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Authors: Hongli Bao, Liang Ge, Wujun Jian, Huan Zhou, Shaowei Chen, Changqing Ye, Fei Yu, Bo Qian, and Yajun Li

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Iron-Catalyzed Vinylic C-H Alkylation with Alkyl Peroxides

Liang Ge⁺, Wujun Jian⁺, Huan Zhou⁺, Shaowei Chen, Changqing Ye, Fei Yu, Bo Qian, Yajun Li, and Hongli Bao^{*}

Dedication ((optional))

Abstract: A variety of alkyl peresters and alkyl diacyl peroxides which are readily accessible from carboxylic acids are utilized as general primary, secondary, and tertiary alkylating reagents for iron catalyzed vinylic C-H alkylation of vinyl arenes, dienes, and 1,3-enynes. This transformation affords the olefinic products in up to 98% yields with high *E/Z* values. A broad range of functionalities including carboxyl, boronic acid, methoxy, ester, amino, and halides are tolerated. This protocol provides a facile approach to some olefins that are difficult to access, and hence offers an alternative to the existing systems. The synthetic utility of this method is demonstrated by late-stage functionalization of selected natural product derivatives.

Introduction

Carboxylic acids are inexpensive, stable, and non-toxic chemical feedstock widely used in numerous transformations. The decarboxylative cross coupling reactions of carboxylic acids and their derivatives have thrived in the past decades and enabled many new organic reactions.^[1-2] Compared with the widely used aryl carboxylic acids, decarboxylative functionalization of alkyl carboxylic acids has been less explored, presumably due to the facile β -hydride elimination from alkyl metal intermediates.^[3] Recently, significant achievements have been made in metal catalyzed decarboxylative alkylation, chlorination, fluorination, and other reactions with alkyl carboxylic acids.^[4] But methods for catalytically decarboxylative vinylic C-H alkylation with alkyl carboxylic acids or their derivatives are still lack.

The activation of alkyl carboxylic acids via formation of redox-active esters has been emerging as a powerful strategy for decarboxylative coupling reactions.^[5-8] Recently, the activated alkyl carboxylic acids has been used by Fu group^[9] and Glorius group^[10] independently for the development of a similar palladium-catalyzed intermolecular decarboxylative vinylic C-H alkylation at mild reaction conditions (Fig. 1a). This method is enabled by blue light irradiation. But methods for vinylic C-H alkylation with alkyl carboxylic acids or their derivatives are still highly needed. It is worth mentioning that vinylic C-H alkylations

with alkyl halides has also been studied.^[11-13]

Alkyl peresters and alkyl diacyl peroxides are readily available from alkyl carboxylic acids and commonly used as oxidants or radical initiators. Other than being used as radical initiators and oxidants, they have been rarely employed in reactions as alkyl electrophiles.^[14,15] One main reason for the lack of this utilization of peroxides might be due to their explosive nature. Actually, peroxides have been utilized safely with precautions as methylation reagents,^[15b,15c,16] stoichiometric oxidants, or radical sources.^[17] We are interested in developing reactions with alkyl peresters and alkyl diacyl peroxides as alkylating reagents.^[17,18] Herein, we report an iron-catalyzed^[19] vinylic C-H alkylation of vinylarenes, dienes and 1,3-enynes, using alkyl peresters and alkyl diacyl peroxides as the alkylating reagents (Fig. 1b). A variety of peresters and diacyl peroxides containing primary, secondary, and tertiary alkyl groups readily undergo this iron-catalyzed transformation to afford multi-substituted alkenes in high yields and excellent selectivities.

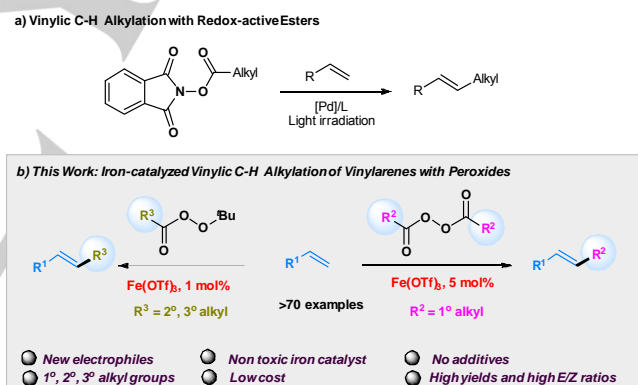


Figure 1. Decarboxylative Vinylic C-H Alkylation with Alkyl Carboxylic Acids.

Results and Discussion

Peresters as the Secondary and Tertiary Alkylating Reagents

We initiated our studies by evaluating the reaction parameters, such as metal catalysts, additives, solvents, and temperatures, for the reaction of styrene with perester **2a** (Table 1). First, the metal catalysts were screened with THF as the solvent under refluxing reaction conditions. Fe(OTf)₃ was found to be the most effective one and the reaction provided the desired product **3aa** in 68% yield (entries 1-8). Several other solvents were then tested (entries 9-14). While anisole and MTBE couldn't promote the desired transformation, solvents such as 1,4-dioxane, NMP, CH₃CN, and DMF showed lower efficiencies than that of THF. The yield of **3aa** increased significantly when the loading of

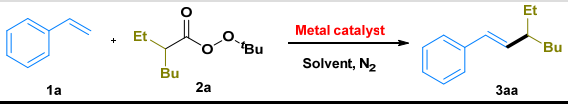
[*] L. Ge,^[†] W. Jian,^[†] H. Zhou,^[†] S. Chen, C. Ye, F. Yu, B. Qian, Y. Li, Prof. Dr. H. Bao
Key Laboratory of Coal to Ethylene Glycol and Its Related Technology, State Key Laboratory of Structural Chemistry, Center for Excellence in Molecular Synthesis
Fujian Institute of Research on the Structure of Matter, University of Chinese Academy of Sciences
155 Yangqiao Road West, Fuzhou, Fujian 350002 (P.R. China)
E-mail: hlbao@fjirsm.ac.cn

[†] These authors contributed equally to this work.

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Fe(OTf)₃ was decreased, presumably due to the controllable generation of alkyl radical with reduced amount of catalyst (entry 15). The reactions conducted with 0.5-2 mol% of Fe(OTf)₃ afforded **3aa** in up to 93% GC yields (entries 16-18). If the peroxide was added in one pot, the isolated yield of **3aa** dropped from 84% to 71% (entry 19). With one equivalent of peroxide, the isolated yield of **3aa** further dropped to 60% (entry 20). In the absence of a metal catalyst, only trace amount of compound **3aa** was detected (entry 21). The result indicates that an iron catalyst might be required for this reaction.

Table 1. Reaction Conditions Optimizations with Perester **2a**^[a]



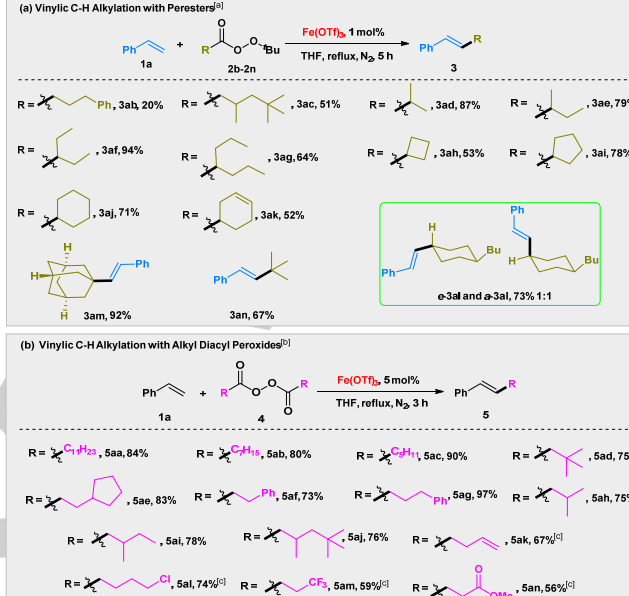
Entry	Metal catalyst (mol%)	Solvent	Yield (%) ^[b]
1	Pd(TFA) ₂ /10	THF	trace
2	Pd(OAc) ₂ /10	THF	6
3	Cu(OAc) ₂ /10	THF	trace
4	AgOTf/10	THF	25
5	Ce(OTf) ₃ /10	THF	12
6	Yb(OTf) ₃ /10	THF	14
7	La(OTf) ₃ /10	THF	11
8	Fe(OTf) ₃ /10	THF	68
9	Fe(OTf) ₃ /10	1,4-Dioxane	37
10	Fe(OTf) ₃ /10	Anisole	trace
11	Fe(OTf) ₃ /10	MTBE	trace
12	Fe(OTf) ₃ /10	NMP	15
13	Fe(OTf) ₃ /10	CH ₃ CN	10
14	Fe(OTf) ₃ /10	DMF	14
15	Fe(OTf) ₃ /5	THF	86
16	Fe(OTf) ₃ /2	THF	93 (84) ^[c]
17	Fe(OTf) ₃ /1	THF	93 (84) ^[c]
18	Fe(OTf) ₃ /0.5	THF	90
19	Fe(OTf) ₃ /1	THF	(71) ^[d]
20	Fe(OTf) ₃ /1	THF	(60) ^[e]
21	–	THF	trace

[a] Reactions were conducted with styrene **1a** (0.5 mmol), perester **2a** (1.5 mmol, added portion-wise), catalyst, and solvent (2 mL), refluxed for 5 h. [b] Yield was determined by GC analysis. [c] Yield of isolated product. [d] Perester **2a** (1.5 mmol) was added in one pot. [e] Perester **2a** (0.5 mmol) was added in one pot.

With the reliable conditions in hand, we proceeded to study the scope of the reaction with respect to the peresters (Table 2a). Primary alkyl peresters **2b** and **2c** reacted with styrene to give the desired products **3ab** and **3ac** in 20% and 51% yield, respectively. The reactions of *t*-butyl peresters, generated from acyclic secondary carboxylic acids, with styrene afforded the corresponding *E*-alkene products **3ad-3ag** in good to high yields (64-94%). *t*-Butyl peresters containing cyclic secondary alkyl group also reacted to provide **3ah-3ak** in moderate to good yields (52-78%). The reaction of cyclic perester **2l** afforded

product **3al** as a 1:1 diastereoisomer. *t*-Butyl perester **2m** bearing a bulky 1-adamantyl group reacted smoothly, producing **3am** in 92% isolated yield. The acyclic tertiary perester **2n** underwent this reaction to afford product **3an** in 67% yield. It is worth noting that all these reactions produced exclusively *E*-olefins, with no hazardous wastes generated in the process.

Table 2. Vinylic C-H Alkylation of Styrene with Alkyl Peresters and Diacyl Peroxides.



(a) Vinylic C-H Alkylation with Peresters^[a]

(b) Vinylic C-H Alkylation with Alkyl Diacyl Peroxides^[b]

[a] Reactions were conducted with styrene (0.5 mmol), perester (1.5 mmol), Fe(OTf)₃ (1 mol%) and THF (2 mL) in a 100 °C oil bath for 5 h. [b] Reactions were conducted with styrene (0.5 mmol), diacyl peroxide (0.75 mmol), Fe(OTf)₃ (5 mol%) and THF (2 mL) in a 90 °C oil bath for 3 h. [c] Reaction was conducted at 70 °C (oil bath).

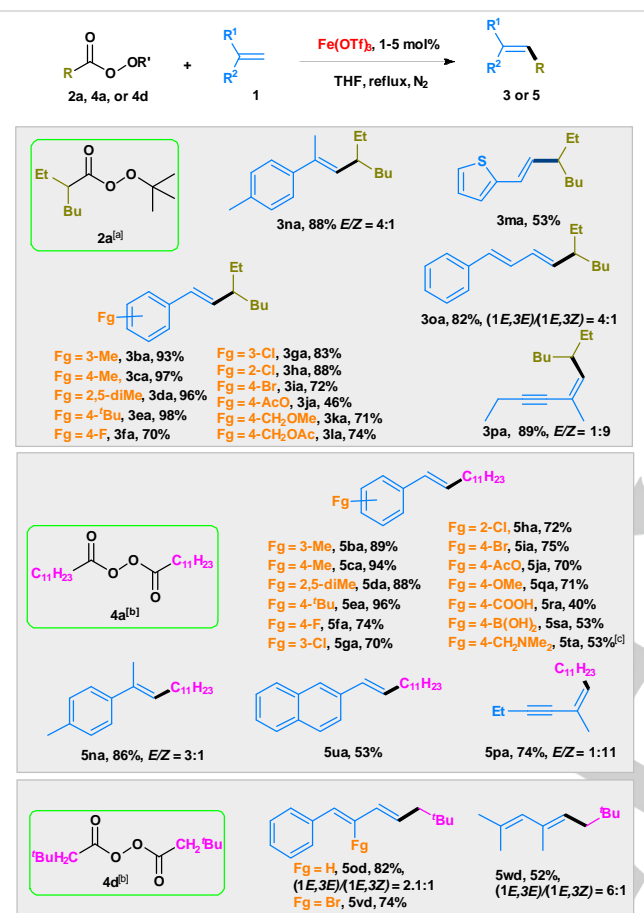
As can be seen from Table 2a, the reaction of *t*-butyl perester containing a primary alkyl group proceeded in a very low yield (**3ab**, 20%). We found that alkyl diacyl peroxides are good alternatives to provide primary alkyl groups in high efficiencies. After an extensive screening of the conditions (for details, please see Supporting Information (SI), Table S2), we found that alkylation of styrene conducted with 1.5 equivalent of lauroyl peroxide (LPO, **4a**) and 5 mol% of Fe(OTf)₃ in THF provided the desired product **5aa** in 84% yield. Subsequently, the substrate scope of alkyl diacyl peroxides, readily synthesized in a one-step process from the corresponding carboxylic acids, were examined under the identified conditions. As shown in Table 2b, reactions of alkyl diacyl peroxides afforded the corresponding products **5aa-5aj** in good to excellent yields (73-97%). The diacyl peroxides with functionalities, such as alkenyl, chloride, trifluoromethyl, and ester group, reacted to give the corresponding products **5ak-5an** in moderate to good yields at a relatively lower temperature (70 °C, oil bath). Excellent *E/Z* selectivities were achieved, with the exclusive formation of *E*-

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alkenes. These results suggest that alkyl diacyl peroxides are suitable for primary alkylation while *t*-butyl peresters are effective for secondary and tertiary alkylation.

Olefin Scope for Vinylic C-H Alkylation of Vinylarenes, Dienes, and 1,3-Enynes

Table 3. Vinylic C-H Alkylation of Vinylarenes, Dienes, and 1,3-Enynes.



[a] Reactions were conducted with olefin (0.5 mmol), perester **2a** (1.5 mmol), Fe(OTf)₃ (1 mol%) and THF (2 mL) for 5 h. [b] Reactions were conducted with olefin (0.5 mmol), diacyl peroxides **4a** or **4d** (0.75 mmol), Fe(OTf)₃ (5 mol%) and THF (2 mL) for 3 h. [c] 3 equiv. of HOTf was added as an additive.

The vinylic C-H alkylation with peresters and alkyl diacyl peroxides were successfully extended to a broad scope of olefins (Table 3). Reactions of alkyl-substituted vinylarenes (*o*-, *m*-, *p*-) afforded products **3ba-3ea**, **5ba-5ea** in high yields (88%-98%). Vinylarenes containing halides reacted to give products **3fa-3ia** and **5fa-5ia** in moderate to good yields (70-88%). Vinylarenes bearing ester and methyl ether substituents also underwent this reaction, affording products **3ja-3la**, **5ja**, and **5qa** in moderate yields (46%-74%), respectively. To our delight, the

functional groups, such as carboxylic acid and boronic acid, were compatible with the reaction conditions (**5ra** and **5sa**). Under the identified conditions, the reaction of *p*-dimethylaminomethyl styrene did not occur, presumably owing to the coordination inhibition of iron catalyst by the tertiary amine moiety. With HOTf (3 equiv.) as an additive, the reaction afforded product **5ta** in 53% yield. α -Methyl-styrene, a 1,1-disubstituted vinylarene, underwent this reaction smoothly with **2a** and **4a**, providing the products **3na** and **5na** in 88% and 86% yields with 4:1 and 3:1 *E/Z* ratios, respectively. The reactions of vinylthiophene and 2-vinylnaphthalene delivered the corresponding products (**3ma**, **5ua**) in modest yields. Remarkably, dienes and 1,3-enynes were suitable substrates for this reaction and the corresponding terminal-cross-coupled products (**3oa**, **3pa**, **5od-5wd**) were obtained in moderate to good yields (52-89%).

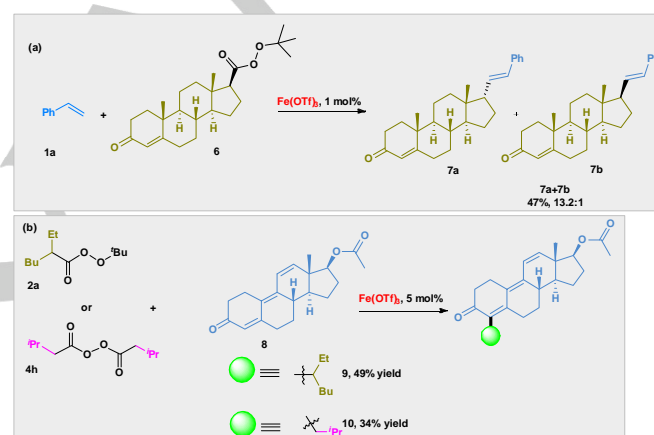


Figure 2. Synthetic Application and Late Stage Functionalization.

Synthetic Utilities in Late Stage Functionalization of Complex Molecules

To test the synthetic utility of this methodology, the peresters **6** readily prepared from the steroidal carboxylic acid was coupled with styrene. Gratifyingly, the vinylic C-H alkylation products were obtained in 47% yield with a high diastereomeric ratio (**7a/7b** = 13:1) for this reaction (Fig. 2a). The reaction has also been examined for the late stage functionalization of natural products and drug molecules by the alkylation of the C=C bonds. The reaction of trenbolone acetate **8** with **2a** or **4h** afforded 4-alkylated derivatives **9** or **10** in moderate yields, respectively (Fig. 2b). These examples demonstrated that this reaction is synthetically useful for the functionalization of complex molecules in the late stage.

To address the safety concerns of scaling up this reaction, we developed a safe and operationally simple protocol. A multigram-scale reaction was conducted using 20 mmol of styrene, 2.5 mol% Fe(OTf)₃ and 1.1 equiv. of LPO (Fig. 3a). LPO was added in 8 portions in interval of 2-3 minutes. The reaction

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proceeded smoothly and afforded product **5aa** in 89% yield (4.59 g).

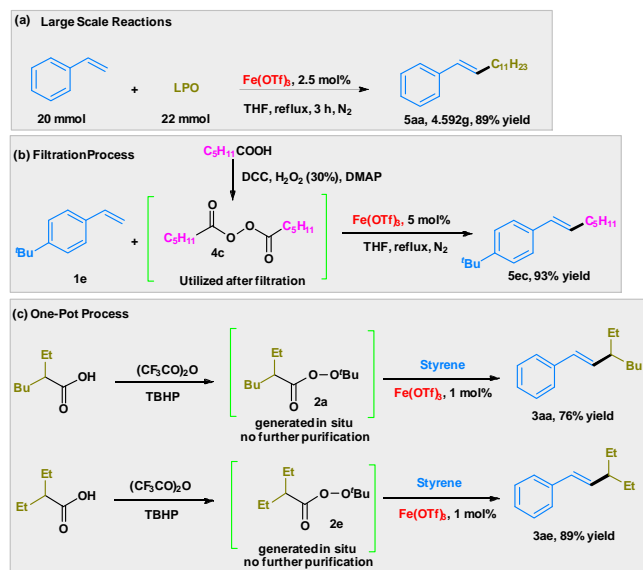


Figure 3. Applications of Carboxylic Acids.

To further simplify the procedure, we have also developed a procedure using peroxides generated in situ from carboxylic acids. As shown in Fig. 3b, diacyl peroxide **4c**, generated by DCC-mediated dehydrative condensation with hydrogen peroxide, was directly, after filtration, subjected to the reaction with **1e**. This reaction afforded **5ec** in 93% yield. The one-pot procedure with carboxylic acids as the starting materials also proved to be feasible.^[20] Peresters **2a** and **2e** generated in situ from the corresponding carboxylic acids with $(CF_3CO)_2O$ and TBHP, reacted smoothly with styrene, providing the alkyl Heck type products **3aa** and **3ae** in 76% and 89% yield, respectively (Fig. 3c).

Mechanistic Studies

We performed control experiments in order to probe the mechanism of the reaction. It is worth noting that this coupling reaction could also be promoted by HOTf.^[21] But the reaction rates of styrenes to the alkylated styrenes catalyzed by 5 mol% $Fe(OTf)_3$ are much faster than that promoted by 20 mol% of HOTf. These results suggest that catalytic amount of HOTf generated from $Fe(OTf)_3$ is not responsible for the reaction rates, and thus the iron metal is the real catalyst species (Fig. S1 and S2).

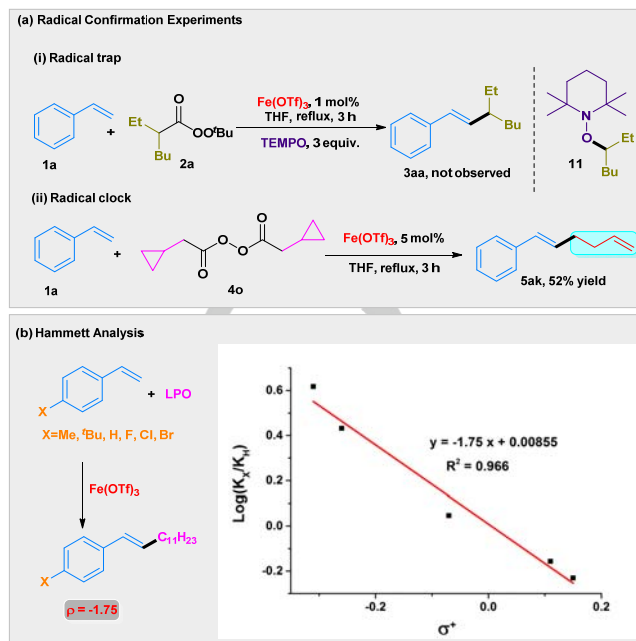
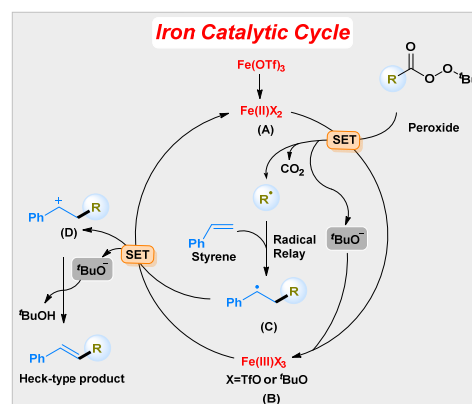


Figure 4. Preliminary Mechanistic Studies.

Next, the radical trapping experiment was conducted with 3 equivalents of TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy). This reaction did not afford any desired product. Instead, compound **11** was detected by GC-MS analysis (Fig. 4a). This is consistent with the radical nature of the reaction, wherein the other-wise propagating radical cycle was effectively intercepted by TEMPO. To further test this possibility, we synthesized diacyl peroxide **4o** bearing a cyclopropylmethyl moiety (radical clock) (Fig. 4a).^[22] As expected, the reaction of styrene with **4o** afforded ring-opening product **5ak** in 52% yield, hence further supporting the involvement of radical species in the reaction.^[23] In addition, Hammett analysis was conducted with substituted styrenes and $\rho_{\sigma^+} = -1.75$ was obtained (Fig. 4b). The negative ρ value suggests that the positive charge formed at the reaction center is the turnover-limiting step.



Scheme 1. Proposed Mechanism.

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Based on Fenton's reaction^[24] and the previous works^[18,25,26], a catalytic cycle involving a single electron transfer is proposed here (Scheme 1). Fe(OTf)₃ is reduced to iron (II) (**A**) by alkyl radicals or vinylarenes. Iron (II) species **A** transfers an electron to perester to form iron (III) species (**B**) and an alkyl radical. The alkyl radical reacts with styrene to form benzylic radical **C**. The benzylic radical (**C**) is oxidized by iron (III) species (**B**) to a carbocation (**D**) and regenerates iron (II) (**A**). The carbocation (**D**) then undergoes deprotonation to deliver the desired product.

Conclusions

This method disclosed effective utilizations of alkyl peresters and alkyl diacyl peroxides as the general primary, secondary, and tertiary alkylating reagents in vinylic C-H alkylation of vinylarenes, dienes and 1,3-enynes. This catalytic reaction is operationally simple, and is compatible with a broad range of functionalities including carboxyl, boronic acid, methoxy, ester, amino and halides. Several late stage functionalization of natural products and drug molecules was conducted to demonstrate the synthetic applications of this reaction. This protocol provided a facile approach to some olefins that are difficult to access previously.

Experimental Section

General procedure for Table 2a: vinylic C-H alkylation of styrene with t-butyl peresters: Styrene **1a** (52 mg, 0.5 mmol, 1 equiv.), Fe(OTf)₃ (2.5 mg, 1 mol%) and THF (2 mL) were added into a dried Schlenk tube (connecting to a water cooling condenser and N₂) with a stirring bar. After perester **2b-2n** (0.5 mmol, 1.0 equiv.) was added, the schlenk tube was inserted in an oil bath. The oil bath was heated from room temperature to reflux. After 30 min and 60 min, the second batch (0.5 mmol, 1.0 equiv.) and third batch of perester (0.5 mmol, 1.0 equiv.) were added, separately. After 5 hours, the reaction mixture was cooled to ambient temperature and concentrated by rotary evaporation under reduced pressure. The residue was purified by fast column chromatography on silica gel (petroleum ether) to yield **3**.

General procedure for Table 2b: Styrene **1a** (52 mg, 0.5 mmol, 1 equiv), diacyl peroxide **4** (0.75 mmol, 1.5 equiv), Fe(OTf)₃ (12.6 mg, 5 mol%) and THF (2 mL) were added into a flame dried Schlenk tube with a stirring bar and the reaction tube was inserted into an oil bath which was heated to 90 °C. The reaction solution was bubbling for 3-5 min then slightly boiling. After 3 hours, the reaction mixture was cooled to ambient temperature and concentrated by rotary evaporation under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether) to yield **5**.

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Keywords: iron catalysis • vinylic C-H alkylation • radical • alkyl diacyl peroxides • peresters

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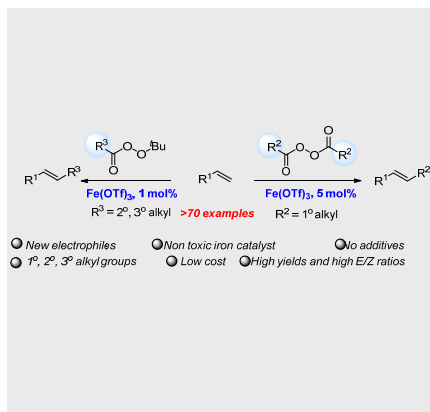
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A variety of alkyl peresters and alkyl diacyl peroxides synthesized from carboxylic acids are utilized as general primary, secondary, and tertiary alkylating reagents for iron catalyzed vinylic C-H alkylation of vinyl arenes, dienes, and 1,3-enynes. This transformation affords the olefinic products in up to 98% yields with high E/Z values. Good functionalities are observed and late-stage functionalizations of selected natural product derivatives are demonstrated.



Liang Ge⁺, Wujun Jian⁺, Huan Zhou⁺,
Shaowei Chen, Changqing Ye, Fei Yu,
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