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Durga Golagani, Sriram Ajmeera, William Erb, Florence Mongin, Srirama Murthy Akondi. Ferrocene catalyzed redox-neutral difunctionalization of alkenes using cycloketone oxime esters: access to distal imido-nitriles. *Chemical Communications*, 2023, 10.1039/d3cc02422a . hal-04166158

HAL Id: hal-04166158

<https://hal.science/hal-04166158v1>

Submitted on 1 Oct 2023

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Ferrocene catalyzed redox-neutral difunctionalization of alkenes using cycloketone oxime esters: access to distal imido-nitriles†‡

Durga Golagani,^{ab} Sriram Ajmeera,^{ab} William Erb,^{ID} *^c Florence Mongin,^{ID} ^c and Srirama Murthy Akondi,^{ID} *^{ab}

A novel ferrocene-catalyzed cyanoalkyl-imidation of aryl alkenes utilizing cycloketone oxime esters in MeCN under redox-neutral conditions is described. In this three-component reaction, the cycloketone oxime ester is employed as a bifunctional reagent, enabling easy access to diverse distal imido-nitriles with 100% atomic utilization. Preliminary mechanistic studies suggest that the ferrocene–ferrocenium catalytic cycle is responsible for the deconstructive functionalization of cycloketone oxime esters.

The difunctionalization of alkenes is widely recognized as a pivotal strategy in the field of organic chemistry owing to its unique ability to introduce molecular complexity in a single synthetic step. Consequently, synthetic organic chemists are actively pursuing the objective of developing sustainable and atom-economic methods for the difunctionalization of alkenes.¹ Recently, difunctionalization of alkenes using a single bifunctional reagent that supplies two units to add across the double bond has garnered significant attention due to its superior atom-economy.² Zard's pioneering research³ has sparked extensive exploration into the use of cycloketone oxime esters for synthesizing a broad range of functionalized alkylnitriles.⁴ Recently, many transition metal or photoredox catalyzed difunctionalization of alkenes using cycloketone photocatalyzed difunctionalization of alkenes using cycloketone oxime esters as bifunctional reagents.⁶ Similarly, Xia's group achieved the cyanoalkyl-amination of alkenes by using α -imino-oxy acid oxime esters as bifunctional reagents under thioxanthone photocatalytic conditions.⁷ Despite these considerable findings, there is a pressing need for the oxime esters have been reported.⁵ However, in most of these reports, cycloketone oxime esters have only been used as sources of cyanoalkyl radicals and carboxylates released from these molecules have been neglected (Scheme 1A). Wu and co-workers demonstrated a *fac*-tris(2-phenylpyridine)iridium

development of new catalytic systems that enable the difunctionalization of alkenes utilizing cycloketone oxime esters as bifunctional reagents, particularly in the absence of precious metal catalysts. Drawing inspiration from Baran's approach on the imidation of (hetero)arenes utilizing ferrocene (Cp_2Fe) as an electronshuttle catalyst,⁸ we were intrigued to explore the reversible and kinetically favourable ferrocene/ferrocenium redox transformation⁹ towards the deconstructive functionalization of cycloketone oxime esters. We subsequently endeavored to validate this hypothesis experimentally, and we report here our preliminary results on the successful imido-cyanoalkylation of aryl alkenes *via* Cp_2Fe -catalyzed deconstructive functionalization of cycloketone oxime esters. Notably, this approach involves the participation of all components of the reaction partners, including the nitrile solvent, resulting in a novel approach for the synthesis of distal imido-nitriles with 100% atomic utilization (Scheme 1B). To the best of our knowledge, this is the first report on the use of stable, easily accessible and cost-effective¹⁰ Cp_2Fe as a catalyst in the deconstructive functionalization of cycloketone oxime esters.

Initially, 4-*t*-Bu-styrene **1a** and cyclobutanone oxime ester **2a** were selected as model substrates to check the feasibility of a Cp_2Fe catalyzed alkene difunctionalization using cycloketone oxime esters (Fig. 1A). An extensive search for the optimal reaction conditions in terms of stoichiometry of the reagents, catalyst loading, solvent molarity and reaction temperature was undertaken (see the ESI†).

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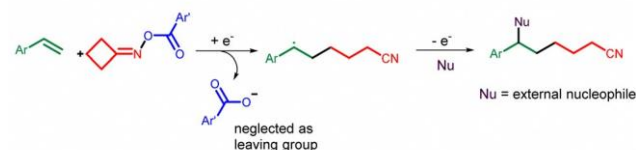
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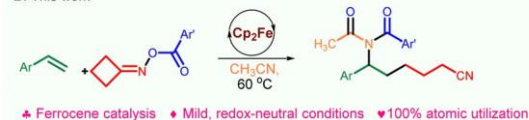
† Dedicated to Dr René Grée on the occasion of his 75th birthday.

‡ Electronic supplementary information (ESI) available.

A. Majority of alkene difunctionalizations using cycloketone oxime esters



B. This work



Scheme 1 Alkene difunctionalization using cycloketone oxime esters.

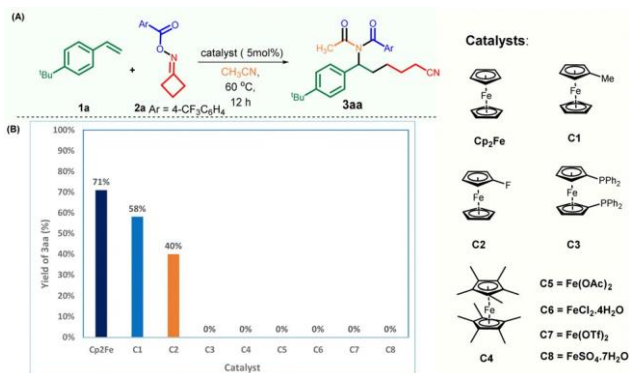


Fig. 1 Development of ferrocene catalyzed cyanoalkyl-imidation of alkenes and reaction optimization. (A) Reaction conditions: styrene **1a** (0.1 mmol), oxime ester **2a** (0.2 mmol), catalyst (0.005 mmol) and CH₃CN (1.0 mL), at 60 °C for 12 h. (B) Screening of various substituted ferrocenes and iron salts as catalysts. Isolated yields are considered.

To our delight, when the 0.1 M CH₃CN solution of these two reagents and 5 mol% Cp₂Fe was heated to 60 °C for 12 h, the four component product **3aa** was formed in 71% yield. After a screening process of various ferrocene-based catalysts, it was discovered that Cp₂Fe was the most optimal candidate for the intended reaction, as depicted in Fig. 1B. Although methylferrocene (C1) and fluoroferrocene (C2) demonstrated efficacy in facilitating the desired reaction, they were found to be inferior to Cp₂Fe. On the other hand, dppf (C3) and Cp*₂Fe (C4) were deemed inadequate for promoting the deconstructive functionalization of oxime ester **2a**. Since Fe(II) salts are established catalysts in cycloketone oxime ester reactions,¹¹ we tested a series of Fe(II) salts (C5–C8) and found that none of them were capable of yielding the desired product **3aa**. This clearly emphasizes ferrocene's superiority over commonly used Fe(II) salt catalysis for this transformation.

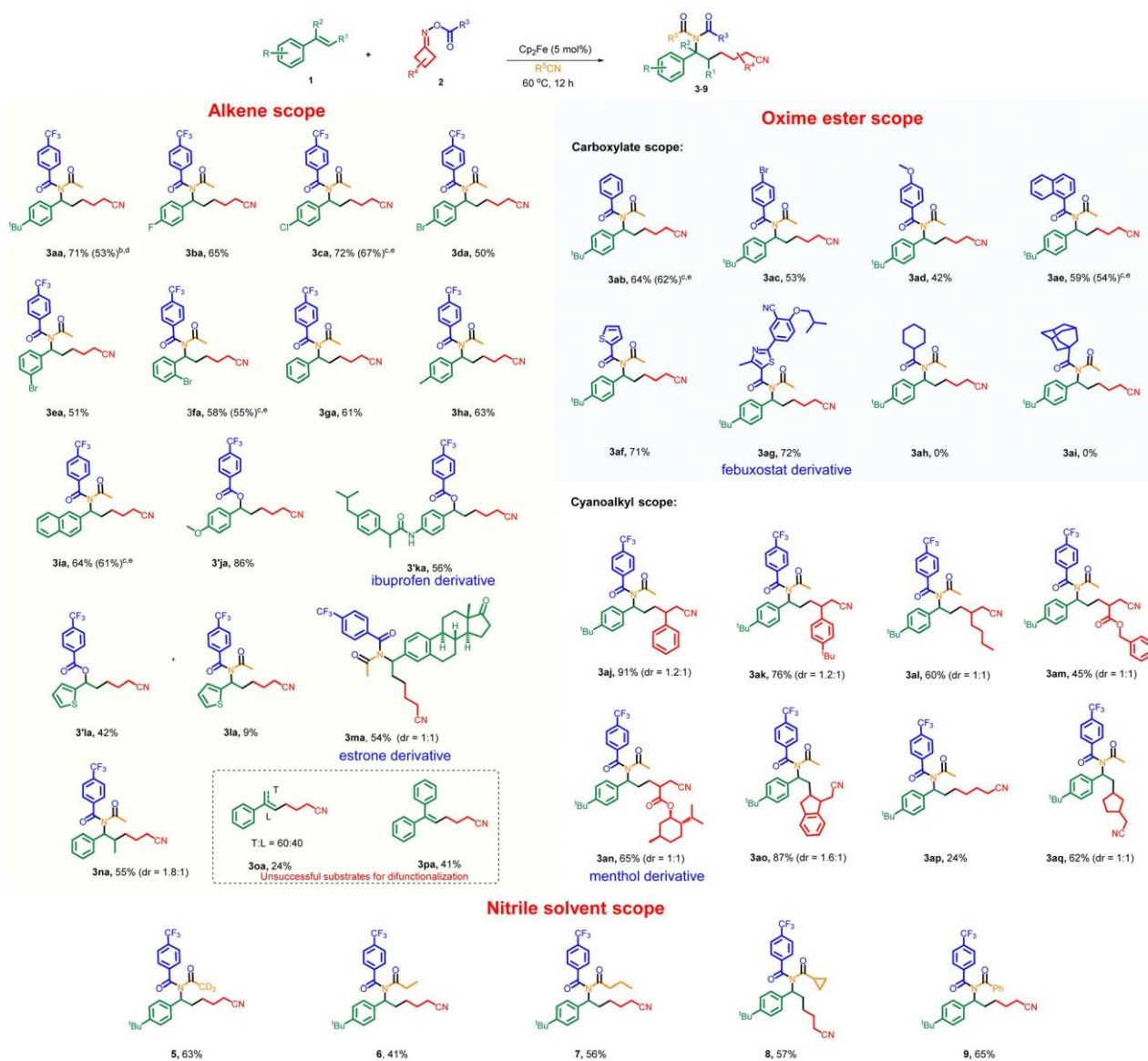
With the optimized conditions in hand, the scope of this protocol was evaluated by applying it to various structurally different styrenes (Table 1). Along with **1a**, styrenes with halogens at various positions reacted well with oxime ester **2a** to confer the products **3ba–3fa** in 50–72% yields. Moreover, simple styrene, 4-methylstyrene and 2-vinylnaphthalene also afforded the anticipated products **3ga–3ia** in good yields. Of particular significance, the difunctionalized products **3'ja** and **3'ka** were obtained from styrenes derived from electronically enriched arenes, such as 4-OMe-Ph (**ij**) and ibuprofen-derived anilide (**1k**), without the involvement of CH₃CN. Additionally,

in the case of 2-vinylthiophene, the formation of the C–O difunctionalized product (**3'la**) was preferred (yielding 42%) over the C–N difunctionalized product (**3la**, yield of 9%). This outcome could be attributed to the selective addition of the more nucleophilic carboxylate to the highly stabilized carbocation intermediate of electronically enriched arenes. Furthermore, styrene derivative **1m**, derived from estrone, reacted efficiently to produce cyano-imide **3ma** in 54% yield. This highlights the potential of this newly developed methodology for practical synthetic applications. Alongside the terminal styrenes, internal *trans*-b-methylstyrene **1n** was also involved in this reaction and furnished the desired cyanoalkylimide **3na** in 55% yield. However, α -substituted styrenes (**1o** and **1p**), afforded Heck-type products (**3oa** and **3pa**) instead of the difunctionalized products.

Next, the extent of applicability of oxime esters was investi-

gated by altering the carboxylate moiety of the oxime ester. In addition to 4-CF₃-benzoic acid derived oxime ester **2a**, aryl carboxylic acid derived oxime esters bearing electronically different substituents such as –H, –Br and –OMe were also found to be suitable for this Cp₂Fe-catalyzed alkene difunctionalization. The desired products **3ab–3ad** were obtained in 42–64% yields. Sterically hindered 1-naphthoic acid and heteroaromatic thiophene-2-carboxylic acid-derived oxime esters were also amenable to this process, giving the corresponding products **3ae** and **3af** in 59% and 71% yields respectively. Markedly, oxime ester derived from the drug molecule febuxostat was also converted to the desired distal cyano-imide **3ag** in an excellent yield of 72%. Whereas the oxime esters derived from aliphatic carboxylic acids including cyclohexanecarboxylic acid and adamantane-1-carboxylic acid (**3ah** and **3ai**) did not undergo deconstructive functionalization under the current catalytic system. This can be attributed to the poor electrophilic ability of alkyl carboxylate components to facilitate a single electron transfer (SET) reduction–fragmentation cascade.¹² Later, variation at the cyanoalkyl component of oxime esters was tested. Cyclobutanone oxime esters bearing aryl (**3aj** and **3ak**), alkyl (**3al**) and ester (**3am** and **3an**) were all well tolerant to afford the desired compounds with good to moderate efficiency. Besides, indene-fused oxime ester was also converted to the target product **3ao** in 87% yield. Importantly, a less strained cyclopentanone-derived oxime ester also participated in this reaction, despite yielding the desired product **3ap** in low yield. However, norbornone derived oxime ester yielded the desired distal imido nitrile compound **3aq** in good yield. Finally, other nitrile solvents such as deuterated acetonitrile, propionitrile, butyronitrile, cyclopropanecarbonitrile and benzonitrile were tested and their corresponding imides **5–9** were isolated in good to moderate yields.

Table 1 Substrate scope of Cp₂Fe catalyzed alkene difunctionalization using cyclobutane oxime esters^a



^a Reaction conditions: styrene **1** (0.1 mmol), oxime ester **2** (0.2 mmol), Cp₂Fe (0.005 mmol) and nitrile solvent (1.0 mL), at 60 °C for 12 h. Isolated yields. ^b 1.6 mmol scale. ^c 0.5 mmol scale. ^d 48 h. ^e 24 h.

To gain insight into the mechanism, some control experiments were conducted (Fig. 2). Firstly, a radical trapping experiment with TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) completely suppressed the formation of desired product and led to the detection of TEMPO-cyanoalkyl adduct **10** in ESI-MS. This clearly indicates a cyanoalkyl radical reaction pathway (Fig. 2A). Next, ¹H NMR studies were carried out to support the interaction of Cp₂Fe with oxime ester (Fig. 2B). The addition of 2 equiv. of cyclobutane oxime ester **2a** to a solution of Cp₂Fe in CD₃CN at room temperature resulted in no change in the Cp₂Fe signal (III). However, additional ferrocene signals were observed after heating this mixture to 60 °C for 12 hours (IV).

Further isolation and characterization revealed the formation of cyanoalkyl-ferrocene **11** (22% isolated yield), which clearly indicates SET-reduction of the oxime ester by Cp₂Fe and subsequent addition of the resultant cyanoalkyl radical to one of the rings of the ferrocene (see ESI†). A similar control

experiment was conducted with styrene **1a**, and both starting materials remained unchanged even after heating (VI and VII). Finally, when an equimolar mixture of **1a**, **2a** and Cp₂Fe was heated to 60 °C in CH₃CN (Fig. 2C), the cyanoalkyl group preferentially added to styrene to form **3aa**, rather than forming cyanoalkyl-ferrocene **11**. This observation clearly rules out the possibility of a catalytic role of compound **11** in this transformation. Based on these observations, a plausible mechanism has been proposed (Fig. 2D). A single-electron transfer from Cp₂Fe to oxime ester (**2**) initiates N–O bond cleavage, resulting in the formation of imine radical **A** and ferrocenium carboxylate. A subsequent C–C σ -bond cleavage of imine radical generates the cyanoalkyl radical **B**. The cyanoalkyl radical selectively adds on to the terminal position of aryl alkene (**1**) to yield the radical **C**.

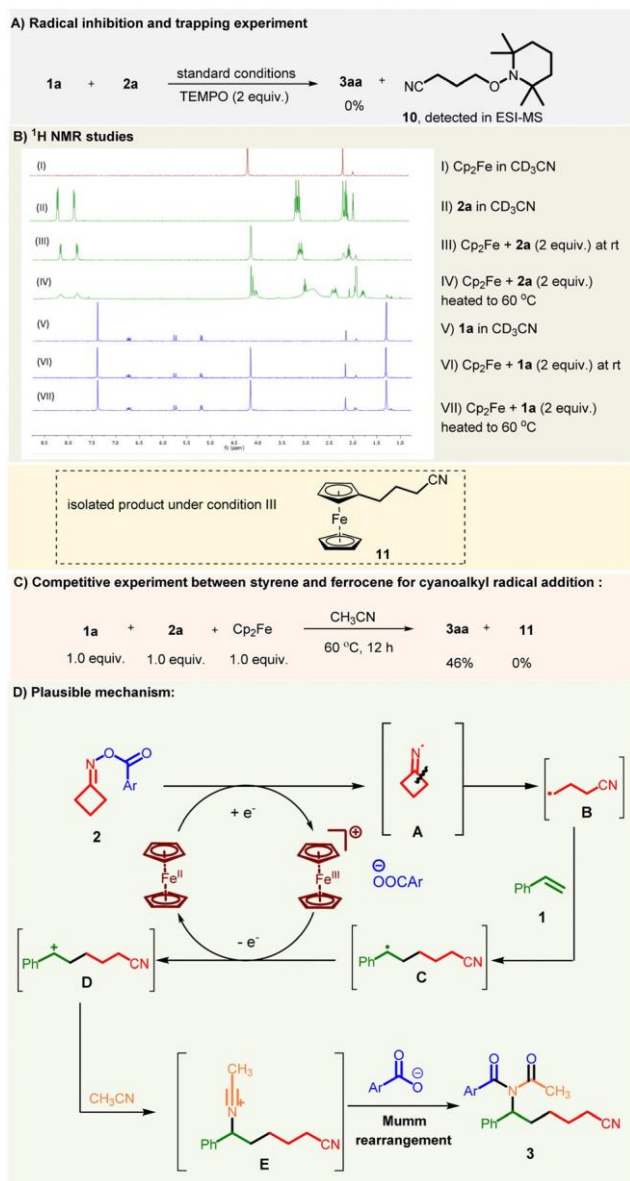


Fig. 2 Mechanistic studies and proposed mechanism.

One-electron oxidation of **C** leads to the formation of benzyl cation **D** and regenerates Cp₂Fe. Nucleophilic attack of nitrile solvent on the cation intermediate **D** results in the formation of intermediate **E**. Finally, Mumm rearrangement of **E** with carboxylate component of oxime ester affords the desired distal cyano-imide (**3**).

In conclusion, for the first time, Cp₂Fe has been demonstrated as an efficient and inexpensive catalyst for alkene difunctionalization using cycloketone oxime esters as bifunctional reagents. This highly atom-economic, mild and redox-neutral protocol has been demonstrated to work over a wide range of substrates, including structurally complex natural products and drug molecules, leading to the formation of structurally diverse remote cyano-imides.

DG thanks University Grants Commission, New Delhi for fellowship. SA thanks Council of Scientific & Industrial Research (CSIR), New Delhi for fellowship. WE, FM and SMA thank the Indo-French “Joint Laboratory for Natural Products and Synthesis towards Affordable Health” program between CSIR-Indian Institute of Chemical Technology and University of Rennes for the platform to carry out the finding jointly (IICT/pubs./2023/183).

Conflicts of interest

There are no conflicts to declare.

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