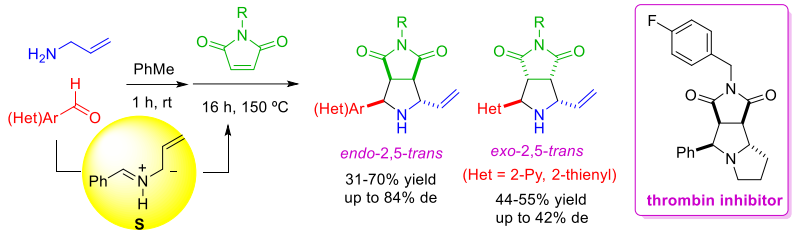
Sequential Metal-free Thermal 1,3-Dipolar Cycloaddition of Unactivated Azomethine Ylides

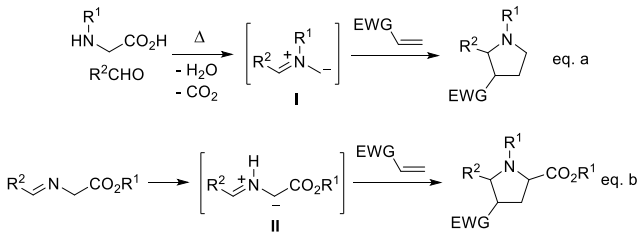
Verónica Selva, [a,b,c] Elisabet Selva,[a,b,c,d] Pedro Merino,[e] Carmen Nájera,*[a,b] and José M. Sansano,*[a,b,c]

[a] Departamento de Química Orgánica. Facultad de Ciencias, Universidad de Alicante, 03080-Alicante, Spain.
[b] Centro de Innovación en Química Avanzada (ORFEO-CINQA).
[c] Instituto de Síntesis Orgánica (ISO).
[d] Medalchemy, S. L. Avenida Ancha de Castelar, 46 – EA, San Vicente del Raspeig, 03690, Alicante.
[e] Instituto de Biocomputación y Física de Sistemas Complejos (BIFI). Universidad de Zaragoza, 50009 Zaragoza, Spain



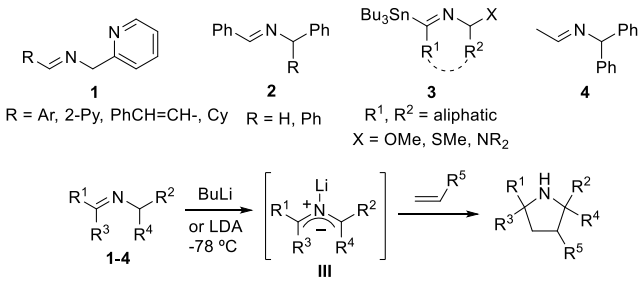
ABSTRACT: The thermal 1,3-dipolar cycloaddition of unactivated azomethine ylides derived from allylamine and aromatic or heteroaromatic aldehydes with maleimides and 1,1- and 1,2-bis(phenylsulfonyl)ethylene affords *endo*-2,5-*trans* cycloadducts in moderate to good yield. DFT calculations provide evidences that the reaction is under thermodynamic control; thus, the final diastereomeric ratio observed depends on the stability of the final adducts rather than the corresponding transition structures (kinetic control). This methodology is applied to the diastereoselective synthesis of a tricyclic thrombin inhibitor.

Classical thermal 1,3-dipolar cycloadditions (1,3-DCs) are performed with activated dipolarophiles and stabilized or non stabilized dipoles.[1,2] The generation of non-stabilized azomethine ylides by condensation of amino acids and aldehydes requires the use of *N*-alkyl amino acids and aldehydes, to generate the corresponding non-stabilized iminium-type dipole **I** after decarboxylation (Scheme 1, eq. a). However, 1,2-prototropy shift processes allow the thermal generation of the stabilized dipoles **II** directly from the preformed imino esters derived from primary α-amino acids (Scheme 1, eq. b). In both cases, an electrophilic alkene is ready to capture the fleeting dipole.[1b]



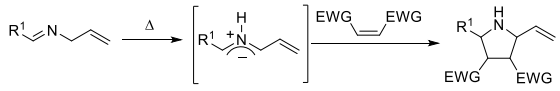
Scheme 1. 1,3-DC by Thermal Generation of Stabilized Azomethine Ylides

These traditional features have been disassembled by the publication of relevant contributions regarding non-classical components. For instance, a 2-pyridyl group was strategically placed instead of the ester group of the imino ester moiety **1**[3] performing the cycloaddition in the presence of a chiral copper(I) complex. Lithium azaallyl anions **III**,[4-10] introduced by Kauffmann,[4] generated from imines **2-4** and strong bases as LDA and BuLi at very low temperature forced the HOMO-LUMO approach to promote 1,3-DC even with non-activated dipolarophiles (Scheme 2).[6] Thus, reactions between **2** and alkenyl arenes[5,7] or dienes[8] or hetero-substituted olefins,[9] starting compounds **3** with alkenyl arenes,[10] **4** and conjugated polyenes,[8] and the highly chelated lithium 2-aza-allyl anions **III** with styrenes and other aliphatic olefins in the presence of Me_2AlCl.[11]



Scheme 2. 1,3-DC Involving Non-activated Azomethine Ylides

We envisaged the possibility of generate non-stabilized azomethine ylides by promotion of a thermal 1,2-prototropy shift on imines derived from allylamine and aromatic and heteroaromatic aldehydes for the diastereoselective synthesis of 2-vinyl-5-arylpyrrolidines, precursors of thrombin inhibitors (Scheme 3).[12]

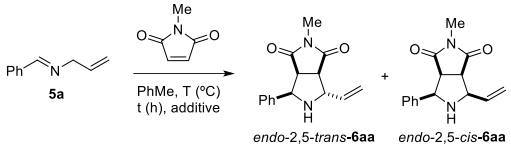


Scheme 3. Proposed 1,3-DC Involving Non-activated Azomethine Ylides Derived from Allylamine

Imine **5a** was initially tested in the presence of *N*-methylmaleimide (NMM) using different conditions described in Table 1.

Following previous thermal cycloadditions reported by our group,[13] toluene was selected as solvent. As it is depicted in Table 1, imine **5a** in the presence of 5 mol% of trimethylamine and silver benzoate at 90 ºC gave a ca. 1:1 mixture of *endo*-2,5-*trans* and *endo*-2,5-*cis* diastereomers **6aa** in low conversion (Table 1, entry 1). However, when 30 mol% of benzoic acid was added to catalyze the process, rather than trifluoroacetic acid and *p*-toluenesulfonic acid high conversion was observed giving **6aa** in 95% (Table 1, entries 2-4). In the absence of acid the reaction failed (Table 1, entry 5). When the amount of benzoic acid was increased to 1 eq, the conversion was 90% (Table 1, entry 6). On the other hand, an increment of the temperature decreased the reaction time rising full conversions in the presence or absence of 30 mol% of benzoic acid at 150 ºC in 16 h (Table 1, entries 7 and 8). Using a lower temperature 130 ºC (Table 1, entry 9) and lower reaction time (7 h) at 150 ºC (Table 1, entry 10) did not improve the previous result. The thermal process without additives afforded cleaner crude reaction products. With respect to the observed diasteroselectivity similar results were observed in most of the cases.

Table 1. Optimization of reaction conditions of 1,3-DC of 5 with NMM



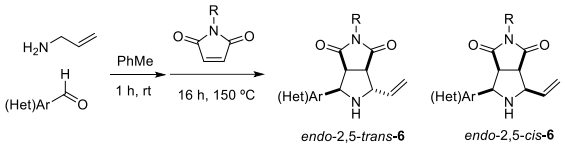
entry	imine	additive (mol%)	T (ºC)	time (h)	Conv. (%)[a]	dr
1	**5a**	Et_3N (5), AgOBz (5)	90	48	15	45:55
2	**5a**	BzOH (30)	90	48	95	68:32
3	**5a**	TFAA (30)	90	72	11	53:47
4	**5a**	*p*-TsOH (30)	90	72	39	[b]
5	**5a**	—	90	48	—	—
6	**5a**	BzOH (100)	110	16	90	65:35
7	**5a**	BzOH (30)	150	16	100	67:37
8	**5a**	—	150	16	100	69:31
9	**5a**	—	130	16	—	—
10	**5a**	—	150	7	58	64:36
11	—[c]	—	150	17	100	71:29

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Mixture of 4 diastereomers. [c] *Sequential reaction*: allylamine and benzaldehyde reacted during 1 h at rt and then NMM was added and stirring continued 16 h at 150 ºC.

When the reaction was carried out using a sequential process generating *in situ* the imine **5a**, cleaner crude product **6aa** in 71:29 dr was obtained (Table 1, entry 11). So, the thermal conditions in a two-step in situ process was employed to study the scope of the 1,3-DC to access molecules **6**. However, when the reaction was performed in a three-component process a complex mixture of products was obtained.

The scope of the reaction was studied by the *in situ* prepared imine **5a** by stirring a solution of allylamine and benzaldehyde in toluene for 1 h at rt. Next, the mixture was allowed to react with maleimide, *N*-alkyl and *N*-arylmaleimides affording the corresponding compounds **6aa**-**6ah** as mixture of *endo*-2,5-*trans* and *endo*-2,5-*cis* diastereoisomers with good conversions and moderate to good dr (Table 2, entries 1-8), which can be easily separated after flash chromatography affording the pure *endo*-2,5-*trans* **6** diasteromers. The chemical yield of the isolated major *endo*-2,5-*trans* diastereomer was good (41-70%) and despite of the temperature reaction the best crude dr achieved corresponded to the process involving *N*-(*o*-methoxyphenyl)maleimide (Table 2, entry 5).

Table 2. Scope of the Thermal *in situ* Two-step 1,3-DC with maleimides

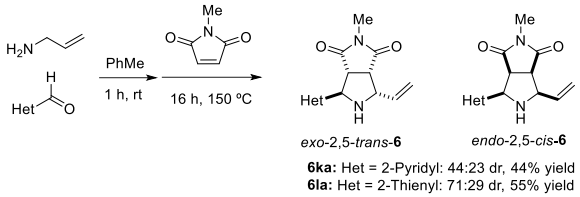


entry	Ar	R	6	dr	yield (%)[b,c]
1	Ph	Me	**6aa**	71:29	67
2	Ph	H	**6ab**	69:31	62
3	Ph	Bn	**6ac**	65:35	64
4	Ph	Ph	**6ad**	72:28	69
5	Ph	2-$MeOC_6H_4$	**6ae**	92:8	70
6	Ph	3-ClC_6H_4	**6af**	83:17	41
7	Ph	4-ClC_6H_4	**6ag**	76:24	68
8	Ph	4-BrC_6H_4	**6ah**	74:26	55
9	2-Naphthyl	Me	**6ba**	58:42	60
10	2-MeC_6H_4	Me	**6ca**	73:27	38
11	3-MeC_6H_4	Me	**6da**	80:20	31
12	4-MeC_6H_4	Me	**6ea**	77:23	40
13	2-(NO_2) C_6H_4	Me	**6fa**	76:24	41
14	3-(NO_2) C_6H_4	Me	**6ga**	66:34	62
15	4-(NO_2) C_6H_4	Me	**6ha**	59:41	56
16	4-BrC_6H_4	Me	**6ia**	69:31	62
17	3-Pyridyl	Me	**6ja**	62:38	53
18	Ph	(4-F-C_6H_4)CH_2	**6ai**	73:26	68

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield after purification (flash silica gel) of the major *endo*-2,5-*trans*-diastereoisomer. [c] The major diastereomer was obtained in >99:1 dr.

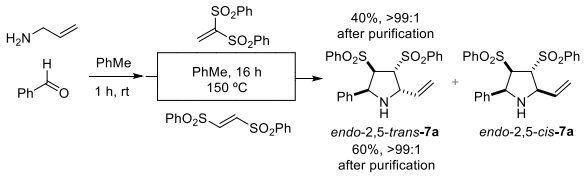
The series of *N*-arylidene allylimines depicted in entries 9-16 of the Table 2 were also appropriate to run this 1,3-DC with NMM. Mixtures of *endo*-2,5-*trans*:*endo*-2,5-*cis* diastereomers were achieved using independently *o*-, *m*- or *p*-substituted azomethine ylide precursors **6b-i** affording high combined chemical yields except for the family of tolyl moieties where yields remained lower. The 3-pyridyl derivative also afforded a high overall chemical yield of the 69:31 *endo*-2,5-*trans*-**6ja**: *endo*-2,5-*cis*-**6ja** mixture (Table 2, entry 17). At this point, product *endo*-2,5-*trans*-**6ja** could be separated and recrystallized obtaining an X-ray diffraction pattern.[14] nOe experiments and ^{1}H NMR coupling constants confirm this structural analysis. In addition, the relative configurations of all-*cis*-*endo*-**6** products were analogously determined (see supporting information). Finally, *N*-(4-fluorobenzyl)maleimide[15,16] was tested in this reaction affording a 69:31 mixture of *endo*-2,5-*trans*-**6ai** : *endo*-2,5-*cis*-**6ai** (Table 2, entry 18) and good yield and higher diastereoselectivity of the major isomer after purification by column chromatography (88:12 dr). Cycloadduct *endo*-2,5-*trans*-**6ai** was furtherly used for the synthesis of a thrombin inhibitor (see below).

A different diasteroselective facial outcome was observed in the case of the cycloadditions with 2-pyridine and 2-thienylcarbaldehyde. In these cases, *exo*- and *endo*-2,5-*trans* **6ka** and **6la** cycloadducts were obtained, respectively (Scheme 4). Compound **6ka** was obtained in a 67:33 dr affording after purification the *exo*-2,5-*trans*-**6ka** isomer in 44% yield. Whereas, in the case of the thiophene derivative a mixture 71:29 of *exo:endo*-**6la** was obtained, which after chromatographic purification afforded *exo*-2,5-*trans*-**6la** in 55% yield.



Scheme 4. 1,3-DC of Imines **5k** and **5l** with NMM

Despite attempting a large number of dipolarophiles using this methodology only bis(phenylsulfonyl)ethylene (BPSE) family gave a notable conversion. Surprisingly, 1,1- and 1,2-(BPSE) afforded the same cycloadducts *endo*-2,5-*trans* **7a** and *endo*-2,5-*cis*-**7a** in different proportion in the crude mixture (56:44 and 70:30 *endo*-2,5-*trans* **7a** and *endo*-2,5-*cis*-**7a**, respectively, Scheme 5). After purification product *endo*-2,5-*trans*-**7a** was exclusively obtained with this relative configuration, which was determined by comparison of its coupling constants a nOe with the analogous results obtained for other *endo*-2,5-*trans*-isomers (see above). The formation of isomer **7a** during the transformation with 1,1-BPSE could be due to a cycloaddition-elimination-Michael type addition of benzenesulfinate anion sequence.[17]

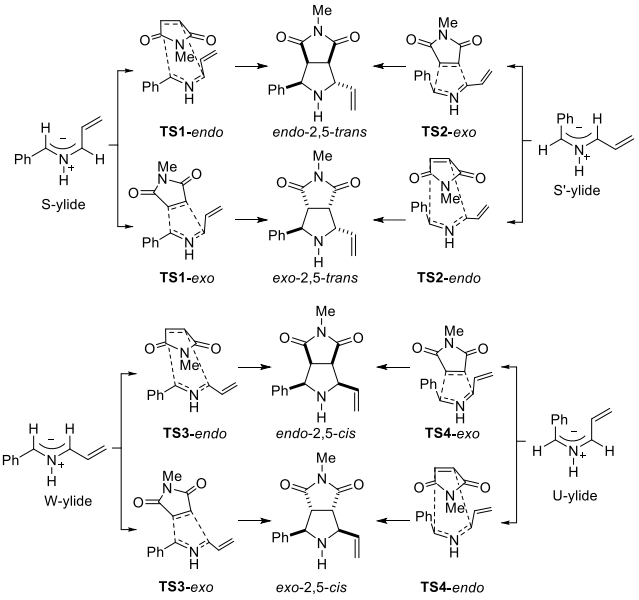


Scheme 5. 1,3-DC of Imine 5a with 1,1- and 1,2-BPSE

The key reaction between the *in situ* formed non-stabilized azomethine ylide and NMM was studied in detail by DFT methods to provide a rationale of the observed diastereoselectivity. The four possible conformations of the ylide (S, W, S' and U), which can stabilize the negative charge at either the allylic or the benzylic position, as well as *endo* and *exo* approaches were evaluated. A total of eight transition structures leading to the four possible adducts were located for the reaction of the azomethine ylide derived from benzaldehyde (Scheme 6).

The relative energies of reactants, transition structures and products are collected in Table 3 (for detailed data and geometries, see SI). According to the values showed in Table 3 the preferred transition structure corresponds to **TS3**-*endo*, leading to *endo*-2,5-*cis* adduct, the expected product provided the reaction is under kinetic control. However, this result is not in agreement with the experimental observations. On the other hand, taken into consideration the stability of the final adducts, the most stable structure corresponds to the *endo*-2,5-*trans* adduct, which is the major product observed experimentally. Moreover, the inverse barriers are in the order of ca. 30 kcal/mol, a value that can be reachable at the temperature (150 °C) to which the reaction is carried out. These results suggest that the reaction is under thermodynamic control. Consequently, the preferred transition structure corresponding to the most reactive ylide conformation is irrelevant, the only factor governing the diastereomeric ratio of the reaction being the stability of the final products.

The study was extended to the azomethine ylides derived from 2-pyridyl- and 2-thienylcarboxaldehyde. Again, the experimental results are more in agreement with a thermodynamic control, although the low differences between the relative energies of the products (*ca*. 1-2 kcal/mol, which are within the DFT error) do not allow a quantitative analysis of the diastereomeric ratio. Admittedly, the observed differences in diastereoselectivity cannot be assessed by DFT calculations which only predict that mixtures of adducts will be obtained. On the other hand, the presence of (un)favorable interactions evidenced by NCI topological calculations can justify the observed trends towards the *exo* adduct in the case of 2-pyridyl and 2-thienyl derivatives (see SI).



Scheme 6. Reaction pathways for the cycloaddition of non-stabilized Azomethine Ylides

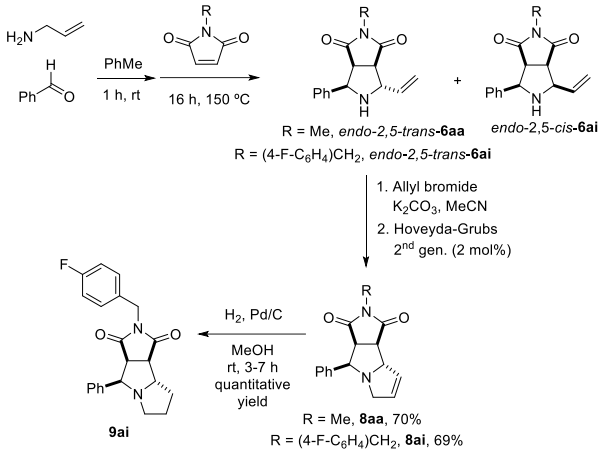
Table 3. Absolute (hartree) and relative (kcal/mol) free energies[a] for the reaction of ylide derived from benzaldehyde and NMM

	G	ΔG[b]	Imaginary frequency
NMM	-398.866809		
S-ylide	-442.432902		
S'-ylide	-442.432884		
W-ylide	-442.436343		
U-ylide	-442.425451		
TS1-*endo*	-841.293053	6.3	-260.4
TS2-*endo*	-841.290929	7.7	-254.7
TS3-*endo*	-841.295888	4.6	-208.5
TS4-*endo*	-841.281165	13.8	-274.8
TS1-*exo*	-841.288470	9.2	-259.7
TS2-*exo*	-841.287269	10.0	-276.1
TS3-*exo*	-841.293894	5.8	-217.4
TS4-*exo*	-841.276113	17.0	-269.0
endo-2,5-cis	-841.347296	-27.7	
endo-2,5-trans	-841.348026	-28.2	
exo-2,5-cis	-841.345979	-26.9	
exo-2,5-trans	-841.346432	-27.2	

[a] Calculated at b3lyp-gd3bj/def2tzvp/pcm=toluene/temp=448 K//b3lyp-gd3bj//def2svp. [b] Referred to NMM and the most stable conformation of the ylide (according to Curtin-Hammett principle).

A direct application of this methodology consisted in a short synthesis of a tricyclic thrombin inhibitors **9** (Scheme 7).[12] In this case, the thermal 1,3-DC was run with NMM[20] and *N*-(4-fluorobenzyl)maleimide (Table 2, entries 1 and 20). Compounds *endo*-2,5-*trans*-**6aa** and *endo*-2,5-*trans*-**6ai**, which possessed the right configuration to access the desired compound **9**, were submitted to the allylation of the nitrogen atom followed

by ring closing metathesis using the 2nd generation Hoveyda-Grubbs' catalyst.[21] Intermediate compounds **8aa** and **8ai** were isolated in 70 and 69% chemical yields, respectively. Final hydrogenation of the double bond only was carried out onto **8ai** under mild conditions [rt, H_2 (1 atm), Pd/C (10% Pd, 8 mg/mmol of substrate][21] affording quantitatively compound **9ai** (Scheme 7). The overall yield of **9ai**, achieved from allylamine, was 47%.



Scheme 7. Synthesis of the tricyclic thrombin inhibitor **9ai**

In conclusion, a thermal allylic C-H activation was successfully promoted in the *in situ* prepared *N*-benzylideneallylamine. The driving force of this activation is the generation of an intermediate azomethine ylide that reacts with the dipolarophile under thermodynamic control. The conformation of the ylide and the corresponding transition structures are irrelevant, the only factor governing the stereochemical outcome of the reaction being the stability of the final adducts. This methodology can be successfully applied to the synthesis of a tricyclic thrombin inhibitor **9ai** in three steps with an overall yield of 47%, which is higher than the reported ones.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website at DOI: Computational methods, details on computational calculations including energies, optimized geometries, NCI topological calculations and cartesian coordinates. Experimental details, characterization data, and NMR spectra for new compounds (PDF), computational data and X-RD analysis.

AUTHOR INFORMATION

*E mail: cnajera@ua.es; *E mail: jmsansano@ua.es

The manuscript was written through contributions of all authors.

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17 1,1-BPSE was stable when maintained alone in toluene at 150 ºC 24 h. So, a transformation of 1,1-BPSE into 1,2-BPSE was discarded.

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