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

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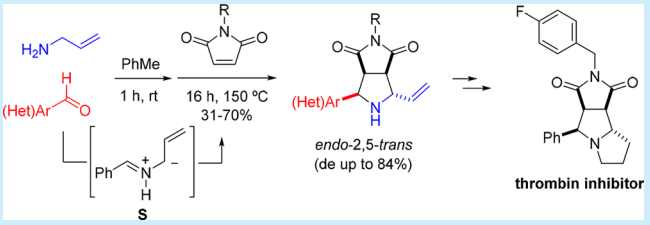
Supporting Information

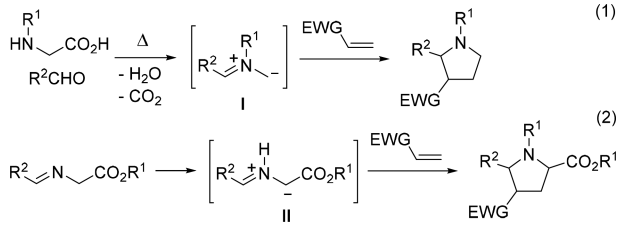
ABSTRACT: The thermal 1,3-dipolar cycloaddition of unactivated azomethine ylides derived from allylamine and aromatic or heteroaromatic aldehydes with maleimides and 1,1- and 1,2-bis(phenylsulfonyl)ethylene affords *endo*-2,5-*trans* cycloadducts in moderate to good yields. DFT calculations provide evidence that the diastereoselectivity observed depends on the isomerization between S- and W-ylides according to Curtin-Hammett's principle. DFT calculations also explain the different diastereomeric ratio observed for 2-pyridyl and 2-thienyl derivatives in which the isomerization is not possible due to the competitiveness between isomerization barrier and the rate-limiting step (ylide formation barrier). This methodology is applied to the diastereoselective synthesis of a tricyclic thrombin inhibitor.



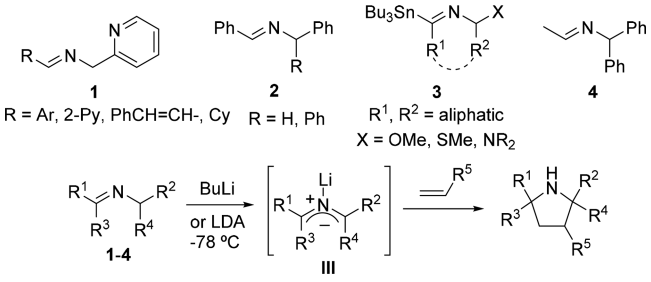
Classical thermal 1,3-dipolar cycloadditions (1,3-DCs) are performed with activated dipolarophiles and stabilized or nonstabilized dipoles.[1,2] The generation of nonstabilized azomethine ylides by condensation of amino acids and aldehydes requires the use of *N*-alkyl amino acids and aldehydes to generate the corresponding nonstabilized iminium-type dipole **I** after decarboxylation (Scheme 1, 1). 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, 2). In both cases, an electrophilic alkene is ready to capture the fleeting dipole.[1b]

These traditional features have been disassembled by the publication of relevant contributions regarding nonclassical 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

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



Scheme 2. 1,3-DC Involving Nonactivated Azomethine Ylides



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

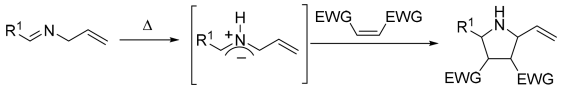


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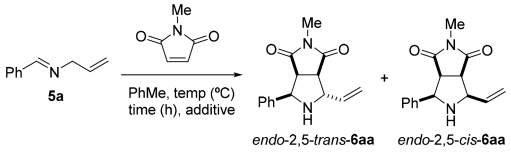
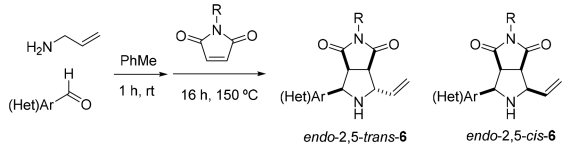
Table 1. Optimization of Reaction Conditions of 1,3-DC of 5 with NMM



entry	imine	additive (mol %)	temp (°C)	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 four 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 °C.

Table 2. Scope of the Thermal in Situ Two-Step 1,3-DC with Maleimides

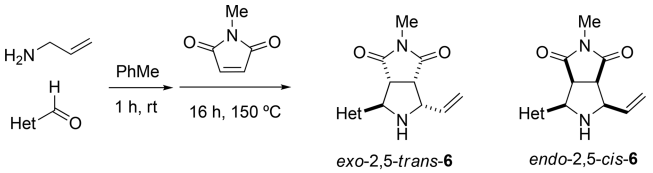


entry	Ar	R	**6**	dr[a]	yield[b,c] (%)
1	Ph	Me	**6aa**	71:29	67[d]
2	Ph	H	**6ab**	69:31	62
3	Ph	Bn	**6ac**	65:35	64
4	Ph	Ph	**6ad**	72:28	69
5	Ph	2-$MeOC_6H_4$	**6ae**	92:8	70
6	Ph	3-ClC_6H_4	**6af**	83:17	41
7	Ph	4-ClC_6H_4	**6ag**	76:24	68
8	Ph	4-BrC_6H_4	**6ah**	74:26	55
9	2-naphthyl	Me	**6ba**	68:32	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-FC_6H_4)CH_2	**6ai**	73:27	68

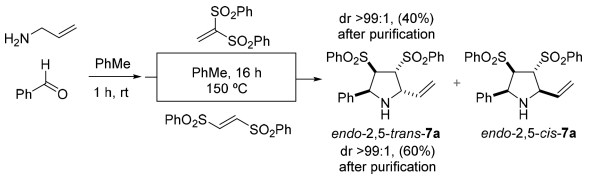
[a]Determined by ^{1}H NMR of the crude reaction mixture. [b]Isolated yield after purification (flash silica gel) of the major *endo*-2,5-*trans*-diastereoisomer. [c]The major diastereomer was obtained in >99:1 dr. [d]This reaction was scaled up to 5 mmol.

such as LDA and BuLi at very low temperature forced the HOMO−LUMO approach to promote 1,3-DC even with nonactivated dipolarophiles (Scheme 2).[5,6] Thus, reactions between **2** and alkenyl arenes,[4,7] dienes,[8] and heterosubstituted

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



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



olefins,[9] as well as **3** with alkenyl arenes[10] and **4** with conjugated polyenes,[8] have been reported. In addition, the reaction of highly chelated lithium 2-aza-allyl anions **III** with styrenes and other aliphatic olefins in the presence of Me_2AlCl has been described.[11]

We envisaged the possibility of generating nonstabilized 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]

Imine **5a** was initially tested in the presence of *N*-methylmaleimide (NMM) using different conditions as described in Table 1. Following previous thermal cycloadditions reported by our group,[13] toluene was selected as solvent. As depicted in Table 1, imine **5a** in the presence of 5 mol % of triethylamine and silver benzoate at 90 °C 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 equiv, the conversion was 90% (Table 1, entry 6). On the other hand, an increment of the temperature decreased the reaction time, leading to full conversion in the presence or absence of 30 mol % of benzoic acid at 150 °C in 16 h (Table 1, entries 7 and 8). Using a lower temperature 130 °C (Table 1, entry 9) and slower reaction time (7 h) at 150 °C (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 diastereoselectivity, similar results were observed in most of the cases.

When the reaction was carried out using a sequential process generating the imine **5a** in situ, cleaner crude product **6aa** in 71:29 dr was obtained (Table 1, entry 11). Thus, the thermal conditions in a two-step in situ process were 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

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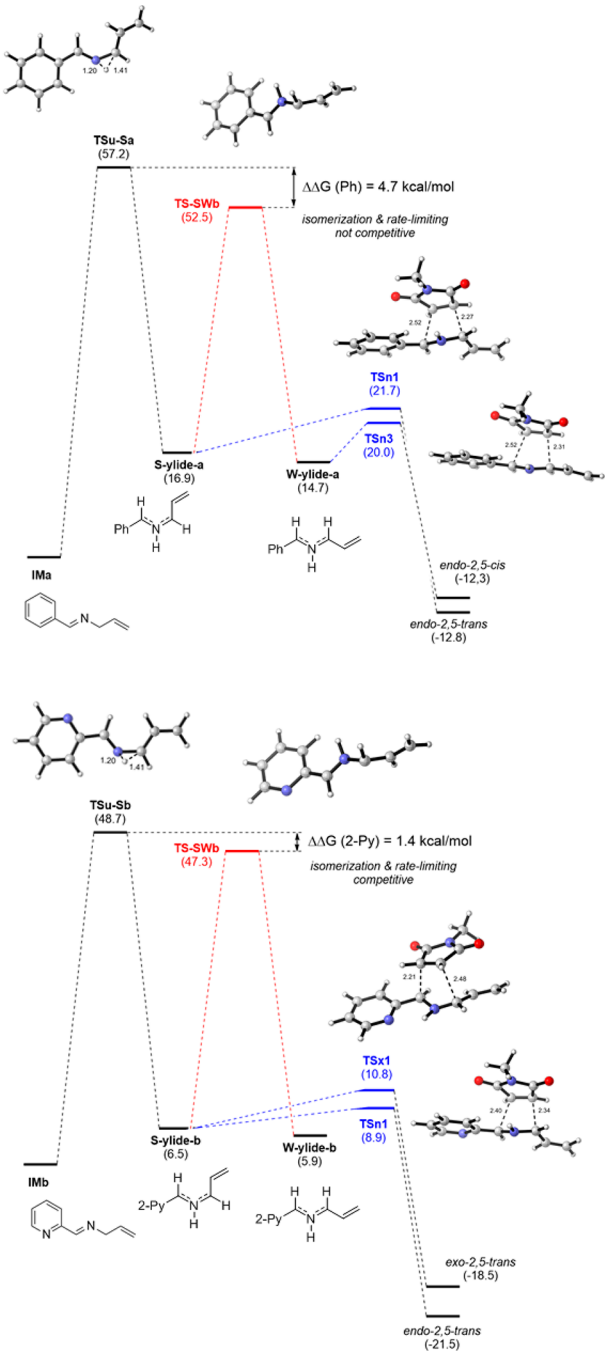
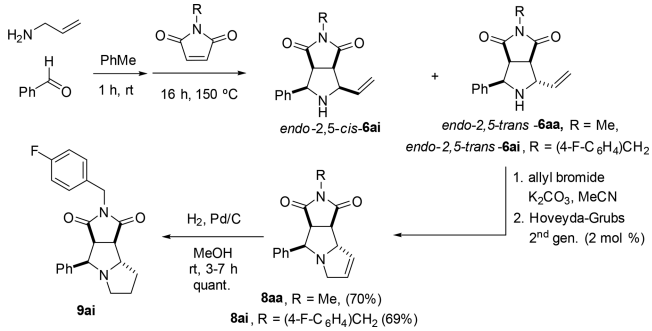


Figure 1. Energy profiles corresponding to reaction with azomethine ylides derived from benzaldehyde (top) and 2-formylpyridine (bottom). For a full view of energy profiles, see the SI.

with maleimide and *N*-alkyl- and *N*-arylmaleimides to afford the corresponding compounds **6aa**−**ah** as mixture of *endo*-2,5-*trans* and *endo*-2,5-*cis* diastereoisomers with good conversion and moderate to good dr (Table 2, entries 1−8), which can be separated after flash chromatography to afford the pure *endo*-2,5-*trans* **6** diastereomers. The chemical yield of the isolated major *endo*-2,5-*trans* diastereomer was good (41−70%), and despite the temperature of the reaction, the best crude dr achieved corresponded to the process involving *N*-(*o*-methoxyphenyl)maleimide (Table 2, entry 5).

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

Scheme 6. Synthesis of the Tricyclic Thrombin Inhibitor 9ai



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** to afford 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. 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 the Supporting Information). Finally, *N*-(4-fluorobenzyl)maleimide[14,15] was tested in this reaction and affforded a 73:27 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 further used for the synthesis of a thrombin inhibitor (see below).

A different diastereoselective outcome was observed in the case of the cycloadditions with 2-pyridine and 2-thienylcarbaldehyde. In these cases, *exo*-2,5-*trans* and *endo*-2,5-*cis* **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. 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.

Despite using a large number of dipolarophiles to attempt this methodology (acrylates, fumarates, cinnamates, chalcones, *β*-nitrosytene, maleic anhydride, methyl vinyl ketone, etc.), only the 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 proportions 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 the benzenesulfinate anion sequence.[16] We also examined several substituted allylamines and aliphatic aldehydes, but the reaction did not occur at all.

The entire process was studied in detail by DFT methods to provide a rationale of the observed diastereoselectivity. We studied for both benzaldehyde and 2-formylpyiridine series the formation of the four possible conformers of the ylide (S, W, S′,

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and U), which can stabilize the negative charge at either the allylic or the benzylic position. The isomerization between the different couples of ylide conformations were also studied, and finally, *endo* and *exo* approaches of the cycloaddition reaction were evaluated. We located four transition states for the formation of the ylides, from which that leading to S-ylide was the preferred, although the W-ylide was the most stable (see the SI). In agreement with experimental observations, a high activation barrier was found (Figure 1). Both the isomerization between ylide conformers and the cycloaddition reactions showed lower energy barriers, so it can be considered that the formation of the ylide is the rate-limiting step of the process. For the cycloaddition reaction, the *endo* approaches always showed lower barriers than *exo* approaches (see the SI). In the case of benzaldehyde-derived ylides, there is a difference of 4.7 kcal/mol between the rate-limiting step and the isomerization barrier between the S-ylide (the fastest to be formed) and the W-ylide (the most stable), so in agreement with the Curtin−Hammet principle,[17] an equilibrium between both conformers can be expected. Consequently, the observed adducts are *endo*-2,5-*trans* and *endo*-2,5-*cis* formed through the preferred pathways from each ylide conformer (Figure 1, top).

In the case of ylides derived from 2-formylpyridine, the barriers corresponding to S-ylide formation (rate-limiting step) and S-ylide isomerization to W-ylide are competitive (only 1.4 kcal/mol of difference in favor of isomerization), and it can be considered that isomerization to W-ylide is negligible (Figure 1 bottom). Consequently, the obtained adducts are *endo*-2,5-*trans* and *exo*-2,5-*trans*, both formed from S-ylide.[18] These results are in complete agreement with experimental observations and can be applied to 2-thienyl-derived ylides.

A direct application of this methodology consisted of a short synthesis of a tricyclic thrombin inhibitor **9** (Scheme 6).[12] In this case, the thermal 1,3-DC was run with NMM[19] and *N*-(4-fluorobenzyl)maleimide (Table 2, entries 1 and 18). Compounds *endo*-2,5-*trans*-**6aa** and *endo*-2,5-*trans*-**6ai**, which possessed the correct configuration to access the desired compound **9**, were submitted to the allylation of the nitrogen atom followed by ring-closing metathesis using the second-generation Hoveyda−Grubbs' catalyst.[20] 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)],[20] affording quantitatively compound **9ai** (Scheme 6). The overall yield of **9ai**, achieved from allylamine, was 47%.

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. The rate-limiting step of the reaction is the formation of the ylide that allows equilibration between S- and W-ylides giving rise to the observed stereoselectivity. In the case of 2-pyridyl and 2-thienyl derivatives, however, the equilibration between ylides is competitive with their formation from the corresponding imine and only the S-ylide is formed, thus explaining the change in stereoselectivity observed for those substrates. 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 yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01292.

Computational methods, details on computational calculations, including energies, optimized geometries, and Cartesian coordinates. Experimental details, characterization data, and NMR spectra for new compounds and X-RD analysis (PDF)

Accession Codes

CCDC 1820733 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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■ DEDICATION

Dedicated to Prof. Ernesto Carmona on the occasion of his 70th birthday.

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(19) The reaction with NMM was performed first in order to optimize the synthetic route for the preparation of the most interesting compound **9ai**. In fact, this *N*-methylated family stopped in compound **8aa**.

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