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1,3-Dipolar Cycloaddition Reactions of Azomethine Ylides with a Cellulose-Derived Chiral Enone. A Novel Route for Organocatalysts Development

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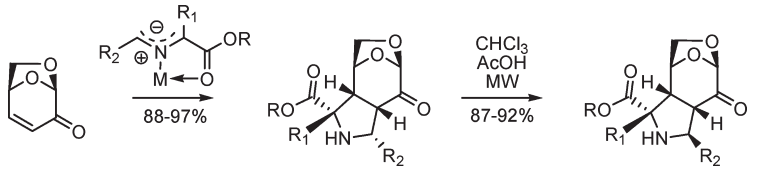
ABSTRACT



Cellulose-derived chiral pyrrolidines were synthesized in excellent yields, regioselectivities, and stereoselectivities via a 1,3-dipolar cycloaddition reaction between levoglucosenone and azomethine ylides. An unprecedented isomerization event led to a new family of pyrrolidines with an unusual relative stereochemistry. Preliminary results showed that these compounds are promising organocatalysts for iminium ion-based asymmetric Diels–Alder reactions.

The synthesis of new chiral organic templates starting from renewable feedstocks is of enormous value in modern organic synthesis. As a result, intensive research activity has been pursued worldwide to identify attractive chemical transformations to convert biomass into highly valuable organic chemicals.[1] Levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose) (**1**) is a versatile and easily available chiral building block from the carbohydrate family.[2] Conventional pyrolysis of cellulose-containing materials such as waste paper is typically used to generate **1**, but microwave irradiation of microcrystalline cellulose was recently found to be an effective alternative.[3] As part of our ongoing interest in the development of new tools for asymmetric synthesis using levoglucosenone derivatives,[4] we envisaged the use of **1** in the preparation of novel enantiomerically pure poly substituted pyrrolidines, molecular scaffolds that are found in

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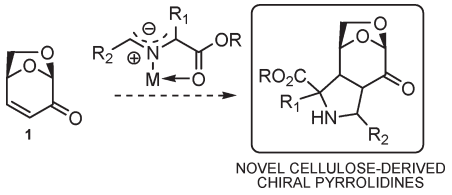
many efficient chiral organocatalysts.[5] Since **1** has a unique dipolarophilic reactivity, as was established with dipoles such as nitrones and nitrile oxides,[6] we foresaw the 1,3-dipolar cycloaddition cycloaddition (1,3-DPC) using azomethine ylides (AMY) as a direct route to achieve our goals (Scheme 1).

Scheme 1. Synthetic Strategy for New Pyrrolidinic Cores Derived from Levoglucosenone

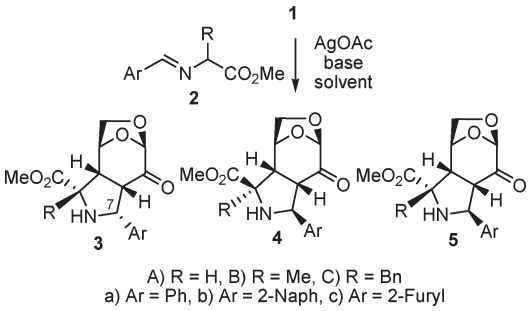


Although this methodology is perhaps one of the best and most used methods for the convergent and stereoselective synthesis of pyrrolidinic cores,[7] examples on the use of carbohydrate-derived enones as the π-deficient counterpart are scarce.[8] Moreover, this strategy represents a conceptually novel route for the synthesis of organocatalysts, since to the best of our knowledge there are no precedents on the use of enantiomerically pure dipolarophiles in the generation of chiral pyrrolidines as potential organocatalysts.[9]

Levoglucosenone was obtained from the microwave-assisted pyrolysis of acid pretreated microcrystalline cellulose.[3] With the chiral enone in hand, we next set the stage for the rapid construction of the pyrrolidine ring. Among the different strategies developed for the formation of azomethine ylides (AMYs), one of the most simple, mild, and reliable procedures consists of the in situ generation of stabilized N-metalated AMYs from iminoesters using silver and lithium counterions.[7]

In order to optimize the reaction conditions, we started our study using the iminoester **2Aa** and silver acetate as metalated-1,3-dipole precursors. As shown in Table 1, up to three stereoisomers were isolated, namely *endo*-**3Aa**, *exo*-**4Aa**, and **5Aa** (C7 epimer of **3Aa**). From the collected data (entries 1−9), we found that the overall yield was highly affected upon changes in solvent, temperature and catalyst load while the influence on the *endo*/*exo* selectivity was not significantly affected. This study allowed us to identified the optimal experimental conditions to carry out this chemical transformation (0.3 equiv of AgOAc, 0.3 equiv of DBU, MeCN, rt, 94%, entry 3).

Table 1. Synthesis of Chiral Pyrrolidines via 1,3-DPC[a]



entry	imine	salt/base (equiv)	solvent	yield[b] (%)	ratio **3**/**4**/**5**
1	**2Aa**	AgOAc/DBU (1.2)	MeCN	24	59:41:0
2	**2Aa**	AgOAc/DBU (0.4)	MeCN	75	56:44:0
3	**2Aa**	AgOAc/DBU (0.3)	MeCN	94	60:40:0
4	**2Aa**	AgOAc/DBU (0.2)	MeCN	60	63:37:0
5	**2Aa**	AgOAc/DBU (0.3)	PhMe	59	65:35:0
6	**2Aa**	AgOAc/DBU (0.3)	CH_2Cl_2	56	63:37:0
7	**2Aa**	AgOAc/DBU (0.3)	MeCN	56[c]	61:39:0
8	**2Aa**	AgOAc/NEt_3 (0.3)	MeCN	73	38:27:34
9	**2Aa**	AgOAc/DBU (0.1)	MeCN	63	47:35:18
10	**2Ab**	AgOAc/DBU (0.3)	MeCN	92	55:45:0
11	**2Ac**	AgOAc/DBU (0.3)	MeCN	94	52:48:0
12	**2Ba**	AgOAc/DBU (0.3)	MeCN	91	100:0:0
13	**2Bb**	AgOAc/DBU (0.3)	MeCN	90	100:0:0
14	**2Bc**	AgOAc/DBU (0.3)	MeCN	95	100:0:0
15	**2Ca**	AgOAc/DBU (0.3)	MeCN	88	100:0:0
16	**2Cb**	AgOAc/DBU (0.3)	MeCN	97	100:0:0
17	**2Cc**	AgOAc/DBU (0.3)	MeCN	95	100:0:0

[a] Unless otherwise shown, all reactions were carried out at room temperature using 1.5 equiv of **2**. [b] Yield corresponds to isolated compounds after column chromatography. [c] The reaction was carried out at 0 °C.

According to entries 1−7 in Table 1, only the *endo* and *exo* isomers were obtained in modest selectivity. The 2,5-*syn* relationship between the phenyl and ester groups on the main products **3** and **4** can be interpreted on the basis of the net preference of the metallo-dipole to adopt a W-shaped geometry.[7] However, with the use of 0.1 equiv of metal salt (entry 9) or NEt_3 as base (entry 8) variable amounts of isomer **5** were detected. There are precedents in the literature in which stereomutated isomers are found,[8−10] a result that is generally explained on the basis of the isomerization of the ylide.[7] However, while in those cases the aromatic moiety and the EWG of the dipolarophile are in a *syn* relationship, in our case both groups are *anti*.

To evaluate the scope of this cycloaddition protocol, a representative set of aryl imines of glycine, alanine and phenylalanine methyl esters were reacted with **1** under the optimized experimental conditions (Table 1, entries 10−17).

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To our delight, very good yields were obtained in all cases. Interestingly, while the stereoselectivity remained modest when using glycine derivatives (entries 10 and 11), the *endo* adducts were exclusively formed after the insertion of a substituent at the α-position of the dipole precursor (entries 12−17). These results suggest that the replacement of an hydrogen atom by bulkier groups (Me or Bn) has a greater impact on the destabilization of the competing *exo* transition state, probably due to unfavorable steric interactions.

The stereochemical assignments of all compounds were unequivocally established via NOE experiments (Figure 1). It is also important to highlight that all reactions displayed complete π-facial selectivity, since the 1,6-anhydro bridge of **1** acts as an efficient element of stereocontrol, directing the attack of the dipole for the less hindered α face of the molecule. Another salient feature of this system is the remarkable levels of regioselectivity achieved. The only isolated regioisomers arise from the bonding of the most electrophilic center of the dipolarophile with the most nucleophilic carbon of the dipole.

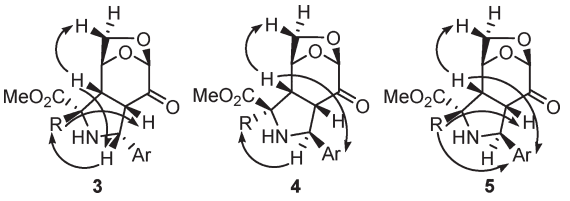

Figure 1. Key NOE correlations for stereochemical assignements of isomers **3** (*endo*), **4** (*exo*), and **5**.

During the course of this study, we realized that **3Ba** suffered slow decomposition after being accidentally left in a $CDCl_3$ solution at room temperature for a period of one month. After column chromatography, we were able to isolate a new compound in low yield, which on the basis of extensive NMR experiments was assigned as **5Ba**, a C7 epimer of **3Ba**. The structure of **5Ba** was further unambiguosly established in the solid by X-ray diffraction analysis as shown in the ORTEP[11] plot of Figure 2.

This result was totally unexpected in view of the fact that no precedents in the literature regarding isomerization at the benzylic position of structurally related 1,3-dipolar adducts could be found. Hence, we next explored this serendipitous outcome more thoroughly. Taking into account the evident slow isomerization rate at room temperature, the use of microwave irradiation to accelerate the process seemed appropriate. Heating a solution of **3Ba** in $CHCl_3$ at 150 °C for 60 min resulted in the total consumption of the starting material, to give the desired product **5Ba** in 63% yield (Table 2, entry 2). Interestingly, the use of toluene as solvent (entry 3) required much longer

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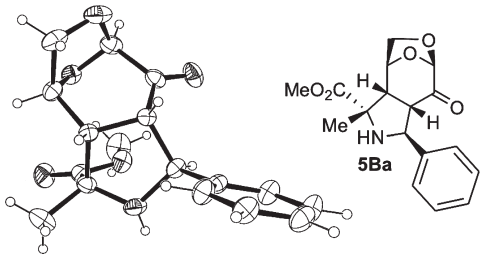
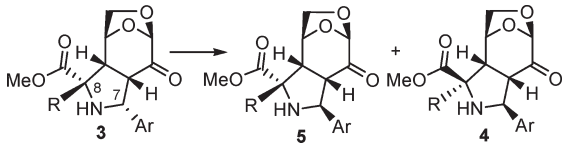


Figure 2. Drawing of the **5Ba** molecule showing the displacement ellipsoids of the non-H atoms at the 30% probability level.

Table 2. Microwave-Assisted Isomerization of Adducts *endo*-**3**

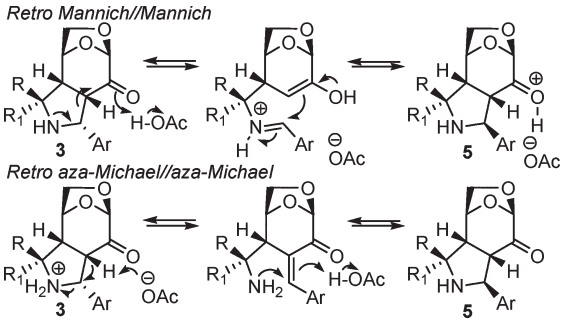


entry	**3**	solvent	additive[a]	temp (°C)	time	yield[b] (%)	ratio **5**/**4**
1	**Ba**	$CDCl_3$		25[c]	30 days	14	100:0
2	**Ba**	$CHCl_3$		150	60 min	63	100:0
3	**Ba**	PhMe		150	210 min	44	100:0
4	**Ba**	$CHCl_3$	NEt_3	150	300 min	23	100:0
5	**Ba**	$CHCl_3$	AcOH	150	20 min	92	100:0
6	**Bb**	$CHCl_3$	AcOH	150	20 min	91	100:0
7	**Bc**	$CHCl_3$	AcOH	150	20 min	87	100:0
8	**Ca**	$CHCl_3$	AcOH	150	20 min	88	100:0
9	**Cb**	$CHCl_3$	AcOH	150	20 min	90	100:0
10	**Cc**	$CHCl_3$	AcOH	150	20 min	90	100:0
11	**Aa**	$CHCl_3$	AcOH	150	20 min	91	0:100
12	**Aa**	$CHCl_3$	AcOH	60	240 min	82	49:51
13	**Ab**	$CHCl_3$	AcOH	60	240 min	80	38:62
14	**Ac**	$CHCl_3$	AcOH	60	240 min	84	52:48

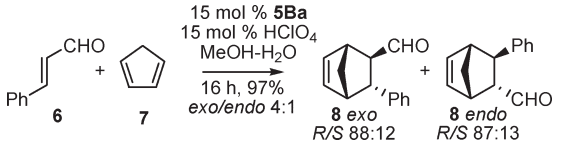
[a] We used 10% v/v of additive in all cases. [b] Yield corresponds to isolated compounds after column chromatography. [c] This reaction was carried out without microwave irradiation.

irradiation time and resulted in lower yield of the product. Considering that small amounts of HCl can be generated by decomposition of chloroform, it can be postulated that the difference in the performance between those two solvents may be due, at least in part, to the tiny acidity of the former one. In fact, the addition of NEt_3 dramatically decreased both the epimerization rate and yield (entry 4). On the other hand, acetic acid was an effective additive, leading to the rapid formation of **5Ba** in high yield (entry 5). The scope of this procedure was further explored by submitting other *endo* adducts to the optimal experimental conditions found. As depicted in entries 6−10, the isomerized compounds **5** bearing a quaternaty carbon at C8 were obtained in very good yields in all cases. Interestingly, the use of **3Aa** resulted in the complete inversion of both stereocenters at C7 and C8, allowing to obtain **4Aa** in good yield (entry 11). The synthesis of epimerized products

Scheme 2. Proposed Mechanisms for the Isomerization



Scheme 3. Diels–Alder Reaction between (*E*)-Cinnamaldehyde and Cyclopentadiene Catalyzed by **5Ba**



5 derived from glycine was achieved at lower temperature (entries 12–14), in good overall yield and modest **5**/**4** selectivity. This novel epimerization proved to be of great synthetic value, allowing access to a new isomer class of polyfunctionalyzed pyrrolidines in a straightforward manner with a relative stereochemistry not accessible vía direct 1,3-DPC. Moreover, this experimental finding might support an alternative path to explain the formation of variable amounts of stereomutated 2,5-anti isomers in AMY dipolar reactions.

The proposed mechanism for the observed epimerization consists in a tandem retro-Mannich–Mannich equilibration (Scheme 2), which have been suggested to explain isomerization in spiro oxindole alkaloids.[12] Another plausible path consists in a retro-aza-Michael transformation followed by an aza-Michael ring closure of the resulting enone.[13] Moreover, we found that after reduction of the ketone group of **3Ba**, the corresponding alcohol remained unchanged after 60 min of irradiation at 150 °C in a $CHCl_3$–AcOH solution. This experimental result indicates that the carbonyl function is necessary for the success of the reaction, supporting both mechanistic proposals. We also computed the Gibbs free energies of compounds **3Ba** and **5Ba** at the B3LYP/6-31G(d) level of theory using Gaussian 09.[14] Our results indicated that the former is 6.75 kcal/mol less stable than its epimer suggesting that, under a thermodynamically controlled process, the equilibrium should be clearly displaced toward **5Ba**, in perfect agreement with the experimental findings.

Finally, to demonstrate proof-of-principle of the usefulness of levoglucosenone-derived chiral pyrrolidines in asymmetric synthesis, some of the compounds synthesized in this work were evaluated as novel organocatalysts in iminium-ion based Diels–Alder reactions between (*E*)-cinnamaldehyde (**6**) and cyclopentadiene (**7**).[15] As a representative example, in Scheme 3 are shown the results obtained with **5Ba**, one of the most promising catalysts.[16] It is important to point out that few organocatalytic systems have been reported to have a marked preference toward the *exo* adducts.[17] Preliminary results showed that the other evaluated compounds are also active catalysts, making this system an excellent candidate for further optimization.[16]

In summary, we have reported the synthesis of chiral pyrrolidines derived from renewable feedstocks using 1,3-dipolar cycloadditions between N-metalated azomethine ylides and levoglucosenone. We have shown that these reactions proceed with excellent yields and selectivities. An unprecedented isomerization event led to the formation of a new family of pyrrolidines with a relative stereochemistry not accessible vía direct 1,3-DPC. The promising results obtained in the organocatalyzed Diels–Alder reactions provided evidence for the potential application of these molecular scaffolds in iminium ion-based organocatalysis, which to the best of our knowledge has no precedents. Further work aimed at the optimization, mechanism elucidation, and broadening the scope of the asymmetric Diels–Alder cycloadditions are currently being undertaken and will be published in due course.

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Supporting Information Available. Experimental procedures for the synthesis of all compounds, characterization data, copies of ^1H and ^{13}C NMR spectra of new products, X-ray data of compound **5Ba**, and computational data associated with this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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