

Efficient organocatalysis with a calix[4]pyrrole derivative

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Received 25 September 2007; revised 25 October 2007; accepted 29 October 2007

Available online 1 November 2007

Abstract—The 10 α ,20 β -bis(4-nitrophenyl)-calix[4]pyrrole was found to act as an effective organocatalyst for the hetero Diels–Alder reaction of Danishefsky's diene with aromatic aldehydes. This discovery is the first reported case of a calixpyrrole that exhibits organocatalytic activity.

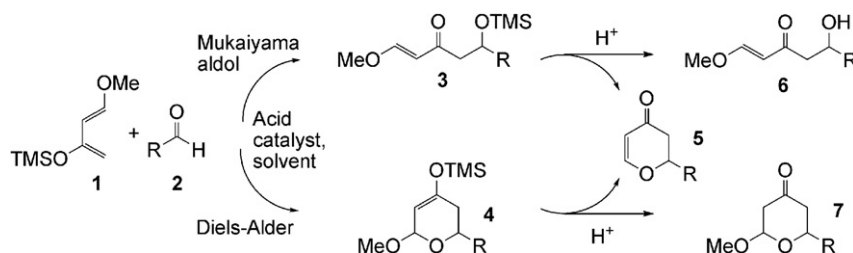
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Calixpyrroles¹ are a class of molecular receptors that are receiving considerable attention because of their ability to bind anions as well as neutral molecules² bearing hydrogen-bond acceptor sites. A considerable number of derivatives have been described, and these have been exploited in a number of applications including separation techniques³ and anion optical sensing.⁴ As hydrogen-bond donors, calixpyrroles have the potential to act as organocatalysts.⁵ However, no example of their use in catalysis has appeared in the literature to date.⁶

To test this possibility we decided to investigate the hetero Diels–Alder reaction (HDA) of Danishefsky's diene **1** with carbonyl compounds. This reaction is one of the most powerful synthetic procedures available for the construction of pyran derivatives, six-membered heterocycles with important applications in the synthesis of

natural bio-active compounds.⁷ The reaction mechanism (Scheme 1) involves either a Diels–Alder cycloaddition pathway or a Mukaiyama aldol pathway depending on the Lewis acid catalyst used.⁸ Very recently, carbonyl activation by hydrogen bonding proved to be an effective choice for several catalytic reactions⁹ and, since the pioneering works by Rawal,¹⁰ the HDA reaction promoted by hydrogen bonds has been achieved by using diol compounds as Brønsted acids.^{5,11}

On the basis of the above considerations, we selected the HDA reaction of Danishefsky's diene **1** with *p*-nitrobenzaldehyde **2** as a model reaction to test the potential ability of the recently reported¹² stereoisomeric calix[4]pyrrole derivatives **8** and **9**, and dipyrromethane **10** to act as organocatalysts. The results are summarised



Scheme 1. The reaction of Danishefsky's diene with aldehydes. In the present study R = *p*-NO₂C₆H₄, macrocycles **8** or **9** or dipyrromethane **10** were used as the acid catalysts, in DCM solvent.

Keywords: Calixpyrrole; Organocatalysis; Diels–Alder reaction; Hydrogen-bonds.

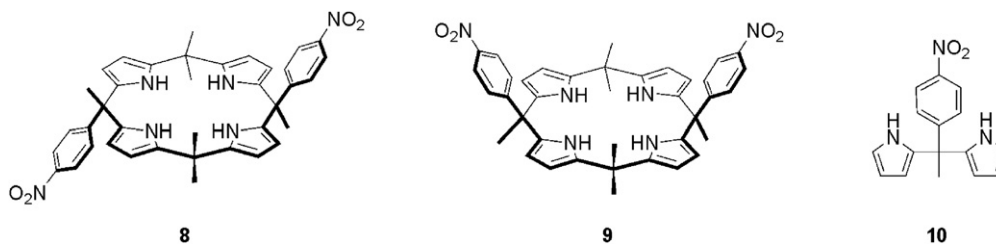
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in Table 1. The reactions were run at room temperature for 24 h using 115 mg (0.67 mmol) of **1** in dichloromethane (DCM) solvent (2 or 4 mL). The crude mixtures were extracted with water and the organic phase analysed by ^1H NMR.

No dihydropyrone **5** was observed when using a diene/aldehyde ratio 1:2 and 10 mol % of the calixpyrrole α,β -isomer **8** but, interestingly, a mixture of aldolic adduct **6** and cycloadduct **7** was produced (entries 2–4). The relative amounts of **6** and **7** depended on the concentration of the reaction system and provide useful information about the reaction pathway.

By using 2 mL of solvent (entry 2) the reaction provided **7** as the major product, hence suggesting a concerted

Calixpyrrole α,α -isomer **9** (entry 7) was totally inactive as catalyst, despite having been reported to be a stronger ligand for anions than its α,β -isomer **8**.¹² Binding constants of **8** or **9** with neutral hydrogen-bond acceptors, such as *p*-nitrobenzaldehyde, are expected to be considerably lower than those observed with negatively charged guests,^{12,13} although their relative magnitudes should reflect the ones observed for anionic guests. Therefore, the lack of catalytic activity of **9** is puzzling. A possible explanation is that **9** binds the aldehyde on the face of the macrocycle bearing the *p*-nitrophenyl units, and these shield the complexed aldehyde from the approach of the diene. This would not be possible in the complex with **8** in which only one face of the carbonyl π -system can be shielded by the *p*-nitrophenyl units.



cycloaddition mechanism as the main path. On the other hand, when the reaction was performed in 4 mL of solvent (entry 3), the predominant formation of **6** was consistent with Mukaiyama aldol condensation as the main pathway. In both cases reaction efficiency was low (25–36%). By increasing the catalyst loading (entry 4) to 20 mol % cycloadduct **7** was isolated in 57% yield and the total conversion was good (60%).

On the basis of our previous studies on organocatalysed reactions,^{9h} we performed the reaction using 5 equiv of aldehyde (entries 5–6). With 20 mol % of the catalyst in 2 mL of solvent (entry 5), the reactants were fully converted: products **5** and **7** were obtained in 33% and 50% yield, respectively, consistent with a predominant cycloaddition pathway.

Dipyrromethane **10** was used as reference compound because it represents a half calixpyrrole. However, it was also inactive as organocatalyst (entry 8), demonstrating that a macrocyclic structure is required for catalytic activity.

Calix[4]pyrrole has been shown² (at least in the solid state) to bind acetone by adopting a 1,3-alternate conformation in which two hydrogen bonds are formed by two distal pyrrole NH units. In contrast, the carbonyl unit of DMF was found to form hydrogen bonds with the NH units of adjacent pyrrole rings whilst the calix adopted a 1,2-alternate conformation. The lack of organocatalytic activity for **10** could originate from a preferred distal binding mode of *p*-nitrobenzaldehyde similar to the one observed for acetone. Therefore, **10** cannot provide a ‘complete’ binding unit that is similar to the one responsible for the catalytic activity of **8**.

Table 1. Conversion data for the cycloaddition of silyloxydiene **1** to the *p*-nitrobenzaldehyde **2** in the presence of **8**, **9** and **10**^a

Entry	2:1 ^b	Solv ^c	Catalyst ^d	Conv. ^e	5 ^f	6 ^f	7 ^f
1	2	2	—	—	—	—	—
2	2	2	8 (10)	36	—	11	25
3	2	4	8 (10)	25	—	20	5
4	2	2	8 (20)	60	—	3	57
5	5	2	8 (20)	90	33	7	50
6	5	4	8 (20)	51	47	4	—
7	5	2	9 (20)	—	—	—	—
8	5	2	10 (20)	—	—	—	—

^a All reactions were performed with 0.67 mmol of diene **1**.

^b Molar ratio of the reagents.

^c Volume of solvent (mL).

^d Amount of catalyst (mol %).

^e Conversion (mol %) determined on the isolated compounds.

^f Yield based on isolated product.

Acknowledgement

This work was sponsored solely by the Universities of Messina and Salerno.

Supplementary data

Experimental procedures for the preparation of catalysts **8**, **9** and **10**, for the cycloaddition reactions, for the isolation of the adducts **5**, **6** and **7**, and their characterisation. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.148.

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