A mild calcium catalysed Beckmann rearrangement has been realised, which forgoes the more traditional harsh reaction conditions associated with the transformation. The catalyst system is shown to be tolerant towards a wide variety of functional groups relevant to natural product synthesis and medicinal chemistry and the synthetic utility of the reaction has also been investigated. A preliminary mechanistic investigation was performed to understand the nature of the incoming nucleophile and a possible reaction pathway is described.

The Beckmann rearrangement of aldoximes and ketoximes to the corresponding amides under acidic conditions is an inherently elegant transformation, and has been used to great success in the synthesis of natural products and pharmaceuticals alike. Although the reaction has clear utility in synthetic organic chemistry, the need for harsh reaction conditions limits its usefulness to carefully chosen substrates.

In response to this problem, many groups have reported modifications of the reaction that allows the transformation to proceed under milder conditions. For example, Giacomelli reported that cyanuric chloride afforded the desired amides in good yield, and Yamamoto and co-workers realized the catalytic variant using an acid co-catalyst. Other catalytic variants have been reported such as the use of TPAC, gold, chloral, mercury and iodine. Recently Mhaske and co-workers reported a facile radical Beckmann rearrangement, while Yadav and colleagues harnessed visible light to power the reaction.

Although all these methodologies provide the amides in good yields, they suffer from intolerance to various functional groups. Additionally, many of the reagents and catalysts used could conceivably take part in side reactions, thus limiting their uptake in industry (Scheme 1). During the course of a medicinal chemistry project targeting epigenetic enzymes, we required a mild and functional group tolerant method to synthesize a library of amides for structure activity relationship studies.

In the synthetic community, which is surprising as calcium is a readily available and non-toxic metal. One major drawback associated with using calcium as a reagent in synthesis is its inherent lack of solubility in traditional organic solvents. However over the past decade, pioneering work by the groups of Niggemann, Kobayashi, France and others have shown...
that calcium can be a highly powerful, yet mild catalyst for a range of transformations.

Our group has a burgeoning interest in using alkaline earth metals such as calcium as redox neutral catalysts to power organic transformations, and we reasoned that through judicious choice of catalyst system we could perform a mild Beckmann rearrangement to afford a wide variety of amides. We anticipated that the Lewis acidic nature of the calcium catalyst would be sufficient in generating the nitrillium ion which subsequently provides the requisite amide.

With this in mind we conducted an initial feasibility study to determine if the reaction could proceed (Table 1). Pleasingly, 10 mol% Ca(NTf₂)/nBu₄NPF₆ at room temperature provided the amide in 10% isolated yield. We were initially concerned that the reaction was proceeding stoichiometrically; however upon heating the mixture at 40 °C, the product was obtained in 49% yield. Increasing the temperature further to 80 °C increased both the rate of reaction and isolated yield, affording the product in 93% yield in 2 hours. We next explored the possibility of decreasing the catalyst loading, but we observed a steady decrease in isolated yield with decreasing catalyst loading; however under prolonged reaction times the yield can be recovered. Additionally, the reaction was set-up without either the calcium or ammonium salt, and as shown the reaction did not proceed. Furthermore, we also attempted the reaction in the presence of HNTf₂, however only trace amounts of product were obtained in all cases.

We next turned our attention to the choice of solvent for the reaction (Table 2). As noted, one of the main drawbacks in using calcium as a reagent is its inherent insolubility in many organic solvents. This is partly circumvented through the use of the NTf₂/nBu₄NPF₆ system, but it was noted early in this study that the reactions performed in 1,2-dichloroethane (DCE), upon prolonged reaction times, became heterogeneous. To combat this, several solvents were tested including dichloromethane (DCM), chlorobenzene, n-methyl-2-pyrrolidone (NMP) and dimethylformamide (DMF), however a reduction in isolated yield was observed in each case. We therefore focused our attention on using solvent mixtures employing DCE as the major constituent. After extensive experimentation, a 4 : 1 mixture of DCE : DME proved optimum and this was used throughout.

With these optimised conditions in hand, we probed the substrate scope of the reaction (Table 3). Substituted aryl groups underwent the rearrangement to afford the requisite amides in good yield with both electron donating (2b, 2e) and electron withdrawing groups (2e) being well tolerated. Similar to other reports on the Beckmann rearrangement, electron withdrawing groups resulted in a much slower reaction rate. Free amines (2d) also underwent the rearrangement in good yields. Heteroaryls containing basic nitrogen atoms such as
As shown, further examples also proved successful (Table 4). Proceeded smoothly to afford the amide in excellent yield. Optimum choice. This proved to be the case, and the reaction has been demonstrated, and we show that the reaction is amenable to one pot. We propose a plausible mechanism for the Beckmann rearrangements have been argued over and subjected to prolonged investigation over the past 50 years. It is generally accepted that after activation and dehydration of the oxime, a reactive nitrillium ion is formed. Consequently, the preformed water attacks this reactive intermediate, which following tautomerization, affords the requisite amide. We wanted to investigate the mechanism of the incoming nucleophile, and whether it was free water or a calcium-alkoxide type species. We therefore attempted the reaction with 1b, employing 4 Å molecular sieves to remove molecular water from the reaction, and observed full conversion to the amide in 2 hours. Based on this preliminary result, a plausible reaction mechanism is described below (Fig. 1). The calcium catalyst activates the hydroxyl moiety of the oxime which produces transient [HO⁻ Ca²⁺ PF₆⁻]. This potentially attacks the nitrilium to form intermediate 3a, and following loss of the amide, the active calcium species is regenerated through recombination with PF₆⁻.

In conclusion we have developed a mild, catalytic Beckmann rearrangement employing a calcium(n) catalyst. Our system is tolerant of a range of functionalities pertinent to natural product synthesis and medicinal chemistry, as well as allowing the use of acid labile moieties. The synthetic utility of the reaction has been demonstrated, and we show that the reaction is amenable to one pot. We propose a plausible mechanism based on preliminary investigations, with further detailed studies underway.
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Conflicts of interest

There are no conflicts to declare.

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