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DOI: 10.1039/C8GC00299A

Journal Name

COMMUNICATION

Benign catalysis with iron: facile assembly of cyclobutanes and cyclohexenes via intermolecular radical cation cycloadditions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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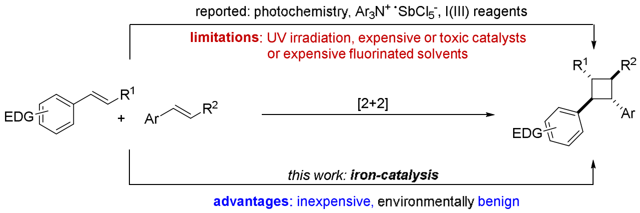
Abstract: We describe a novel and facile iron-catalyzed crossed intermolecular radical cation cycloadditions of styrenes. This catalysis features high efficiency, atom-economy, stereospecificity, scability and very mild reaction conditions, and thus represents a benign and sustainable strategy for the synthesis of valuable functionalized cyclobutanes and cyclohexenes.

Cyclobutanes are highly prominent structural motifs concerning both their important synthetic values and strong bioactivity profiles.[1] As a result, synthetic studies toward this class of molecules have been pursued intensively. The most straightforward and atom-economic strategy is alkene [2 + 2] cycloaddition and studies in this regard has been centered on photochemical methods under ultraviolet or visible light conditions.[2] Despite many advantages and significant advances in the past decades, high-energy irradiation or expensive photocatalysts are generally required. In addition, electrochemical methods as a clean approach have also been utilized.[3] However, the reaction efficiency and standardized and simplified instrumentation are yet to be addressed to facilitate their practical application.[4]

In this context, the radical cation cycloaddition of alkenes provides an efficient and alternative strategy for constructing cyclobutane rings.[5] Radical cations constitute an important class of intermediates due to their versatile reactivity in forming C–C and C–X bonds.[6] A highly fascinating aspect regarding these species is the reversal of electronic nature of an inherently nucleophilic precursor into an electrophilic counterpart upon one-electron oxidation. The synthetic value of such an umpolung event has been shown in many fundamentally important transformations such as pericyclic reactions,[7] rearrangement reactions.[8] Regarding alkene substrates, chemical oxidants are much less exploited in comparison to photochemical approach[5a,c-f] to trigger the radical cation cycloaddition reactions. In this regard, aminium cationic radical salts have often been utilized,[9] which, however, might get decomposed and induces side reactions.[10] Moreover, as the most powerful oxidant, tris(4-bromophenyl)aminium hexachloroantimonate (TBPA$^{+\bullet}$) has some adverse effect to environments and human health.[11] Very recently, Donohoe and co-workers disclosed an elegant study on hypervalent iodine reagents catalyzed radical cation [2 + 2] dimerization of styrenes, but unfortunately with the requisite use of relatively expensive fluorinated solvents.[12] Concerning the limitations of these existing methods, the call for a green and powerful method for radical cation cycloadditions of alkenes is therefore urgent.



Scheme 1 Catalytic intermolecular crossed [2+2] dimerization of styrenes

Iron is recognized as one of the most attractive metals, given its natural abundance, low price, environmental benignity and occurrence even in sophisticated biological systems.[13] Owning to their inherent multiple oxidation states, iron complexes exhibit versatile catalytic reactivity and hold a great promise to achieve sustainable synthetic protocols when compared to other metals. In this context, iron compounds have proven to be robust catalyst for C–H oxidation,[14] cross-coupling reactions[15] and other reactions. It has been disclosed in some early studies that Fe(III) salts as oxidants could catalyze cation radical homodimerization of N-vinylcarboazole.[16] However, their effect in crossed intermolecular cyclobutanation of alkenes remains surprisingly unknown. These crossed coupling processes are generally more challenging due to associated competitive homodimerization, E/Z isomerization or cycloreversion.[5a,e] In

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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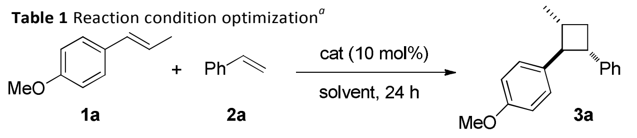
this study, we report a benign and sustainable iron catalysis toward the efficient assembly of unsymmetrical cyclobutanes (Scheme 1).

Our initial aim was to identify a powerful iron complex for alkene radical cation dimerization. To this end, the effect of different Fe(III) catalysts was first evaluated on the model reaction between anethole **1a** and styrene **2a** under air (Table 1). Considering its competitive homodimerization, styrene **1a** was introduced to the reaction mixture via syringe pumper. Pleasingly, the first instance with catalytic quantities of $FeCl_3$ led to the formation of the desired cyclobutane **3a** as a major product (46%, entry 1). Apart from it, unreacted starting materials and homodimer of **1a** were also detected. The reaction also proceeded with ferric nitrate and perchlorate, but iron(III) acetylacetonate was ineffective, implying the significant influence from the organic ligands (entries 2–5). The best performance came from Iron(III) perchlorate hydrate, furnishing **3a** in 52% yield. While other metals such as $AgNO_3$ and MnO_2 failed to deliver the desired product, copper(II) perchlorate hexahydrate was an effective catalyst (entries 6–9). Notably, despite a slightly superior result with anhydrous iron salt (entries 1–2), Iron(III) perchlorate hydrate was taken for further optimization for better practicality. Subsequent screening of solvents identified ethyl acetate as the best reaction medium (entry 10 & table S1). Further improvement was attained by employing excess of styrene **2a** (entry 11) and a slightly elevated reaction temperature (40 °C), whereby the yield of cyclobutane **3a** was improved to 88% (entry 12).

Table 1 Reaction condition optimization[a]

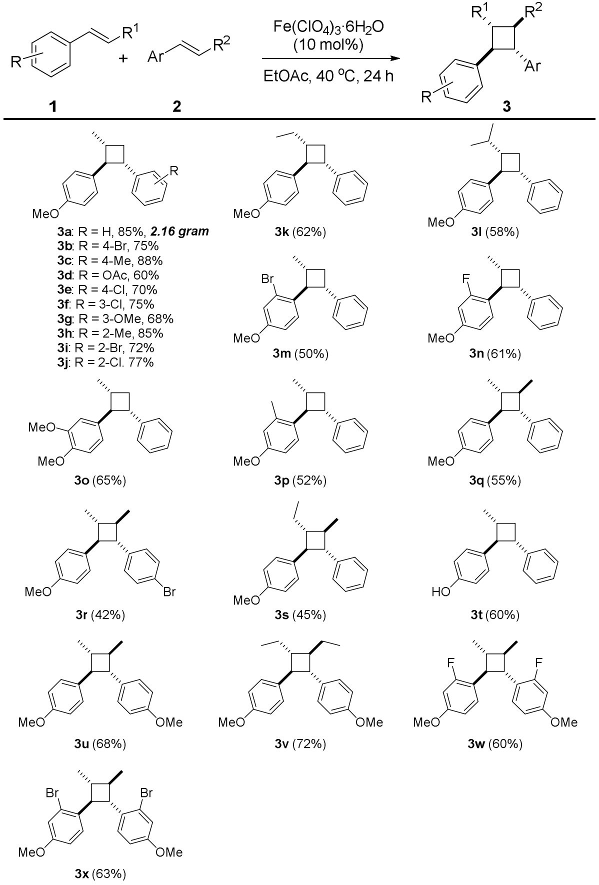


entry	cat.	solvent	T/ °C	yield[b]
1	$FeCl_3$	CH_3CN	25	46
2	$FeCl_3•6H_2O$	CH_3CN	25	39
3	$Fe(NO_3)_3•9H_2O$	CH_3CN	25	20
4	$Fe(ClO_4)_3•6H_2O$	CH_3CN	25	52
5	$Fe(acac)_3$	CH_3CN	25	0
6	$AgNO_3$	CH_3CN	25	0
7	MnO_2	CH_3CN	25	0
8	$NiCl_2$	CH_3CN	25	0
9	$Cu(ClO_4)_2•6H_2O$	CH_3CN	25	34
10	$Fe(ClO_4)_3•6H_2O$	EtOAc	25	62
11[c]	$Fe(ClO_4)_3•6H_2O$	EtOAc	25	82
12[c]	$Fe(ClO_4)_3•6H_2O$	EtOAc	40	88

[a] reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol), catalyst (10 mol%) in solvent (4.0 mL) under air. [b] Isolated yield. [c] 5.0 mmol of **2a** was used.

The optimal reaction conditions were then applied to cycloaddition for other substrates (Table 2). Styrenes bearing electronically diverse substituents on phenyl rings were firstly employed to couple with anethole **1a**. Delightfully, all these compounds were readily processed, providing various unsymmetrically substituted cyclobutanes **3b**–**g** in good to excellent yields (60-88%). Despite potential steric effect, *ortho*-substituted styrenes were also proven to be suitable reaction partners, and the corresponding four-membered rings were constructed efficiently (**3h**–**3j**, 72–85%). Anethole analogues possessing different β-alkyl chains or various substituents at their phenyl rings were all well tolerated, and 50–65% yields were recorded for adducts **3k**–**p**. In addition, substitution at the β-position of **2** led to slightly decreased reactivity. Nevertheless, tetrasubstituted cyclobutanes **3q**–**s** were obtained in higher yields (55% and 42%, respectively) than the only known protocol.[12] Notably, the reaction of *para*-hydroxystyrene also proceeded smoothly to give product **3t** in comparably good yield (60%). This case represents the only methodology yet available for one-step synthesis of cyclobutane containing a phenol moiety. Moreover, the success in the isolation of symmetrical dimers **3u**–**x** showcased the applicability of this catalytic system also for homo [2 + 2] cycloaddition of styrenes. In all cases described above, the cyclobutane products were isolated in diastereomerically pure form. Pleasingly, a gram-scale experiment (**3a**, 2.16 g, 85%) with 5 mol% of catalyst demonstrated the scalability of this protocol.

Table 2 Substrate scope of iron-mediated cyclobutanations[a,b]



[a] reaction conditions refer to table 1, entry 12. [b] Isolated yield.

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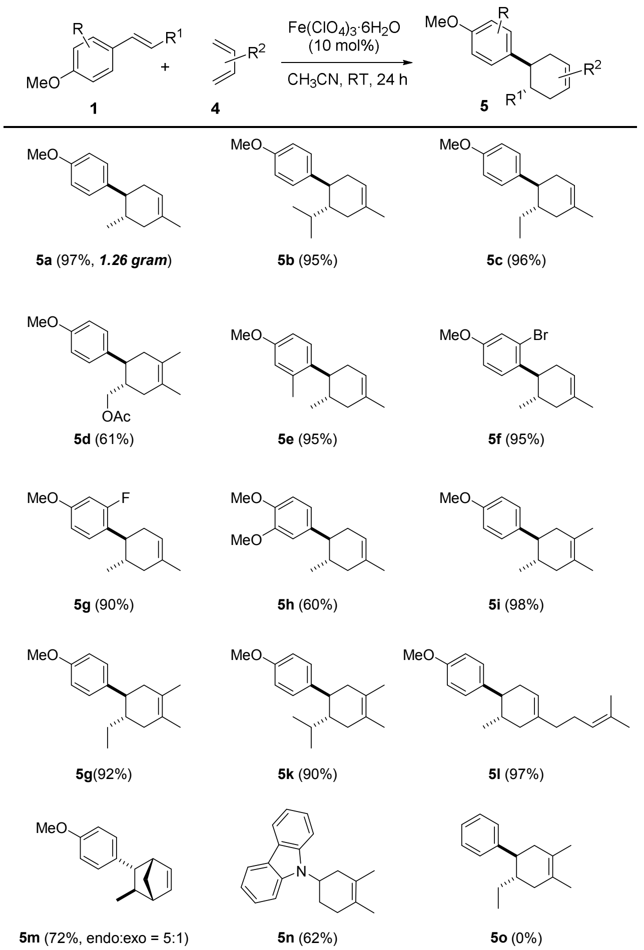
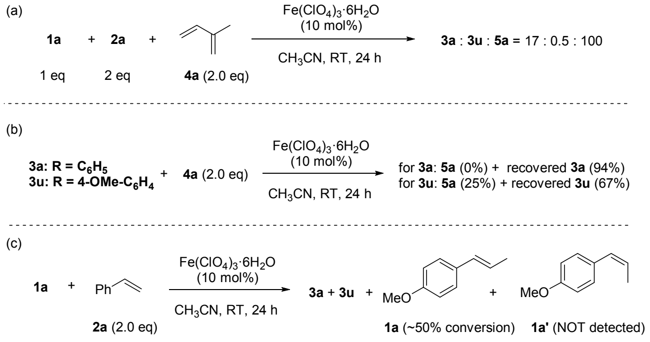
The success of the above cyclobutanation reactions encouraged us to attempt an analogues radical cation [4 + 2] cycloaddition[17] of styrenes with dienes for the synthesis of functionalized cyclohexenes, an important class of six-membered carbocycles.[18] To our delight, under slightly modified conditions, a variety of styrenes **1** as dieneophile efficiently participated in the anticipated Diels-Alder reaction in combination with different dienes, furnishing cyclohexenes in excellent yields and with perfect regio- and stereoselectivities (Table 3). A gram-scale synthesis of **5a** could be achieved quantitatively with 5 mol% of catalyst. Ester substrate and N-vinylcarbazole were also tolerated, delivering adducts **5d** and **5n,** albeit with lower yields. In addition, no cycloaddition (**5o**) occurred when β-methylstyrene was utilized In lieu of **1a**; however, the presence of two methoxy groups induced decomposition of the resulting cyclohexene **5h** (60%). These results imply that the electronic nature of both reactants and adducts has impact on the isolated yields of cycloaddition products.

Table 3 Substrate scope of [4+2] cycloaddition[a,b]

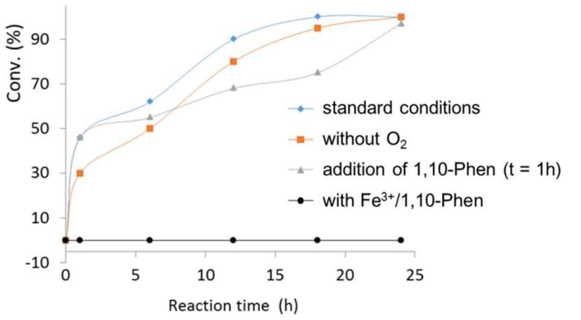


[a] reaction conditions: **1** (1.0 mmol), **4** (2.0 mmol), iron catalyst (10 mol%) in solvent (3.0 mL) under air. [b] Isolated yield.

Some further studies were performed to gain more mechanistic insight. First, control experiments showed that TEMPO and BHT as radical scavengers interrupted both [2 + 2] and [4+2] cycloadditions (see SI), suggesting a radical process is likely involved. Competition experiments revealed that radical cation of **1a** was preferentially captured by diene **4a** over **2a**, while homodimerization was disfavored (**3a** : **3u** : **5a** = 34 : 1 : 200, scheme 2a). Principally, these different reactivities could be interpreted by oxidative potentials of involved substances. Indeed, we measured an oxidation potential of +1.62 V vs. SCE for Fe(ClO$_4$)$_3$•6H$_2$O, which would be able to oxidize **1a** (+ 1.1 V) but not styrene **2a** (+ 2.05 V).[19] However, oxidation potentials for **3a** (+ 1.59 V), **3u** (+ 1.27 V) and **5a** (+ 1.74 V) render them susceptible to be oxidized as well. Thus we performed crossover reactions using these three adducts as reactants. The mixture of **3a** and isoprene **4a** under the catalytic conditions resulted in almost full recovery of starting materials, and no [4 + 2] adduct **5a** was detected, ruling out the cycloreversion path of **3a**. However, we indeed isolated **5a** in 25% yield when **3u** was treated in the same protocol, confirming the oxidation of cyclobutane **3u** back to **1a** (Scheme 2b). Not any cycloreversion of **5a** was detected (see SI), which was in line with the interpretation based on their oxidation potentials. Moreover, careful examining reaction mixture comprising **1a**, **2a** and iron salt at appropriately 50% conversion proved that E/Z isomerization of anethole did not occur (Scheme 2c), thus underlining a potential advantage of this chemical method over irradiation conditions. On the other hand, the reaction of a mixture of *cis*- and *trans*-anethole with diene **4a** gave diastereomerically pure cyclohexene **5a** (see SI). This outcome implies that the respective radical cations adopt more stable anti conformation by C-C bond rotation.



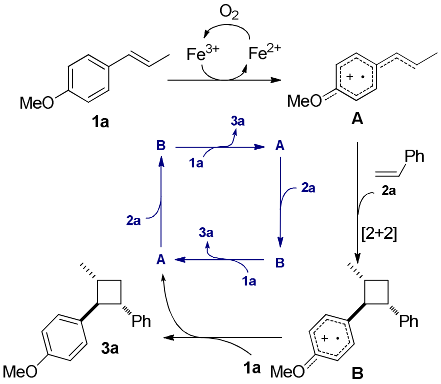
Scheme 2 Mechanistic studies



DOI: 10.1039/C8GC00299A

Figure 1 Progress of iron-catalyzed [2 + 2] cycloaddition of **1a** with **2a** under controlled conditions

Additional experiments were conducted by introducing 1,10-phenanthroline as a ligand (10 mol%) to the [2 + 2] reaction mixture (t = 1 h, *ca.* 45% conversion). ^{1}H NMR studies showed that the cyclobutanation was still progressing to reach full conversion but at a slightly dropped rate as compared to standard conditions (Figure 1). In sharp contrast, pre-formed iron complex of this ligand completely interrupted the formation of **3a**. The results suggest that chain propagation is likely involved in this radical cation [2 + 2] reactions.[18] On the other hand, although a beneficial influence of oxygen was observed, performing the cycloaddition in degassed acetonitrile under argon also led to full translation of **1a** at a slightly dropped rate. We thus conclude a possible role of aerobic atmosphere to turn over the iron(II) to iron(III), which accordingly contributes to the overall efficiency of the reaction. Taken together, a plausible mechanism is proposed (Scheme 3, shown in [2 + 2] dimerization). Anethole **1a** is initially oxidized by iron(III) to radical cation species **A**, which is coupled with styrene **2a** to generate radical cation **B**. This intermediate regains an electron dominantly from the neutral substrate **1a** and concurrently releases product **3a**, consequently affording a new radical cation **A** to continue the chain. The turnover of iron(III) is crucial to trigger the oxidation of **1a** once the chain termination occurs.



Scheme 3 A plausible reaction mechanism

In summary, we have developed the first intermolecular radical cation cycloadditions of styrenes using catalytic amount of ferric salts. The method reported represents a novel, efficient and green approach to selectively assemble various functionalized cyclobutanes and cyclohexenes under very mild reaction conditions. Given both synthetic and biological values of these classes of skeletons, as well advantages of iron catalysis in many aspects, we believe our methodology disclosed herein will find widespread applications in synthetic chemistry. Further investigations to apply radical cation intermediates in other organic reactions are underway.

Acknowledgements

The authors thank financial supports from the National Natural Science Foundation of China (21602067). The authors are also grateful to the Analytical and Testing Centre of HUST, Analytical and Testing Centre of School of Chemistry and Chemical Engineering (HUST) as well as 100 Talents Program of the Hubei Provincial Government. Prof. Yuefa Gong and Dengfu Lu (HUST) are acknowledged for helping with cyclic voltammetry studies.

Conflicts of interest

There are no conflicts to declare.

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Benign catalysis with iron: facile assembly of cyclobutanes and cyclohexenes via intermolecular radical cation cycloadditions

Yushuang Yu, Yu Fu and Fangrui Zhong*