intermolecular versions.^[8] The only enantioselective version described to date is the recently reported approach by Jacobsen and co-workers, who used a bifunctional primary amine/thiourea catalyst and generated the pyrylium ylide dipole from a 6-benzoyloxypyranone derivative by condensation with the aminocatalyst (Scheme 2).^[9] As an alternative, we propose herein the use of chiral secondary amines as catalysts for the [5+2] cycloaddition between α,β -unsaturated aldehydes and oxidopyrylium ylides on the basis of dienamine activation (Scheme 2).^[10] We propose that such a dienamine intermediate formed after condensation of the enal with the catalyst could play the role of a suitable electron-rich alkene, which might participate as a chiral dipolarophile in a reaction with oxidopyrylium ylides generated in situ from a conveniently substituted acetoxy-pyranone in the presence of a Brønsted

Previous report: Activation of dipole



Our work: Activation of dipolarophile



Scheme 2. Catalytic enantioselective intermolecular [5+2] cycloaddition reactions with oxidopyrylium ylides as dipoles.

[*] A. Orue, Dr. U. Uria, Prof. E. Reyes, Prof. L. Carrillo, Prof. J. L. Vicario
Department of Organic Chemistry II
University of the Basque Country (UPV/EHU)
P.O. Box 644, 48080 Bilbao (Spain)
E-mail: efraim.reyes@ehu.es
joseluis.vicario@ehu.es
Homepage: <http://www.ehu.es/GSA>

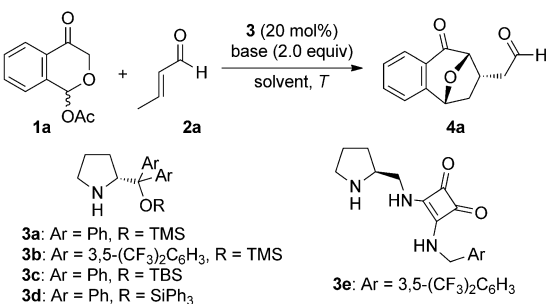
[**] We thank the Spanish MINECO (CTQ2011-22790 and Juan de la Cierva contract to U.U.), the Basque Government (IT328-10, OSALAN14/02, and fellowship to A.O.), and UPV/EHU (UFI QOSYC 11/22 and EHUA12/09) for financial support.

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base. The chiral information at the secondary-amine catalyst would be responsible for differentiation of the enantiotopic faces of the dipolarophile, and the diastereoselectivity of the process should be controlled by the fixed geometry of the dienamine and the oxidopyrylium ylide.

We started our study by surveying the viability of the reaction by using benzopyranone **1a** and crotonaldehyde (**2a**) as a model system (Table 1).^[11] We first surveyed a range of Brønsted bases for the generation of the ylide in the presence

Table 1: Optimization of the experimental conditions.



3a: Ar = Ph, R = TMS
3b: Ar = 3,5-(CF₃)₂C₆H₃, R = TMS
3c: Ar = Ph, R = TBS
3d: Ar = Ph, R = SiPh₃
3e: Ar = 3,5-(CF₃)₂C₆H₃

Entry	Catalyst	Base	Solvent	T [°C]	Yield [%] ^[a]	ee [%] ^[b]
1	3a	Et ₃ N	THF	RT	19	70
2	3a	DMAP	THF	RT	17	76
3	3a	DBU	THF	RT	20	67
4	3a	DABCO	THF	RT	40	78
5 ^[c]	3a	DABCO	THF	RT	64	84
6 ^[c]	3a	DABCO	toluene	RT	42	86
7 ^[c]	3a	DABCO	CHCl ₃	RT	54	75
8 ^[c]	3a	DABCO	AcOEt	RT	45	80
9 ^[c]	3b	DABCO	THF	RT	< 5	—
10 ^[c]	3c	DABCO	THF	RT	55	87
11 ^[c]	3d	DABCO	THF	RT	65	83
12 ^[c]	3e	DABCO	THF	RT	73	93
13 ^[c]	3e	DABCO	THF	10	91	96
14 ^[c,d]	3e	DABCO	THF	10	92	97

[a] Yield of the pure product. [b] The ee value was determined by HPLC analysis on a chiral stationary phase (see the Supporting Information). [c] H₂O (3.0 equiv) was used as an additive. [d] The reaction was carried out with 8 mol % of the catalyst and 1.5 equivalents of DABCO. DABCO = 1,4-diazabicyclo[2.2.2]octane, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DMAP = N,N-dimethylaminopyridine, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.

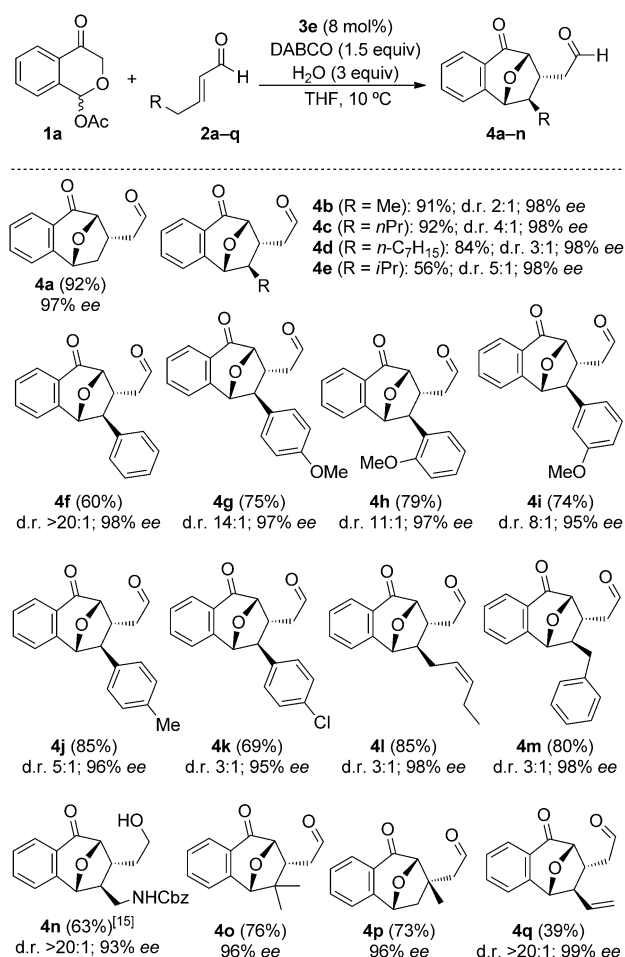
of the archetypal *O*-TMS-substituted diphenylprolinol **3a** (Table 1, entries 1–4), which is recognized as a reliable catalyst for the activation of enolizable enals via dienamine intermediates.^[12] Whereas Et₃N, DMAP, and DBU performed very poorly (Table 1, entries 1–3), a cleaner reaction was observed with DABCO (entry 4). In all cases, cycloadduct **4a** was isolated as a single diastereoisomer, albeit with moderate enantioselectivity. Importantly, the addition of water (3.0 equiv), which most likely facilitates catalyst turnover, was observed to be very beneficial, especially in terms of the yield of the reaction (Table 1, entry 5).

The influence of several solvents on the performance of the reaction was also studied (Table 1, entries 5–8), and we observed that the use of a less polar solvent, such as toluene

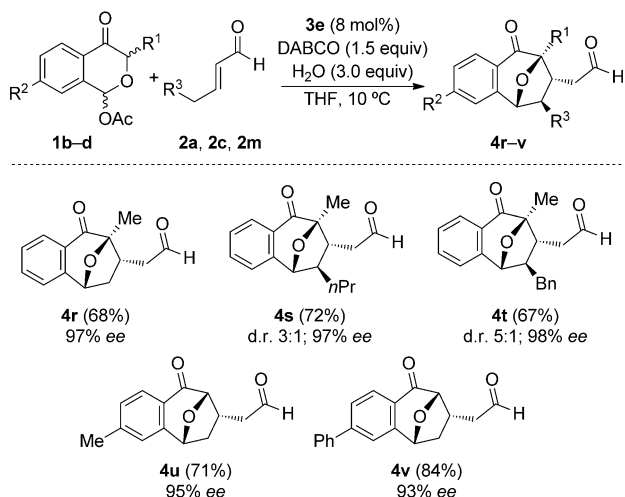
(entry 6), led to a decrease in the yield, thus indicating the necessity of a polar medium for the stabilization of the dipole intermediate. Other polar solvents did not improve the results previously obtained with THF. We next evaluated several variations of the catalyst architecture and observed that catalyst **3b** was completely inactive (Table 1, entry 9), whereas bulkier catalysts **3c** and **3d** only provided a slight improvement in the enantioselectivity but furnished **4a** in moderate yield (entries 10 and 11). Remarkably, the use of a pyrrolidine–squaramide bifunctional catalyst developed by Jørgensen and co-workers^[13] resulted in a significant improvement in both yield and enantioselectivity (Table 1, entry 12), which was further increased by carrying out the reaction at 10°C (entry 13). We could even decrease the catalyst loading to 8 mol % of **3e** and the amount of base used without any negative effect on the yield or stereoselectivity (Table 1, entry 14). The reaction promoted by **3e** furnished **4a** with the same absolute configuration as that observed for the reaction catalyzed by diaryl prolinol derivatives **3a–d**, in which case the configuration of the stereocenter at the pyrrolidine moiety is the opposite to that in **3e**. This result points to the participation of **3e** as a bifunctional catalyst that directs the approach of the ylide through hydrogen-bonding interactions, whereas **3a–d** induce face selectivity through the steric lock of one of the stereotopic faces of the dienamine intermediate.

Having established a robust experimental protocol for the reaction, we next proceeded to explore other α,β -unsaturated aldehydes with different substitution patterns (Scheme 3). We investigated the use of enals other than crotonaldehyde for the formation of cycloadducts **4** with an additional stereocenter. In all cases, the reaction proceeded satisfactorily to provide the corresponding cycloadduct **4** in good yield with moderate to high diastereoselectivity and excellent enantioselectivity (> 93 % ee in all cases).^[14] Aliphatic enals were good substrates regardless of the length of the alkyl substituent (compounds **4b–e**), although a slightly inferior yield was observed when the steric bulk of this substituent was increased (compound **4e**). β -Benzyl-substituted enals were also excellent substrates: Products **4f–k** were formed in good yield with good diastereo- and enantioselectivity regardless of the electronic nature of the aromatic ring and the position of the substituent. Some success was observed with functionalized enals, thus showing the functional-group compatibility of the methodology (compounds **4l–n**).^[15] The reaction also performed well with the more challenging substrates 4-methyl-2-pentenal and itaconaldehyde, which were converted into **4o** and **4p** in high yield with high enantioselectivity. Finally, we tested 2,4-hexadienal (**2q**), which could present regioselectivity problems owing to the additional possibility for the trienamine intermediate generated after organocatalytic activation to show δ,ϵ -reactivity. The expected dienamine-mediated cycloaddition gave **4q** with excellent diastereo- and enantioselectivity, albeit in moderate yield, without the formation of any of the by-product that would arise from δ,ϵ -attack on the dienal.

We tested several other pyranones in the reaction (Scheme 4). In particular, the sterically congested methyl-substituted benzopyranone **1b** reacted efficiently with several representative α,β -unsaturated aldehydes to furnish adducts

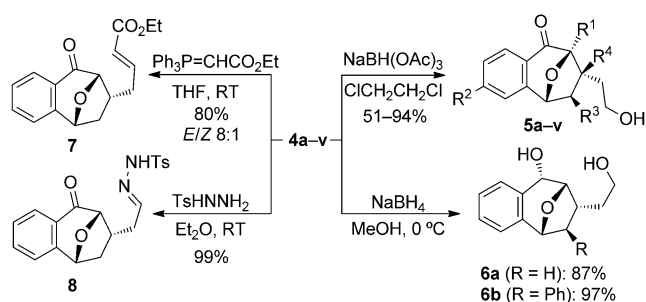


Scheme 3. Scope of the reaction. Cbz = benzyloxycarbonyl.



Scheme 4. Use of different benzopyranones. Bn = benzyl.

4r–t containing a quaternary stereocenter in good yield and with good diastereo- and enantioselectivity. Pyranones **1c** and **1d** with different substituents on the aromatic moiety were transformed efficiently into compounds **4u** and **4v**.



Scheme 5. Chemical manipulation of adducts **4**. Ts = *p*-toluenesulfonyl.

Finally, we surveyed the reactivity of the obtained adducts to illustrate their potential application as chiral building blocks in organic synthesis (Scheme 5). For example, selective reduction of the formyl moiety was possible with NaBH(OAc)₃ as the reducing agent, whereas the use of NaBH₄ led to the reduction of both the formyl and the ketone group. The latter reaction proceeded with complete diastereoselectivity, as shown by two representative examples. The reactivity of the formyl group towards hydrazone formation and Wittig olefination was also addressed with success. The absolute stereostructure of the cycloadducts prepared was established by single-crystal X-ray analysis of the diol **6b**;^[16] the configuration found was extended to other adducts **4** by analogy. This result is consistent with the stereochemical outcome observed in other reactions in which catalyst **3e** has been used with α,β -unsaturated aldehydes under dienamine activation.^[13,17] The absolute stereostructure of the minor diastereoisomers was also established by X-ray crystallography, in this case after isolation and crystallization of the minor diastereoisomer obtained in the reaction that furnished cycloadduct **4b**.^[16]

In conclusion, we have demonstrated that the HOMO-raising effect associated with the catalytic formation of dienamines can be applied to the [5+2] cycloaddition of α,β -unsaturated aldehydes with oxidopyrylium ylides generated in situ from 1-acetoxyisochroman-4-ones. These dienamine intermediates show exclusive β,γ -reactivity^[18] and provide direct access to compounds with the 8-oxabicyclo-[3.2.1]octane framework in high yield with high diastereo- and enantioselectivity. In particular, the use of a bifunctional secondary-amine/squaramide catalyst able to engage in hydrogen-bonding interactions with the ylide was found to be particularly effective in terms of chemical efficiency and stereoselectivity.

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- [15] Compound **4n** was isolated as an equilibrating mixture of the hemiaminal and the corresponding open-chain isomer. It was therefore subjected to chemoselective reduction (NaBH(OAc)₃) to the corresponding primary alcohol after isolation. The overall yield for the two steps is given in Scheme 3.
- [16] See the Supporting Information for details. CCDC 1032323 and 1032366 contain 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.
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