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Fe-Catalyzed Reductive Coupling of Unactivated Alkenes with β-Nitroalkenes

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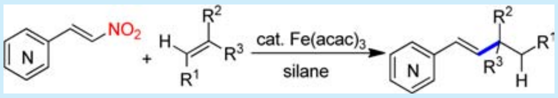
Supporting Information

ABSTRACT: An Fe-catalyzed reductive coupling of unactivated alkenes with β-nitroalkenes has been developed. The reaction proceeds through a radical pathway, with β-nitroalkenes serving as the vinylating reagents and the nitro group being cleaved in the process. Therefore, this method provides a viable synthetic approach to valuable secondary- and tertiary-alkylated styrene derivatives. Furthermore, control experiments were conducted and a plausible mechanism is proposed.



Alkylated styrenes represent an important structure in natural products and pharmaceuticals, such as Pitavastatin, Vorapaxar, Metanicotine, Tamoxifen, and Zuclopenthixol (Figure 1).[1] Therefore, the development of facile syntheses of alkylated styrenes has attracted considerable attention. The classical approaches include Wittig reaction and Julia olefination,[2] and these reactions rely on the requisite phosphonium salts and sulfone starting materials. The Heck reaction is another powerful method for access to styrenes, but sometimes suffers from a limited substrate scope.[3] Alternatively, Oshima has developed a cobalt-catalyzed Heck-type reaction of alkyl halides with styrenes that affords alkylated styrenes, and this transformation proceeds through a radical pathway.[4] Recently, Nishikata reported an efficient generation of a functionalized tertiary-alkyl radical for a copper-catalyzed tertiary-alkylative Heck-type reaction, via a similar type of radical mechanism.[5] Despite these advances, the development of a mild and general method for the facile synthesis of secondary- and tertiary-alkylated styrenes from simple starting materials remains an important challenge.

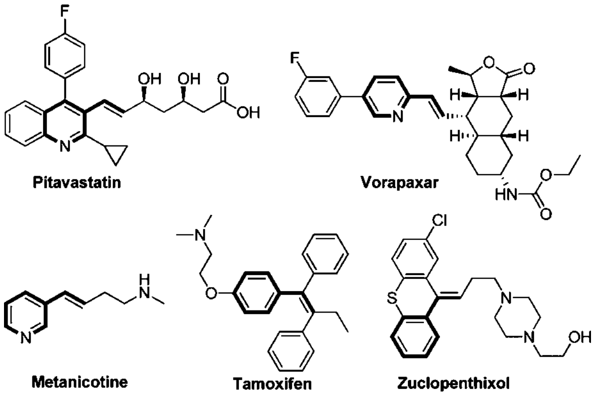
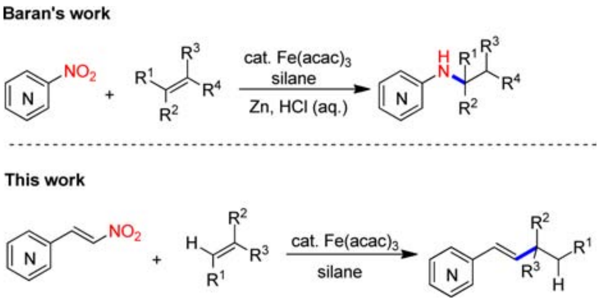


Figure 1. Selected drugs with structure of alkylated alkenes.

Recently, the Fe-catalyzed coupling of unactivated alkenes has emerged as a powerful and distinct method for the facile construction of C−C, C−N, and C−X (X = F, Cl, S) bonds that allows divergent functionalization. These transformations revealed that unactivated alkenes could be converted to putative radical species which can be trapped by various acceptors. For example, Boger demonstrated the hydrofluorination and hydroazidation of unactivated alkenes,[6] while Baran developed a practical olefin cross-coupling and hydromethylation of unactivated alkenes.[7] These methods have provided rapid access to many compounds that were difficult or perhaps impossible to access using other methods. Recently, Baran further invented a practical olefin hydroamination of nitroarenes, in which the nitro group can be reduced in situ to nitrosoamine and sequentially intercepted by the radical species (Scheme 1).[8]

In continuation of our research on the functionalization of unactivated alkenes,[9] herein we report an Fe-catalyzed reductive coupling of unactivated alkenes with β-nitroalkenes (Scheme 1). Interestingly, the nitro group is cleaved in this

Scheme 1. Fe-Catalyzed Coupling of Unactivated Alkenes with Nitro Compounds



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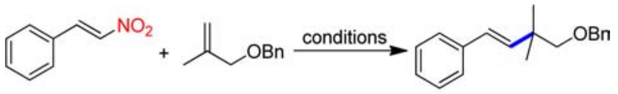
reductive coupling to furnish the valuable secondary- and tertiary-alkylated styrene derivatives.

We commenced our study by investigating β-nitrostyrene **1a** and unactivated alkene **2a**. When the reaction was subjected to Boger's $Fe_2(ox)_3{\cdot}6H_2O$ and $NaBH_4$ conditions in ethanol, at either 0 or 60 °C, the reductive coupling product was not observed (Table 1, entries 1−2). Variation of the reductant revealed that $EtSiH_3$ also was not effective (entry 3), but gratifyingly, the utilization of $PhSiH_3$ at 60 °C gave a product **3a** in 60% yield (entry 4). Standard methods of identification showed that the nitro-group had been cleaved and the product was a tertiary-alkylated styrene derivative. This promising result encouraged us to further optimize the reaction conditions, and we next switched the Fe(III) salt to $Fe(acac)_3$. The combination of $Fe(acac)_3/EtSiH_3$ was inferior, and **3a** was not detected (entry 5). Replacement of $EtSiH_3$ with $PhSiH_3$ led to the formation of **3a** in a significant 90% yield (entry 6). To unravel the synthetic potential, a 5 mmol scale reaction was carried out and the reaction was still efficient, affording the product in 82% yield. Decreasing the temperature to 0 °C completely suppressed the reactivity (entry 7). When the reaction was carried out at rt, **3a** was formed in 75% yield (entry 8). Moreover, shifting the solvent to THF at 60 °C led to a decreased yield (entry 9). Since the β-nitrostyrene **1a** served as a vinylation reagent in this process,[10] other vinylation reagents such as (*E*)-(2-(phenylsulfonyl)vinyl)benzene **4** and cinnamonitrile **5** were tested and found not applicable in this protocol (Figure 2).[11]

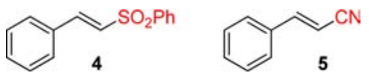
Table 1. Optimization Experiments[a]



1a **2a** **3a**

entry	Fe(III) salt	reductant	solvent	*t* (°C)	yield (%)[b]
1	$Fe_2(ox)_3{\cdot}6H_2O$	$NaBH_4$	EtOH	0	<5
2	$Fe_2(ox)_3{\cdot}6H_2O$	$NaBH_4$	EtOH	60	<5
3	$Fe_2(ox)_3{\cdot}6H_2O$	$EtSiH_3$	EtOH	60	<5
4	$Fe_2(ox)_3{\cdot}6H_2O$	$PhSiH_3$	EtOH	60	60
5	$Fe(acac)_3$	$EtSiH_3$	EtOH	60	<5
6	**$Fe(acac)_3$**	**$PhSiH_3$**	**EtOH**	**60**	**90 (82)**[c]
7	$Fe(acac)_3$	$PhSiH_3$	EtOH	0	<5
8	$Fe(acac)_3$	$PhSiH_3$	EtOH	25	75
9	$Fe(acac)_3$	$PhSiH_3$	THF	60	67

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), Fe(III) salt (10 mol %), reductant (0.4 mmol), argon, 8 h. [b] Yield of isolated product. [c] The value in parentheses refers to 5 mmol scale.

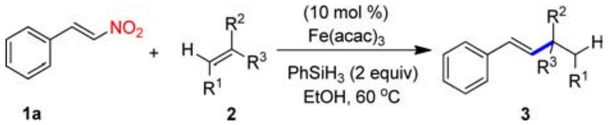


4 **5**

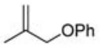
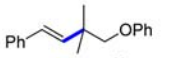
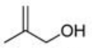
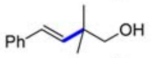
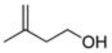
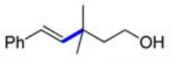
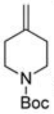
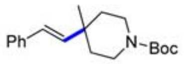
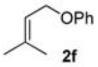
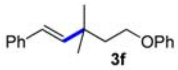
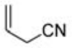
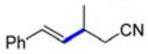
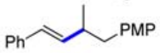
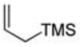
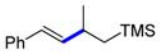
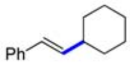
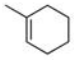
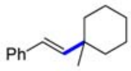
Figure 2. Other vinylation reagents unsuccessfully screened.

With the optimized conditions in hand, we next investigated the scope with various unactivated alkenes (Table 2). Disubstituted terminal alkenes served as viable donor substrates in this reductive coupling providing tertiary alkylated styrenes (**3b**−**3e**) in good to excellent yields (Table 2, entries 1−4), with exclusive bond formation occurring at the most substituted side of the alkenes. Notably, ether, hydroxy, and even piperidine ring functionality were well tolerated in this process, thus offering opportunities for further derivatizaiton. Trisubstituted alkenes were also applicable furnishing the product **3f** in good yield (entry 5). Additionally, when monosubstituted terminal alkenes with valuable cyano, *para*-methoxyphenyl, and trimethylsilyl functional groups were subjected to this process, the reaction proceeded smoothly to enable access to secondary-alkylated styrenes in moderate to good yields (entries 6−8). Moreover, cyclic alkenes such as cyclohexene and 1-methylcyclohexene were amenable to this transformation delivering the corresponding products in moderate yields (entries 9−10). Interestingly, when the more hindered norbornene was used in this protocol, the reaction furnished the endocyclic tethered styrene **3l** in moderate yield (entry 11), which is difficult to access with conventional methods.

Table 2. Substrate Scope of Unactivated Alkenes[a]



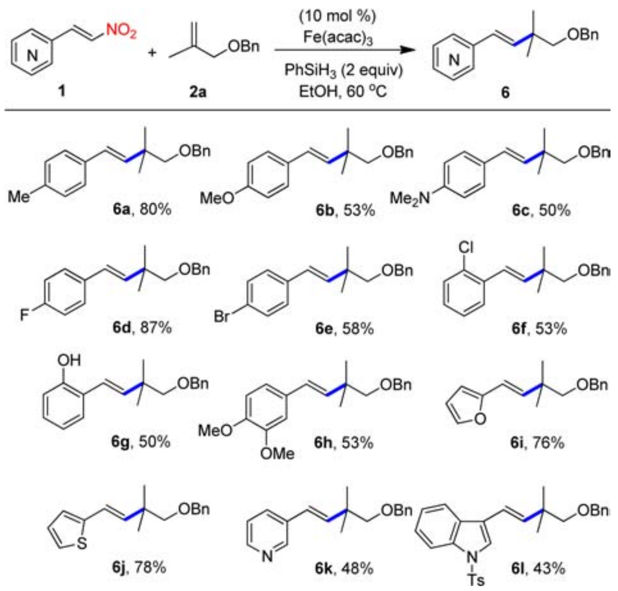
1a **2** **3**

entry	alkene	product	yield (%)[b]
1	 **2b**	 **3b**	84
2	 **2c**	 **3c**	70
3	 **2d**	 **3d**	63
4	 **2e**	 **3e**	42
5	 **2f**	 **3f**	62
6	 **2g**	 **3g**	56
7[c]	 **2h**	 **3h**	72
8	 **2i**	 **3i**	45
9	 **2j**	 **3j**	42
10	 **2k**	 **3k**	45
11	 **2l**	 **3l**	50

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Fe(acac)_3$ (10 mol %), $PhSiH_3$ (0.4 mmol), in EtOH at 60 °C for 8 h, argon. [b] Yield of isolated product. [c] PMP = *para*-methoxyphenyl.

Next, a variety of nitroalkenes were utilized as vinylation reagents to react with unactivated alkene **2a** to construct diverse alkylated styrenes (Table 3). Gratifyingly, many substituents, such as fluoro, chloro, bromo, methyl, methoxy, dimethylamino, and hydroxy, were well tolerated in this reductive coupling to provide the functionalized alkylated

Table 3. Substrate Scope of Nitroalkenes[a]

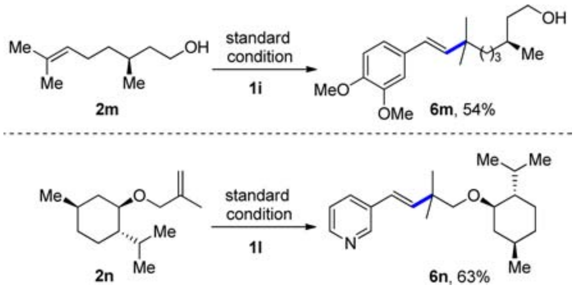


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), Fe(acac)$_3$ (10 mol %), PhSiH$_3$ (0.4 mmol), in EtOH at 60 °C for 8 h, argon; yields refer to isolated products.

styrenes in good yields (**6a**–**6g**). And the electron properties did not show significant effects on the reactivity. Additionally, polysubstitution in the aromatic ring of the nitroalkenes was also compatible with this process generating the corresponding product in moderate yield (**6h**, 53%). Interestingly, when heterocyclic nitroalkenes containing the furan, thiophene, pyridine, and indole moieties were utilized in this reductive coupling, the process delivered the desired alkenes in moderate to good yields (**6i**–**6l**). Considering the wealth of alkylated alkenes accessible, this process represents a powerful and distinct approach toward their construction under mild reaction conditions and with readily available starting materials.

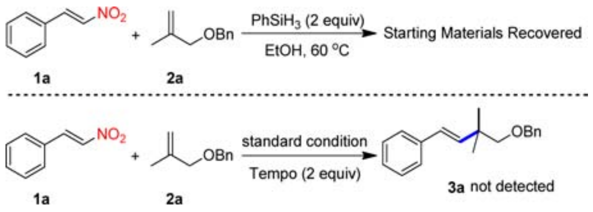
Furthermore, the synthetic utility of this reductive coupling protocol was demonstrated by vinylation of alkenes with a natural product derivative (Scheme 2). For example, the (*S*)-(−)-*β*-citronellol **2m** could be easily coupled with nitroalkene **1i** for access to alkylated styrene derivative **6m** in 54% yield under standard conditions. Meanwhile, the L-menthol derived alkene **2n** could be converted to corresponding vinylpyridine derivative **6n** in 63% yield upon coupling with nitroalkene **1l**. Therefore, this protocol can provide an expedient approach to those olefins with natural product moieties.

Scheme 2. Scope of Alkenes with Natural Products Derivatives



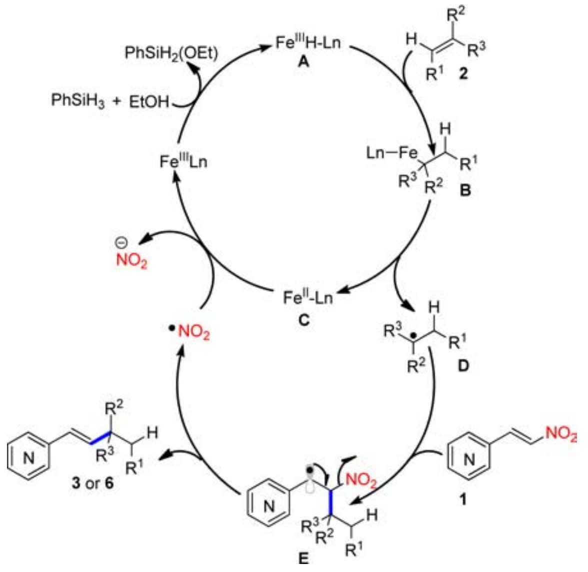
To gain insight into the possible reaction mechanism, control experiments were carried out (Scheme 3). Omission of Fe(acac)$_3$ completely shut down the reactivity and the starting materials were recovered, demonstrating the necessity for the Fe catalyst. Moreover, when a radical scavenger such as Tempo was added, the reductive coupling product **3a** was not observed, indicating a radical-mediated reaction pathway.

Scheme 3. Control Experiments



Based on these results and past literatures, a plausible mechanism is proposed in Scheme 4.[7,10,12]Initially, the Fe(III)-catalyst is converted to Fe hydride species **A** in the presence of phenylsilane and ethanol.[13,14] Then **A** regioselectively adds to alkene **2** to form **B**, placing the Fe atom on the more substituted carbon atom. The dissociation of **B** delivers Fe(II) species **C** and alkyl radical **D**, which is trapped by nitroalkene **1** to generate the *β*-nitro radical **E**. The sequential elimination of **E** would furnish the alkylated styrene products (**3** or **6**) and a nitro radical,[15,16]which would reoxidize **C** to an Fe(III) species to enable the catalytic cycle.

Scheme 4. Proposed Mechanism



In summary, we have developed an Fe-catalyzed reductive coupling of unactivated alkenes with nitroalkenes. The unactivated alkenes are converted to alkyl radicals which are trapped by the nitroalkene, while the nitro group is cleaved in the sequential elimination to furnish the products to enable the catalytic cycle. Therefore, this method provides a rapid and efficient access to alkylated styrene derivatives, with simple and readily available starting materials.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02294.

Full experimental procedures and spectra data (PDF)

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Notes

The authors declare no competing financial interest.

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