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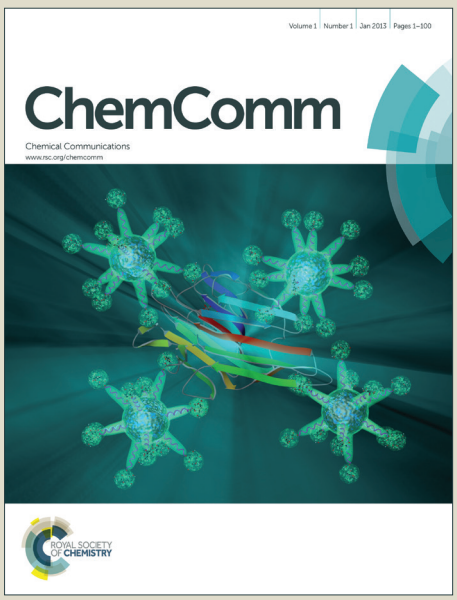

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The First Calcium-Catalyzed Nazarov Cyclisation†

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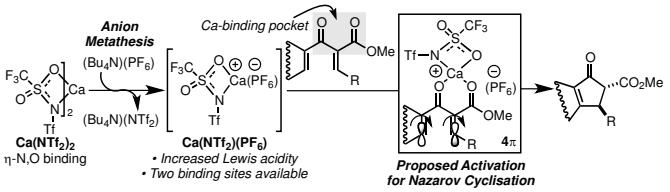
The first calcium-catalysed Nazarov cyclisation is described. The $Ca(NTf_2)(PF_6)$ complex is found to be a very active catalyst for 4π electrocyclisations. The remarkable catalytic activity of this complex is attributed to its increased Lewis acidity compared to other Ca complexes. Spectroscopy studies have provided an insight into the chelating interactions between the substrate and the Ca catalyst.

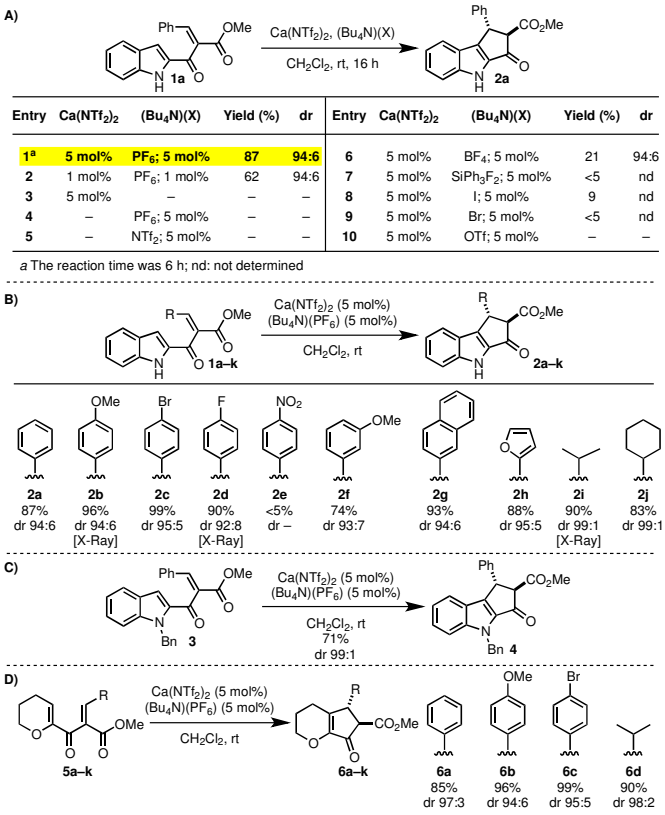
The use of metal complexes as Lewis acids (LAs) is a cornerstone of modern organic synthesis.[1] However, factors such as cost, toxicity and waste disposal render the development of sustainable and non-expensive catalytic protocols necessary.[2] Among the alkaline Earth metals, calcium has great potential to fulfil these criteria and to serve as a suitable LA due to its abundance, low toxicity and ease of disposal.[3] Niggemann have pioneered the use of Ca complexes as LAs in organic synthesis for the functionalization of alcohols and olefins.[4,5] Their catalytic system is based on the readily available and moisture stable $Ca(NTf_2)_2$ [NTf_2 = bis(triflimide)] and requires the use of $(Bu_4N)(PF_6)$ as an additive. This additive promotes anion metathesis that results in the formation of $Ca(NTf_2)(PF_6)$, a complex with increased Lewis acidity (Scheme 1).[4,6] The chemistry of metal triflimidates is strongly affected by the unique properties of the Tf_2N^- anion.[7] In fact, while Tf_2NH is a weaker Brønsted acid than TfOH, metal triflimidates are stronger LAs than metal triflates.[8] This is due to (i) the extensive delocalisation of the negative charge on the Tf_2N^- anion, and (ii) its relatively large volume.[9] As a result the Tf_2N^- anion behaves like a ligand and adopts a η^2-O,O binding geometry to the metal with the exception of Ca, Sr and Ba complexes where it adopts a η^2-N,O geometry.[10] We were intrigued by the fact that after reaction of $Ca(NTf_2)_2$ with $(Bu_4N)(PF_6)$ not only a more Lewis acidic $Ca(NTf_2)(PF_6)$ complex is generated, but also two binding sites become available on Ca.[11] Therefore, a 1,3-dicarbonyl compound could chelate to the metal center and be activated.[12] Among the plethora of transformations that can be envisaged *via* this interesting activation mode, we decided to focus on the Nazarov cyclisation.[13] This 4π conrotatory ring closure allows the efficient, stereoselective synthesis of cyclopentenones and some remarkable advancements have been reported in recent years.[14] However, the use of expensive, toxic metal-based LAs [e.g. Sn, Cr, Ir] is a major limitation. To address this challenge, we envisaged the identification of conditions where sub-stoichiometric amounts of a Ca-based catalyst could successfully promote this transformation (Scheme 1). In this communication we report the development of the first Ca-catalysed Nazarov cyclisation. This also represents the first reported example of an electrocyclic process promoted by Ca.



Scheme 1.

Early work from Frontier has lead to the development of the "polarised" Nazarov cyclisation. This process requires the use of divinyl ketones with strategically placed electron donating and electron withdrawing groups to avoid issues associated with the formation of isomeric products.[15] We therefore started our investigations by preparing substrates of this kind. The electron rich olefin is encapsulated in the indole substituent and incorporation of an ester as the EWG creates a suitable Ca-binding pocket (Scheme 2, see SI). The feasibility of the proposed cyclisation was first examined using indole **1a** and 5 mol% of the Niggemann catalyst[Error! Bookmark not defined.] [$Ca(NTf_2)_2$ and $(Bu_4N)(PF_6)$] in CH_2Cl_2 at room temperature. As reported in Scheme 2A entry 1, the desired Nazarov cyclisation was accomplished and product **2a** was formed in 87% yield and excellent 97:3 *cis:trans* selectivity.[16] Other solvents of different polarity were evaluated but gave inferior results (see SI). The high diastereoselectivity of the product was preserved when the catalyst loading was decreased to 1 mol%, albeit with a slightly diminished yield (entry 2). Control experiments using solely $Ca(NTf_2)_2$, or $(Bu_4N)(PF_6)$ or $(Bu_4N)(NTf_2)$ (the stoichiometric anion metathesis by-product) did not give any product (entries 5–7). These observations rule out the possibility that traces of Tf_2NH were catalysing the process and confirm that $Ca(NTf_2)(PF_6)$ is the active

catalyst.[17] The activity of many LA metals is often affected by the nature of their counterion.[18] We decided to investigate this effect and several $(Bu_4N)(X)$ salts were evaluated in combination with $Ca(NTf_2)_2$. As shown in entries 6–10, none of the salts that were screened proved to be as efficient as $(Bu_4N)(PF_6)$, and **2a** was obtained in low yields (if any). With the optimised conditions in hand, the scope of this novel Ca-catalysed Nazarov cyclisation was evaluated (Scheme 2B). Both electron rich and electron poor aryl and alkyl substituted starting materials **1a–j** reacted well and tricyclic products **2a–j** were generally obtained in high yields and dr.[19] When the *N*-Bn protected indole **3** was exposed to the same reaction conditions product **4** was obtained in similar high yield and selectivity (Scheme 2C). Moreover, we expanded the scope of the process to pyran-containing substrates **5a–c**. Also in this case the cyclised products **6a–c** were obtained in high yields and selectivity favouring the *trans* product (Scheme 2D).

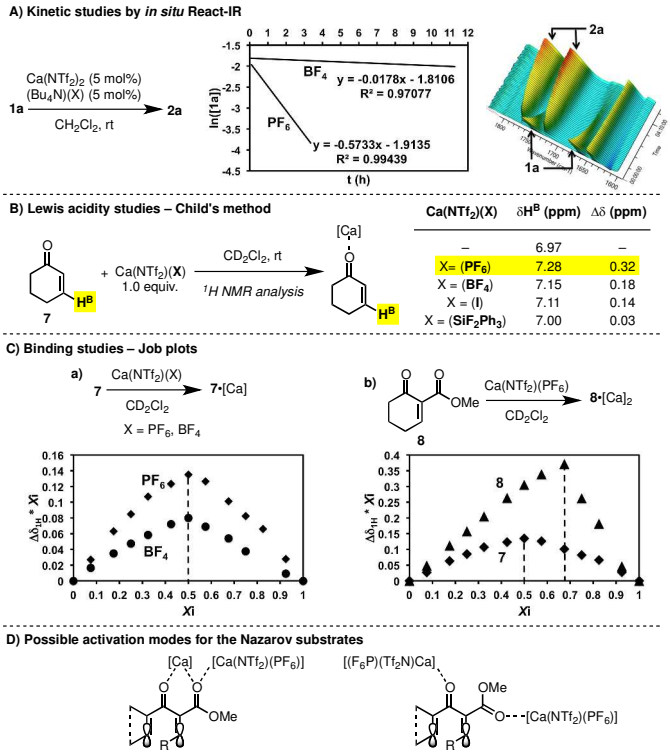


Entry	$Ca(NTf_2)_2$	$(Bu_4N)(X)$	Yield (%)	dr	Entry	$Ca(NTf_2)_2$	$(Bu_4N)(X)$	Yield (%)	dr
1[a]	**5 mol%**	**PF_6; 5 mol%**	**87**	**94:6**	**6**	5 mol%	BF_4; 5 mol%	21	94:6
2	1 mol%	PF_6; 1 mol%	62	94:6	**7**	5 mol%	$SiPh_3F_2$; 5 mol%	<5	nd
3	5 mol%	–	–	–	**8**	5 mol%	I; 5 mol%	9	nd
4	–	PF_6; 5 mol%	–	–	**9**	5 mol%	Br; 5 mol%	<5	nd
5	–	NTf_2; 5 mol%	–	–	**10**	5 mol%	OTf; 5 mol%	–	–

a The reaction time was 6 h; nd: not determined

Scheme 2.

Having evaluated the substrate scope, we performed mechanistic studies to explore the nature of the catalyst further. We were intrigued by the difference in catalytic activity that the counterion X imparted to the various $Ca(NTf_2)(X)$ complexes that were screened during the reaction optimisation. As an example, the rate difference in catalytic activity between $Ca(NTf_2)(PF_6)$ and $Ca(NTf_2)(BF_4)$ in the cyclisation of **1a** was determined by React-IR kinetic studies[20] to be $k_{obs}(PF_6) \approx 30 \times k_{obs}(BF_4)$ (Scheme 3A, see SI). In our proposed mode of activation, the substrate was chelated at both coordination sites on Ca and therefore such a strong counterion effect was not expected. Because $Ca(NTf_2)_2$ is itself catalytically inactive we considered whether incomplete anion metathesis was thwarting the formation of the active Ca catalysts but ^{19}F NMR studies confirmed complete anion exchange in all cases.[21] Alternatively, we reasoned that a difference in Lewis acidity of the Ca complexes might be the explanation for the observed trend in reactivity. This hypothesis was evaluated by measuring the variation of the chemical shifts of H^B of **7** upon binding of the C=O group to the Ca-based LAs (Child's method, see SI).[22] As reported in Scheme 3B, addition of $Ca(NTf_2)(PF_6)$ to **7** resulted in the largest variation in chemical shift for the H^B with the other complexes showing inferior or no variations with a trend mirroring the catalytic activity observed in the Nazarov cyclisation: PF_6>BF_4>I>$SiPh_3F_2$. These results support the hypothesis that Lewis acidity is counteranion-dependent, which consequently affects the ability of the Ca complexes to activate the substrates and promote the electrocyclic ring closure.



Scheme 3.

Analysis of the binding of **7** with $Ca(NTf_2)(PF_6)$ and $Ca(NTf_2)(BF_4)$ by the method of continuous variation (Job's method[23]) revealed a 1:1 stoichiometry for both **7**•[Ca] complexes, and confirmed a stronger binding for $Ca(NTf_2)(PF_6)$ (Scheme 3C-a). Even if $Ca(NTf_2)(PF_6/BF_4)$ complexes have two vacant binding sites it is plausible that, upon complexation of the first molecule of **7**, the new [Ca]•**7** complex displays a diminished Lewis acidity so that it cannot overcome the entropic cost of accepting a second molecule of ligand. Further evidence for complex formation was obtained by diffusion-ordered spectroscopy (DOSY).[24] This analysis revealed a decrease in the translational diffusion coefficient, D_a, of **7** upon exposure to stoichiometric amounts of $Ca(NTf_2)(PF_6)$ that is in line with a formation of a complex (D_a = 26.7 10^{-10} m^2s^{-1} → 15.4 10^{-10} m^2s^{-1}) (see SI). In the case of substrates containing two binding sites (e.g. **1**, **3** and **5**), a stronger binding can be expected. Spectroscopic studies carried out on the model ß-ketoester **8** did indeed confirm an increase in the strength of binding but a change in the complex stoichiometry from 1:1 to 1:2 (**8**•$[Ca]_2$) was determined from the observed shift in the Job-plot maximum from *Xi* = 0.5 to 0.66 (Scheme 3C-b). Also, in this case, DOSY experiments corroborated the formation of a complex between **8** and the Ca catalyst (see SI). Due to the close resemblance of **8** to **1**, **3** and **5**, it is plausible to consider an analogous binding stoichiometry of the Ca catalysts in the activation of the Nazarov substrates used in this study. However,

it is difficult at this stage to distinguish between a 1:1 or a 1:2 substrate:[Ca] stoichiometry due to the low catalyst loading required (5 mol%). Nevertheless, this unexpected finding can account for the variation in catalytic activity of the different Ca(NTf_2)(X). While the first Ca catalyst would sit between the ketone and ester carbonyls, the second might be associated to the ester carbonyl. This second binding is expected to be counterion-dependent and can affect the overall substrate activation. Alternatively, each carbonyl group might chelate a molecule of Ca catalyst (Scheme 3D).

In conclusion we have reported the development of the first Ca-catalysed Nazarov cyclisation. This study shows that Ca(NTf_2)-based catalysts are competent LAs that upon binding to 1,3-dicarbonyls, can promote 4π processes under very mild conditions. Mechanistic investigations have revealed that the nature of the counterion at Ca significantly affects the Lewis acidity of the complex and that up to two Ca complexes can bind to the Nazarov substrates.

Notes and references

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Electronic Supplementary Information (ESI) available: experimental data, React-IR kinetic data, DOSY, Job plots data, ^{1}H and ^{13}C spectra. See DOI: 10.1039/c000000x/

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