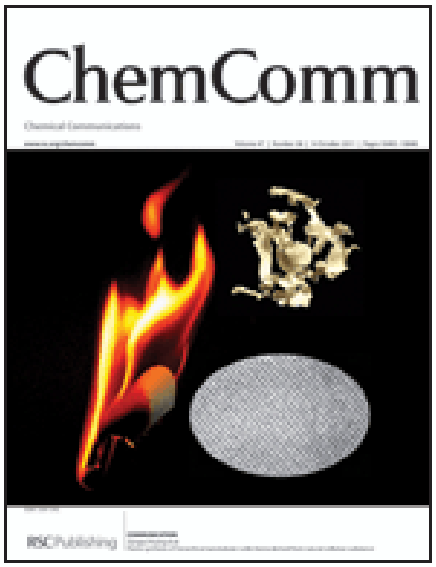

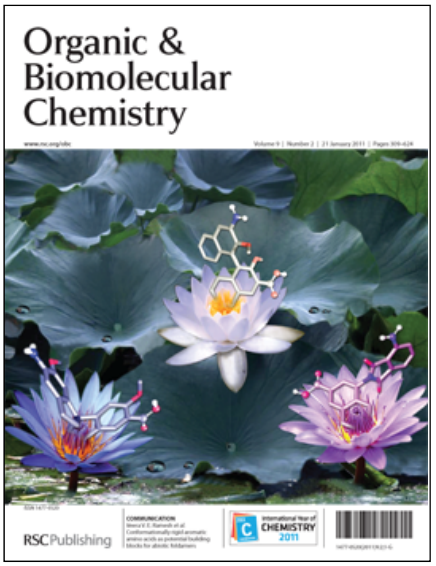

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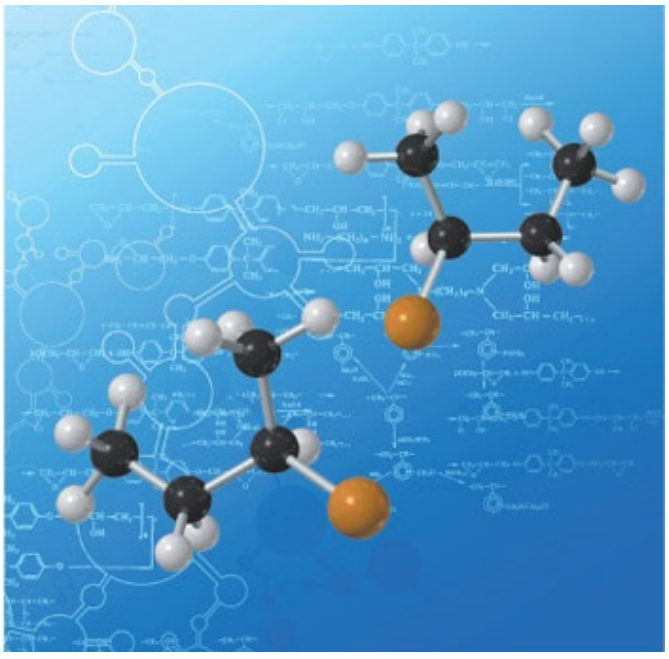

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COMMUNICATION

Organocatalytic enantioselective (3 + 2) cycloaddition using stable azomethine ylides†‡

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We have developed a highly efficient procedure for carrying out the catalytic enantioselective (3 + 2) cycloaddition between enals and stable azomethine ylides such as isoquinolinium and phthalizinium methylides. Under the optimized reaction conditions highly substituted chiral pyrroloisoquinolines and pyrrolophthalazines have been obtained in high yields and excellent diastereo- and enantioselectivities.

The (3 + 2) cycloaddition reaction between alkenes and azomethine ylides is one of the most powerful and direct methodologies for the preparation of polysubstituted pyrrolidines,[1] which is a structural architecture present in many natural products. In particular, the catalytic enantioselective version of this transformation shows up as a highly attractive approach for building up this heterocyclic moiety in a stereocontrolled way.[2] In this context, several metal-based catalytic systems have been developed which allow carrying out this reaction with excellent levels of stereocontrol. In addition to this approach, the advent of organocatalysis has also contributed to the field with some examples which show the excellent performance exhibited by small organic molecules to promote this transformation by activating the dipole or the dipolarophile by means of H-bonding interactions or by iminium ion formation.[3]

However, despite all these efforts, all the methodologies reported up to date have focused on the use of α-imino esters as azomethine ylide precursors,[2,3] being these usually unstable species generated *in situ* in the reaction medium by means of a deprotonation/metallation sequence in the metal-catalyzed reactions or, alternatively, by a prototropy process in the related organocatalytic versions. Surprisingly, the use of iminium methylide reagents as 1,3-dipoles in catalytic enantioselective (3 + 2) cycloadditions still remains elusive in the chemical literature even though their ability to participate as 1,3-dipoles in other examples which proceed in a non-enantioselective fashion is well documented.[4] It should also be pointed out that many examples of compounds of this type have been prepared and isolated and are known to be stable reagents that can be handled without special precautions.

With these precedents in mind, we decided to survey the use of isoquinolinium and phthalizinium methylides in the organocatalytic enantioselective (3 + 2) cycloaddition reaction with α,β-unsaturated aldehydes using a chiral secondary amine as catalyst (Fig. 1). This reaction was initially developed for the first time in our laboratories using α-iminomalonates as azomethine ylide precursors and relies on the ability of the secondary amine catalyst to activate the dipolarophile by reversible iminium ion formation.[5] The use of this particular class of stable azomethine ylides proposed herein would open a direct and highly modular way for the stereoselective preparation of pyrroloisoquinolines and pyrrolophthalazines which is a structure present in several useful compounds with applications as therapeuticals or in materials chemistry.[6]

We started using the reaction between isoquinolinium-2-dicyanomethylide[7] and crotonaldehyde, as a representative model system in which we could optimize the different experimental parameters (Table 1). We initially tested the conditions

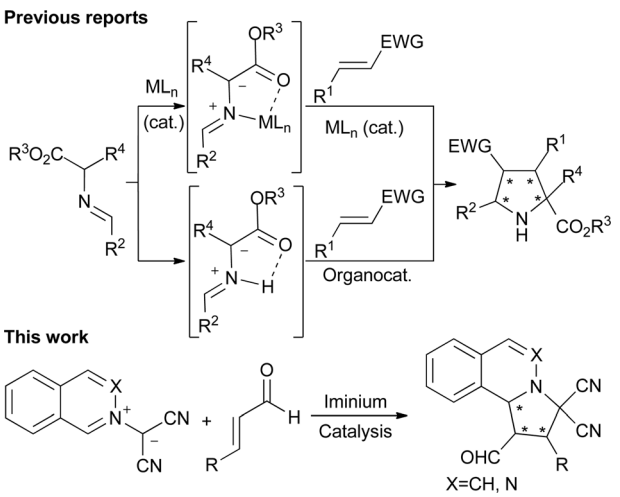

Fig. 1 The different approaches reported for catalytic enantioselective (3 + 2) cycloadditions through *in situ* formation of azomethine ylide and the use of stable isoquinolinium/phthalizinium methylides studied herein.

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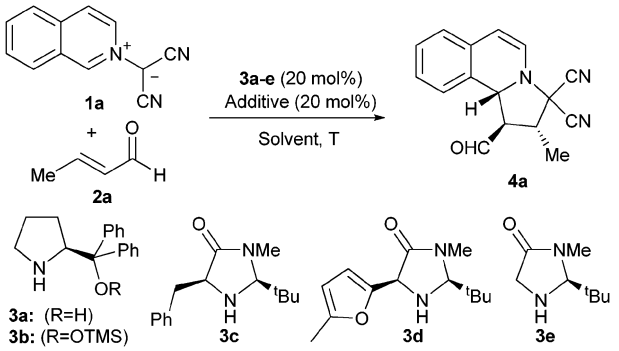
‡ Electronic supplementary information (ESI) available: Experimental procedures, characterisation of all new compounds, copies of ^{1}H and ^{13}C-NMR spectra and chiral HPLC traces. Crystal data file for compound **4d** is also provided. CCDC 844312. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15671c

Table 1 Screening for the best reaction conditions



Entry	Catalyst	Additive	Solvent	T/°C	Yield[a] (%)	*endo*/*exo*[b]	ee[c] (%)
1	**3a**	H_2O[d]	THF	r.t.	52	47 : 53	82
2	**3a**	—	THF	r.t.	38	45 : 55	83
3	**3b**	$PhCO_2H$	THF	r.t.	83	80 : 20	20
4	**3c**	TFA	THF	r.t.	87	88 : 12	88
5	**3d**	TFA	THF	r.t.	32	71 : 28	46
6	**3e**	TFA	THF	r.t.	33	> 95 : < 5	44
7	**3c**	TFA	Et_2O	r.t.	64	67 : 33	88
8	**3c**	TFA	1,4-Dioxane	r.t.	66	83 : 17	74
9	**3c**	TFA	Toluene	r.t.	36	77 : 23	68
10	**3c**	TFA	$CHCl_3$	r.t.	50	> 95 : < 5	38
11	**3c**	TFA	CH_3CN	r.t.	31	77 : 33	16
12	**3c**	TFA	DMF	r.t.	40	83 : 17	8
13	**3c**	TFA	EtOH	r.t.	80	99 : 1	46
14	**3c**	TFA	THF	4	57	82 : 18	87
15	**3c**	TFA	THF	−30	53	94 : 6	88
16	—	—	THF	r.t.	40	< 5 : > 95	—
17	—	TFA	THF	r.t.	70	33 : 67	—

[a] Yield of major diastereoisomer after flash column chromatography purification. [b] Determined by ^{1}H-NMR analysis of crude reaction mixture. [c] ee of pure *endo* diastereoisomer determined by HPLC (see ESI‡). [d] 4.0 equiv. of water were used as additive.

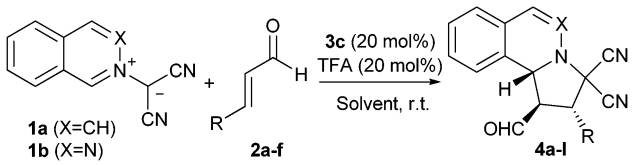
previously used in our initial report which comprised the use of **3a** as catalyst in the presence of 4 equiv. of water as an additive in THF at r.t. (entry 1)[5] but in this case the reaction proceeded with moderate yield, furnishing an almost 1 : 1 mixture of *endo*/*exo* diastereoisomers with the *endo* isomer being formed in 82% ee.[8] The reaction in the absence of water performed similarly in terms of stereocontrol but with a poorer chemical yield (entry 2). We next switched to the use of derivative **3b** (entry 3), which was employed together with a Brønsted acid co-catalyst.[9] In this case, a cleaner reaction occurred but the enantioselectivity of the major *endo* cycloadduct resulted affected. We next evaluated the performance of catalyst **3c** in the presence of TFA as co-catalyst (entry 4), a combination that had proven its efficiency in the (3 + 2) cycloaddition between nitrones and enals,[10] observing that this system performed very well with respect to the *endo*-selectivity control and furnished cycloadduct **4a** in good yield and a promising 88% ee. It should be stressed that, under these conditions, a remarkably fast reaction occurred, observing that all the starting material had been consumed after 30 min, in deep contrast with the other experiments involving proline-based catalysts **3a** and **3b** for which typically 3–4 days were required to bring the reaction to completion. Other related imidazolidinone catalysts were also tested (entries 5 and 6) but without observing any significant improvement when the overall efficiency of the reactions in terms of yield, *endo* selectivity and/or enantioselectivity is considered as a whole.

We continued our work with the identification of the best solvent for the reaction (entries 7–13). As it can be seen in the table, in general ethereal solvents were found to be the most efficient ones in terms of enantioselectivities (entries 4, 7 and 8), still observing that THF was the most appropriate one in terms of both chemical efficiency and stereoselectivity (entry 4). In general, the reaction proceeded with significantly lower enantioselectivity with the other solvents employed (entries 9–13). We also evaluated the temperature of the reaction observing that, working at 4 °C furnished cycloadduct **4a** with lower yield and similar diastereo- and enantioselectivity (entry 14) for a longer reaction time (4 days) and that carrying out the reaction at even lower temperature (entry 15) resulted in an improvement of the *endo*-selectivity, although the yield resulted significantly affected. After all these experiments, it was concluded that the best conditions for the reaction were those depicted in entry 4 of Table 1.

We also decided to evaluate the possible occurrence of an uncatalyzed background reaction as the origin of the loss of stereoselectivity. Interestingly, when **1a** and **2a** were stirred in THF for 4 days in the absence of any catalyst (entry 16), cycloadduct **4a** was formed in 40% yield as a single *exo* diastereoisomer. Moreover, we also observed that TFA was also able to accelerate the reaction, leading to the formation of **4a** in higher yield after 2 days, although as a mixture of diastereoisomers (entry 17). These two experiments indicate the tendency of the system to undergo reaction without any catalyst which can explain the low stereoselectivities obtained in cases in which the yield was rather high and also points towards an active role of the **3c**/TFA catalytic system to participate in the acceleration of the reaction which provides cycloadduct **4a** in good yields for a much shorter reaction time and in high *endo*-selectivity and enantioselectivity.

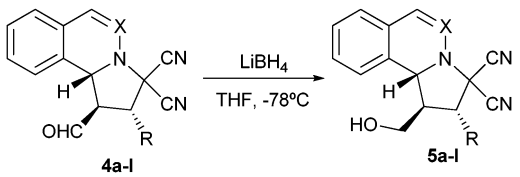
Once the best protocol for the reaction had been found, we proceeded next to evaluate the scope of the reaction with regard to the use of other α,β-unsaturated aldehydes and to the performance of phthalizinium dicyanomethylide[11] **1b** as 1,3-dipole in this transformation. As it can be seen in Table 2, the reaction proceeded in a satisfactory way in most of the cases studied, furnishing cycloadducts **4a–f** in moderate to good yields, high *endo*-selectivity and enantioselectivities in the range of 85 ≥ 99% ee.[12] The reaction tolerates well the use of different β-alkyl substituted α,β-unsaturated aldehydes, although both the yield and the diastereoselectivity of the process became importantly affected as the size of the chain increased (entries 1–3). In contrast, β-aryl substituted enals reacted efficiently regardless of the electronic nature of the aromatic ring (entries 4–6). It should be noted that, when phthalizinium dicyanomethylide **1b** was employed using **2a** as dipolarophile, cycloadduct **4g** was isolated with good yield but as a 3 : 2 mixture of diastereoisomers (entry 7). Nevertheless, the major *endo* isomer was isolated as a highly enantioenriched material. This led us to survey modified conditions in order to improve this result and, after several attempts, it was found that the reaction proceeded in a very efficient manner by changing to toluene as solvent (entry 8). These conditions were further extended to other α,β-unsaturated aldehydes **2b–f** with the same general behavior as that observed for **1a** but obtaining, in general, a better performance with regard to enantioselection (entries 9–13).

Table 2 Scope of the reaction



Entry	Ylide	Aldehyde	R	Prod.	Solvent	Yield[a] (%)	*endo*/*exo*[b]	ee[c] (%)
1	**1a**	**2a**	Me	**4a**	THF	87	88 : 12	88
2	**1a**	**2b**	^{n}Pr	**4b**	THF	51	65 : 35	84
3	**1a**	**2c**	$^{n}C_8H_{17}$	**4c**	THF	45	63 : 37	84
4	**1a**	**2d**	Ph	**4d**	THF	70	>95 : <5	94
5	**1a**	**2e**	*p*-(MeO)C_6H_4	**4e**	THF	63	>95 : <5	88
6	**1a**	**2f**	*p*-(NO_2)C_6H_4	**4f**	THF	73	>95 : <5	84
7	**1b**	**2a**	Me	**4g**	THF	98	63 : 44	>99
8	**1b**	**2a**	Me	**4g**	Toluene	91	86 : 14	>99
9	**1b**	**2b**	^{n}Pr	**4h**	Toluene	72	83 : 17	>99
10	**1b**	**2c**	$^{n}C_8H_{17}$	**4i**	Toluene	64	77 : 23	95
11	**1b**	**2d**	Ph	**4j**	Toluene	61	91 : 9	97
12	**1b**	**2e**	*p*-(MeO)C_6H_4	**4k**	Toluene	63	71 : 29	90
13	**1b**	**2f**	*p*-(NO_2)C_6H_4	**4l**	Toluene	60	80 : 20	99

[a] Yield of pure *endo* diastereoisomer after flash column chromatography purification. [b] Determined by ^{1}H-NMR analysis of crude reaction mixture. [c] ee of pure *endo* diastereoisomer determined by HPLC (see ESI‡).



Scheme 1 Reduction of cycloadducts **4a–l**.

All cycloadducts **4a–l** were found to be rather unstable compounds and, for this reason, these were reduced under standard conditions (Scheme 1), obtaining the corresponding primary alcohols which could be isolated and correctly characterized. At this point, we could also grow crystals for compound **4d** suitable for X-ray analysis. This also allowed us to unambiguously establish the absolute configuration of all compounds **4a–l**.

In conclusion we have demonstrated that isoquinolinium and phthalizinium methylides can be used as efficient azomethine ylides which participate in (3 + 2) cycloaddition reaction in the presence of chiral imidazolidinone **3a** as catalyst leading to the formation of pyrroloisoquinoline and pyrrolophthalazine cycloadducts in good yields and high diastereo- and enantioselectivities under the optimized reaction conditions.

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