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Iron(III)/O_2-Mediated Regioselective Oxidative Cleavage of 1-Arylbutadienes to Cinnamaldehydes

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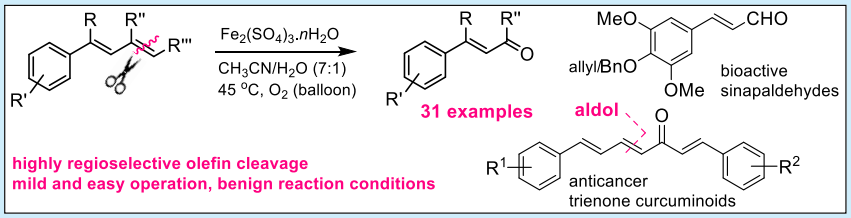
Supporting Information



ABSTRACT: A simple, efficient, and environmentally benevolent regioselective oxidative cleavage of 1-arylbutadienes to cinnamaldehydes mediated by iron(III) sulfate/O_2 has been developed. The reaction offered good yields and excellent regioselectivity and showed good functional group tolerance (31 examples). The method is important, as few reports with limited substrate scope are available for such excellent oxidative cleavage of conjugated dienes.

Oxidative cleavage of double bonds through ozonolysis is perhaps the most common method in synthetic laboratories and as well on industrial scale.[1] However, it has inherent demerits being explosive and requiring special handling procedures.[2] Methods for oxidative cleavage of single double bond in a substrate are available.[3] However, there are few reports with limited examples for regioselective cleavage of dienes.[4] Neumann and co-workers developed [*cis*-Ru(II)-$(dmp)_2(H_2O)_2](PF_6)_2$[5] along with H_2O_2 (10−15 equiv) for cleavage of nonconjugated dienes with selectivity toward terminal/primary alkenes.[4a] Alternatively, the method of Gebbink et al.[4c] using [$Fe(OTf)_2$(mix-BPBP)] along with H_2O_2 (1.5 equiv) and $NaIO_4$ (1.5 equiv) showed preference for cleavage of electron-rich and internal double bonds. Liu et al.[4b] used the MnCl-tetrakis(4-hydroxyphenyl)porphyrin-poly-(ethylene glycol) complex along with $NaIO_4$ (1.5−7 equiv) for oxidative cleavage of monoalkenes, with limonene as the only diene example for selective internal double bond cleavage.

A few reports with limited examples for aryl-butadiene cleavage have appeared in the literature.[6] Aronovitch and Mazur[6a] reported the oxidative cleavage of **1a** and **2a** (only two diene examples) absorbed on inorganic supports with light and oxygen (Scheme 1A). The 9,10-dicyanoanthracene (DCA) sensitized photooxidation of 1,4-diphenylbutadiene **2a** (only diene example) in mixed surfactant vesicles was investigated by Tung and co-workers[6b] to give benzaldehyde and cinnamaldehyde (Scheme 1B). At the same time, Grossi and co-workers[6c] reported the peroxynitrous acid mediated nonselective cleavage of **2a** to give cinnamaldehyde (10%) along with the 1,2-diol (15%), 1,2-adduct (10%), and 1,4-adduct (65%) being formed (Scheme 1C). A recent report by Xiong et al.[6d] disclosed the conversion of various styrenes to α-azido acetophenones using TMS-N_3 and $Cu(OTf)_2/O_2$. In this work, **1a** (only example) under the latter conditions provided benzaldehyde (25%) and cinnamaldehyde (32%) by a nonselective olefin cleavage (Scheme 1D). While there exists a good number of methods for oxidative cleavage of styrene-type compounds to benzaldehydes,[7] the corresponding regioselective oxidative cleavage of 1-arylbutadienes to cinnamaldehydes is underdeveloped, with limited substrate scope. Cinnamaldehydes are important compounds in explorative research as starting materials[8] as well as commercially in the food, cosmetic, flavor, and fragrance industries[9] and medicinally for antifungal,[10] antibacterial/antibiotic,[11] and antitermitic activities.[12] Due to low toxicity, these are also used as fungicides and pesticides.[13] While cinnamaldehydes are prepared by different methods,[14] a recent paper used allyl benzenes in oxidation with DDQ to prepare cinnamaldehydes,[15] although similar procedures with allyl/alkyl benzene were reported earlier.[16] An alternative method selectively cleaving the terminal double bond of 1-arylbutadienes to cinnamaldehydes (and not benzaldehydes), without overoxidation to cinnamic acid or benzoic acid, with a wider substrate scope would be highly desirable.

Our work was a serendipitous discovery. We recently reported efficient alternative methods for Wacker oxidation of aliphatic terminal olefins and styrenes using $Fe_2(SO_4)_3{\cdot}nH_2O$ or DMP as terminal oxidants along with an appropriate Pd-catalyst[17] (Scheme 1E). In an attempt to oxidize (*E*)-1-(4-Methoxyphenyl)butadiene **1b** under our $Fe_2(SO_4)_3.nH_2O$/$PdCl_2$ conditions[17a] to styryl methyl ketone (Wacker oxidation), we observed the formation of 4-methoxycinnamaldehyde **3b** exclusively (Scheme 1F). The reaction in the absence of $PdCl_2$ catalyst also delivered the same results. We

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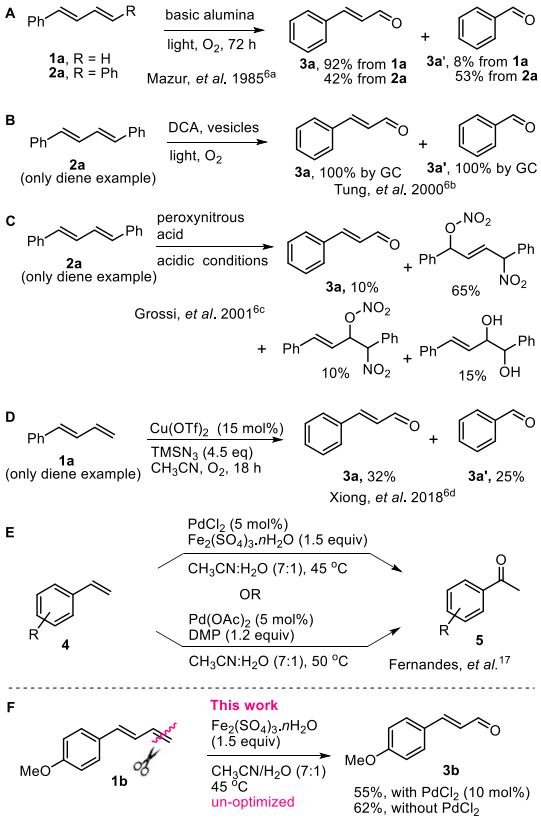
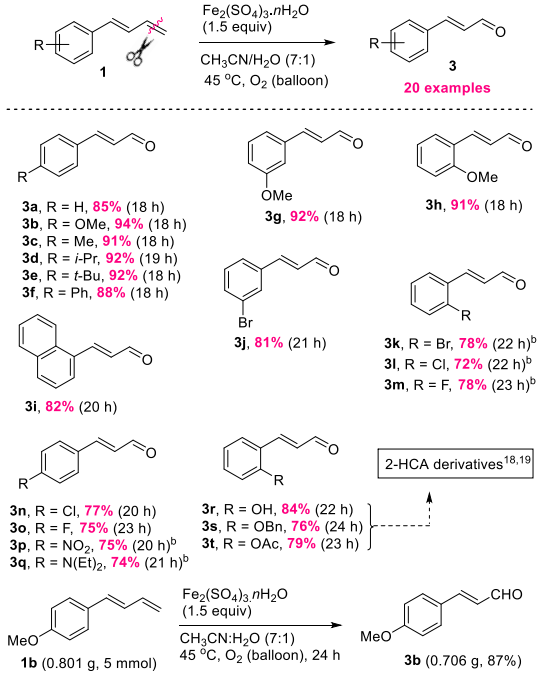
Scheme 1. Synthesis of Cinnamaldehydes and Wacker Oxidation of Styrenes



planned to explore this chemistry for efficient cleavage of the terminal olefin bond of 1-arylbutadienes to cinnamaldehydes. The reaction also offers scope for the synthesis of drug molecules and valuable compounds.[9−13,18,19] The 1-arylbutadiene unit could be looked upon as a latent functionality to be unveiled as cinnamaldehyde in a multistep synthesis.

We screened various iron salts, different solvents, and temperature for the oxidative cleavage of 1-(4-methoxylphenyl)butadiene **1b** as a model substrate (see Table S1, in Supporting Information for details). This study revealed that $Fe_2(SO_4)_3{\cdot}nH_2O$ (1.5 equiv) in CH_3CN/H_2O (7:1) at 45 °C under an oxygen atmosphere (balloon) was optimal. The scope and limitations of this method were next investigated on a series of substituted 1-arylbutadienes **1** (Scheme 2). Substrates with OMe, alkyl, or Ph substituents **1a−h** delivered the corresponding cinnamaldehydes **3a−h** in good to excellent yields (85−94%). 1-(Naphthalen-1-yl)butadiene **1i** furnished **3i** in 82% yield. Halogenated substrates **1j−o** also worked well in giving the corresponding cinnamaldehydes **3j−o** in good yields (72−81%). Substrates with electron-withdrawing groups like NO_2 (**1p**) provided the cinnamaldehydes **3p** in 75% yield. The diethylamine moiety on the arylring compound **1q** was also well tolerated providing the corresponding cinnamaldehyde **3q** in 74% yield. The phenolic substrate **1r** and its corresponding derivatives like benzyl **1s** and acetyl **1t** all gave the cinnamaldehydes **3r−t** in good yields (76−84%). These compounds (**3r−t**) are bioactive and can also lead to important 2-hydroxycinnamic acid (2-HCA) derivatives.[18,19] A reaction on larger scale, **1b** (0.801 g, 5.0 mmol), led to **3b** (0.706 g) in 87% yield, indicating possibility for scale up of the reaction (Scheme 2).

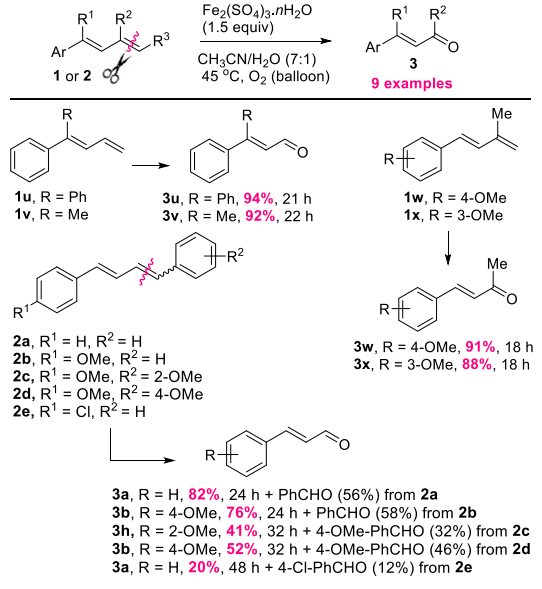
Scheme 2. Substrate Scope for Oxidative Cleavage of 1-Arylbutadienes 1[a]



[a]**1** (0.5 mmol), $Fe_2(SO_4)_3{\cdot}nH_2O$ (1.5 equiv), CH_3CN/H_2O (4 mL, 7:1) at 45 °C, O_2 (balloon), 18−24 h. [b]For **3k−m**, **3p**, and **3q**, the (*E*/*Z*)-**1k−m**, **1p**, and **1q** were used.

The oxidative cleavage using $Fe_2(SO_4)_3{\cdot}nH_2O/O_2$ was extended to substituted 1-arylbutadienes **1u−x** and **2a−e** to provide the mono-olefin cleaved products **3** in good to excellent yields (Scheme 3). The 1,1-diphenylbutadiene **1u** and (*E*)-1-methyl-1-phenylbutadiene **1v** provided *β*-phenylcinnamaldehyde **3u** and *β*-methylcinnamaldehyde **3v** in

Scheme 3. Oxidative Cleavage of Substituted 1-Arylbutadienes 1 or 2[a]



[a]**1** or **2** (0.5 mmol), $Fe_2(SO_4)_3{\cdot}nH_2O$ (1.5 equiv), CH_3CN/H_2O (7:1, 4 mL), 45 °C, O_2 (balloon), 18−48 h.

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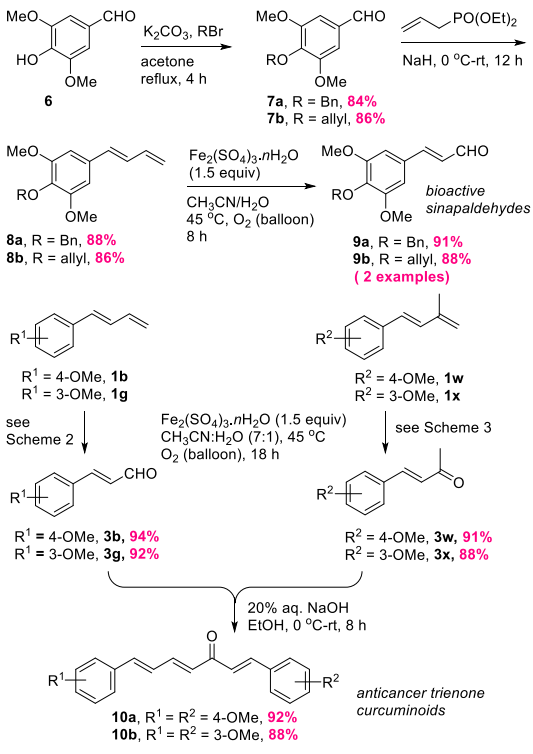
excellent yields of 94% and 92%, respectively. 1-(4-Methoxyphenyl)-3-methylbutadiene **1w** and 1-(3-methoxyphenyl)-3-methylbutadiene **1x** on oxidative cleavage provided the α,β-unsaturated methyl ketones **3w** and **3x** in 91% and 88% yields, respectively. No trace of 4-methoxy- or 3-methoxybenzaldehyde was obtained here, even though the two double bonds were equally substituted. The (*E,E*)-1,4-diphenylbutadiene **2a** displayed an excellent monocleavage of butadiene to provide cinnamaldehyde **3a** in 82% yield. Here benzaldehyde was obtained as a second product in 56% yield. The reaction was selective and did not yield only benzaldehyde as the product by cleavage of both the double bonds. Similarly, the unsymmetrical (*E,E*)-1-(4-methoxyphenyl)-4-phenylbutadiene **2b** on oxidative cleavage provided 4-methoxycinnamaldehyde **3b** in 76% yield. Here also we obtained benzaldehyde in 58% yield with no formation of cinnamaldehyde **3a** as the second product, displaying selectivity for cleavage of the C1−C2 double bond. Similarly, the (*E,E*)-1-(2-methoxyphenyl)-4-(4-methoxyphenyl)butadiene **2c** and (*E,Z*-1,4-bis(4-methoxyphenyl)butadiene **2d** on oxidative cleavage provided 2-methoxycinnamaldehyde **3h** (41%) and 4-methoxycinnamaldehyde **3b** (52%), respectively, along with 4-methoxybenzaldehyde formed in each case in 32% and 46% yields, respectively. The 1-(4-chlorophenyl)-4-phenylbutadiene **2e** was sluggish in reaction and partly decomposed providing cinnamaldehyde **3a** in 20% yield along with 4-chlorobenzaldehyde isolated in 12% yield.

The present oxidative cleavage method was employed in the synthesis of bioactive substituted sinapaldehydes[20] and the trienone curcuminoids[21] as shown in Scheme 4. Alkylation of phenol **6** provided the benzyl ether **7a** or allyl ether **7b**, which on olefination gave the dienes **8a** and **8b**, respectively. The oxidative cleavage of these dienes furnished the sinapaldehyde

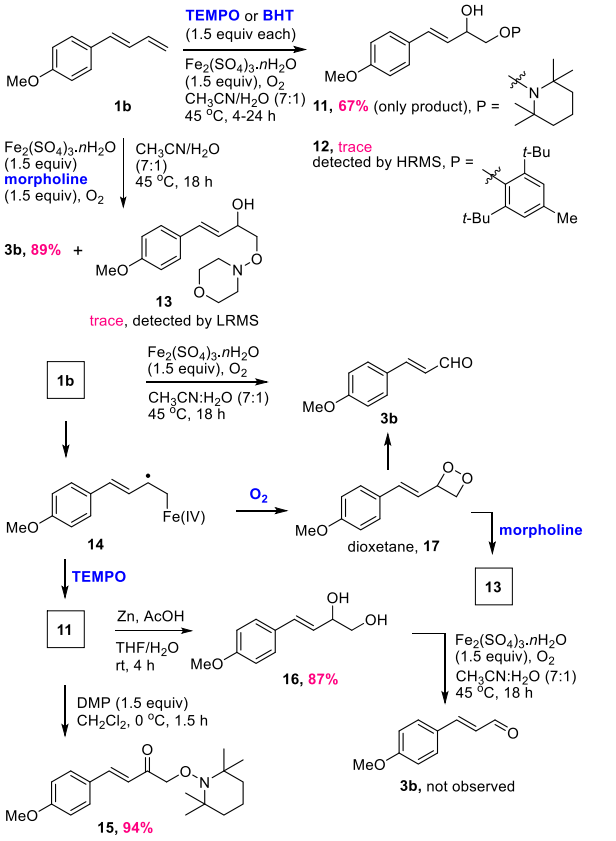
Scheme 4. Synthetic Application of Oxidative Cleavage of 1-Arylbutadienes



derivatives **9a** and **9b** in 91% and 88% yields, respectively. Remarkably the allyl double bond in **9b** was intact. The aldehydes **3b** and **3g** (obtained by oxidative cleavage of dienes **1b** and **1g**) (Scheme 2) on aldol condensation with methylstyryl ketones **3w** and **3x** (obtained from **1w** and **1x**) gave the trienones **10a** and **10b** in 92% and 88% yields, respectively. These have been studied as anticancer compounds.[21]

To gain insight in the mechanism, we investigated the reaction of **1b** in the presence of TEMPO and BHT, which are generally used to trap radical intermediates (Scheme 5). In

Scheme 5. Control Experiments and Plausible Mechanism



either case product **3b** was not observed. TEMPO (1.5 equiv) led to the adduct **11** (67%), whose structure was further confirmed by oxidation to the keto compound **15** indicating a terminal TEMPO adduct.[22] Further, the hydrolysis of **11** with Zn/AcOH gave terminal diol **16**, which under the optimized oxidative conditions did not provide **3b**. Thus, a diol intermediate is ruled out in this oxidative cleavage. With BHT, a trace amount of the adduct **12** was detected by HRMS. This indicated that the reaction to be proceeding via radical intermediates formed by electron transfer by iron(III). Hence the radical **14** initially formed undergoes oxygen addition to give the terminal dioxetane **17**.[3h,23] Morpholine was used to trap the dioxetane moiety as reported in literature.[24] This reaction led to the formation of the product **3b** in 89% yield. In this reaction a trace amount of morpholine adduct **13** was detected by LRMS. Thus, dioxetane **17** formation is evident, which then leads to cleavage by reverse opening leading to the formation of observed cinnamaldehyde product **3b**.

In summary, in this paper we have developed an efficient Fe(III)/O_2-mediated regioselective oxidative cleavage of the

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terminal double bond of 1-arylbutadienes to various cinnamaldehydes in good to excellent yields. The method can be executed in a simple operation under an oxygen atmosphere and aqueous media. Thus, the method holds promise in organic synthesis being environmentally benevolent and that limited procedures are available for such excellent oxidative cleavage.[4,6]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03562.

Experimental procedures and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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