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A Fe(III)/$NaBH_4$-Promoted Free-Radical Hydroheteroarylation of Alkenes

Bingyu Liang,[‡] Qinglong Wang,[§] and Zhong-Quan Liu*[,†,‡]

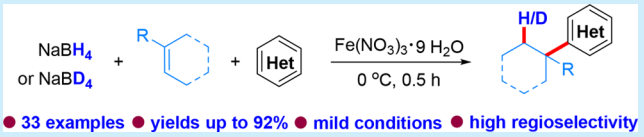
[†]State Key Laboratory Cultivation Base for TCM Quality and Efficacy, College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, China

[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

[§]Henan University of Animal Husbandry and Economy, Zhengzhou 450011, China

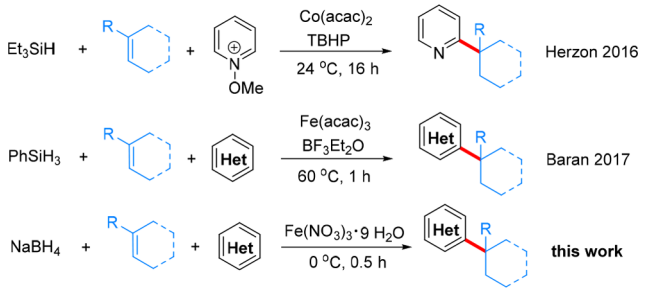
Supporting Information

ABSTRACT: A free-radical-mediated intermolecular hydroheteroarylation of simple alkenes was developed. Through simply mixing heteroarenes, alkenes, Fe(III), and $NaBH_4$ at 0 °C together, a wide range of alkylated heteroarenes could be afforded in moderate to excellent yields within 1 h.



Free-radical alkylation of a heteroaryl C−H bond, usually called Minisci reaction, is a highly valuable process in synthetic medicinal chemistry.[1] The most commonly used alkyl radical precursors are aliphatic acids, alkyl halides, organoborons, Barton esters, xanthates, etc.[2,3] Heteroaromatic alkylation by utilizing olefin as an alkyl source has rarely been studied in the past decades. Minisci and co-workers reported two examples. One is the 2-alkylation of 4-cyanopyridine using acetone and 1-octene mediated by $AgNO_3/K_2S_2O_8$.[4] The other is perfluoroalkylation of heteroarene via a radical tandem reaction of perfluoroalkyl iodide with alkene.[5] As demonstrated in Scheme 1, Herzon and co-workers described a Co(II)/

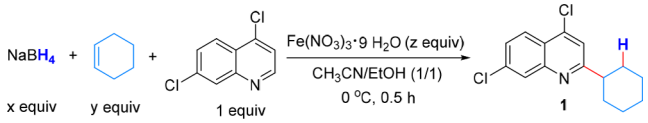
Scheme 1. Olefin-Based Minisci Alkylation Reaction



TBHP-promoted olefin-based Minisci reaction by using $EtSiH_3$ and simple alkenes in 2016.[6] Recently, a Fe(III)/$PhSiH_3$-mediated hydroheteroarylation of olefin was reported by Baran.[7] We developed an azidoheteroarylation of olefins by a free-radical promoted intermolecular multicomponent cascade reaction very recently.[8] Herein we report a modified Minisci alkylation by using $NaBH_4$ with alkenes (Scheme 1).

Inspired by the previous studies of Boger[9] and others,[10] we wondered whether an Fe(III)-mediated radical alkylation of heterocycle could be accomplished by using $NaBH_4$ with alkenes. Initially, we chose 4,7-dichloroquinoline and cyclohexene as the model compounds to optimize the reaction conditions (Table 1; see also the Supporting Information (SI)).

Table 1. Optimization of the Reaction Conditions[a]



entry	x	y	z	yield (%)[b]
1	2	2	0	0
2	2	2	2	48
3	2	2	4	75
4	2	2	5	80
5	2	2	6	92
6	2	3	6	92
7	4	2	6	90

[a]Reaction conditions: 4,7-dichloroquinoline (1 equiv, 0.4 mmol), CH_3CN/EtOH (1/1, 20 mL), 0 °C, 0.5 h. [b]^1H NMR yields using mesitylene as an internal standard.

No reaction happened without Fe(III) salt (entry 1). Increasing the amounts of iron salts led to improvement of the yields (entries 2−5). However, additional equivalents of both hydrides and alkenes failed to raise the yield of the product in this case (entries 6 and 7).

With the information in hand, we first examined the scope of the olefins in this system. As demonstrated in Scheme 2, a variety of alkenes were screened to be effective substrates. An array of cyclic alkenes afforded the desired alkylation products in good to excellent yields (**1**−**5**). To our delight, this reaction could be scaled up to gram level without losing its efficiency (**1**). 1-Methylcyclohex-1-ene enabled a quaternary carbon

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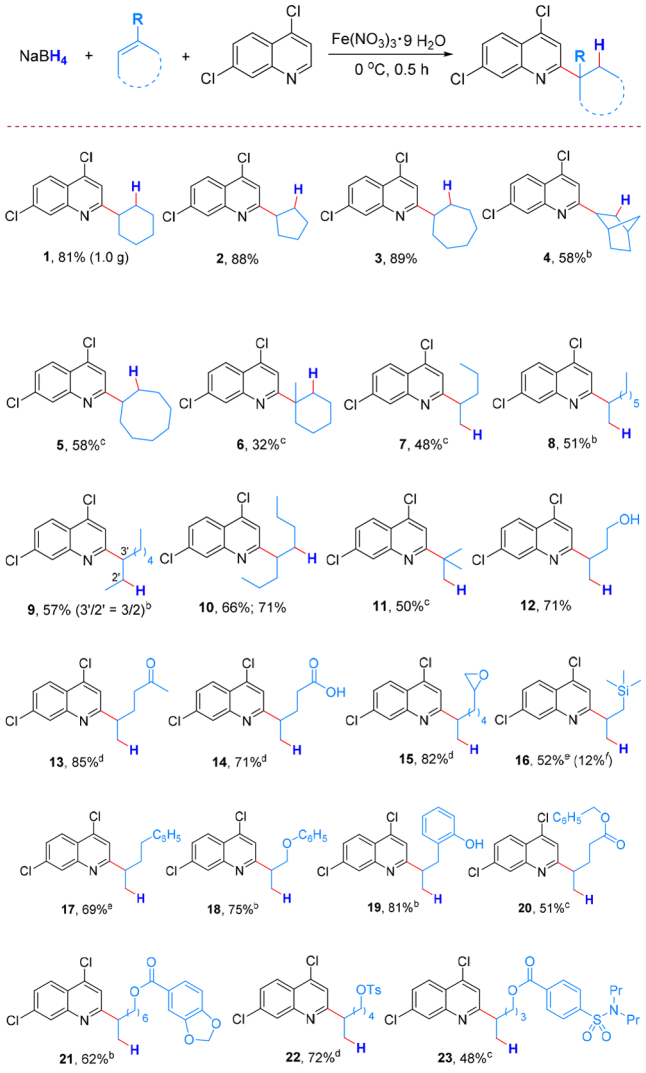
Scheme 2. Examination of the Olefins[a]

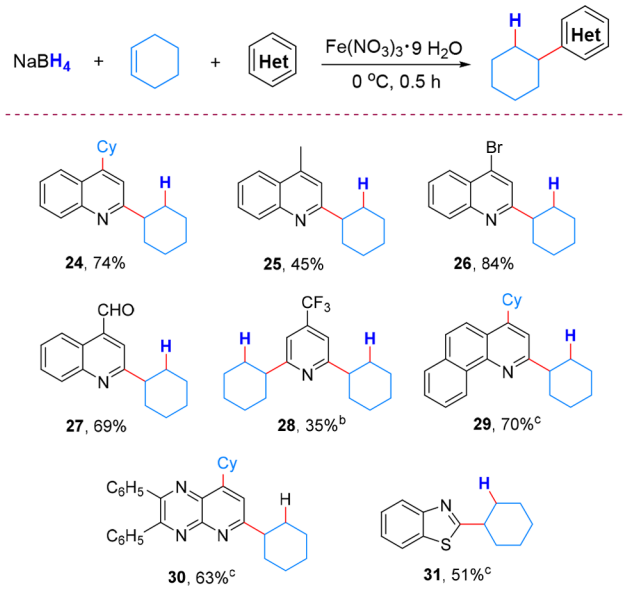


[a]Reaction conditions: 4,7-dichloroquinoline (1 equiv, 0.4 mmol), alkenes (2 equiv, 0.8 mmol), $NaBH_4$ (2 equiv, 0.8 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (6 equiv, 2.4 mmol), CH_3CN/EtOH (1/1, 20 mL), 0 °C, 0.5 h. Isolated yields. Unless otherwise noted, for the details, see the SI. [b]Alkenes (2 equiv), $NaBH_4$ (4 equiv). [c]Alkenes (2 equiv), $NaBH_4$ (6 equiv). [d]Alkenes (5 equiv), $NaBH_4$ (4 equiv). [e]Alkenes (5 equiv), $NaBH_4$ (8 equiv). [f]A TMS-group eliminated product was isolated in 12% yield.

center to be formed in 32% yield (**6**). Then, a broad range of linear olefins were examined (**7**−**22**). As a result, simple alkenes were amenable to this reaction (**7**−**11**). Among them, the same product (**10**) was obtained in 66% and 71% yields with (*E*)-oct-4-ene and (*Z*)-oct-4-ene, respectively. It indicated that the steric effect in the formation of the secondary alkyl radical is not remarkable. In addition, it is noteworthy that a large number of functionalized alkenes were compatible with this system (**12**−**23**). Diverse functional groups such as hydroxyl, carbonyl, carboxylic acid, epoxy, silyl, aryl, phenol, ester, sulfonate, sulfoxamide, etc. could be tolerated under the reaction conditions. Interestingly, a sensitive carbonyl group applied to $NaBH_4$ could also survive in the radical alkylation reaction (**13**).

To further evaluate the generality of this reaction, we then examined a series of heteroaromatics. As depicted in Scheme 3,

Scheme 3. Examination of the Heteroaromatic Substrates[a]

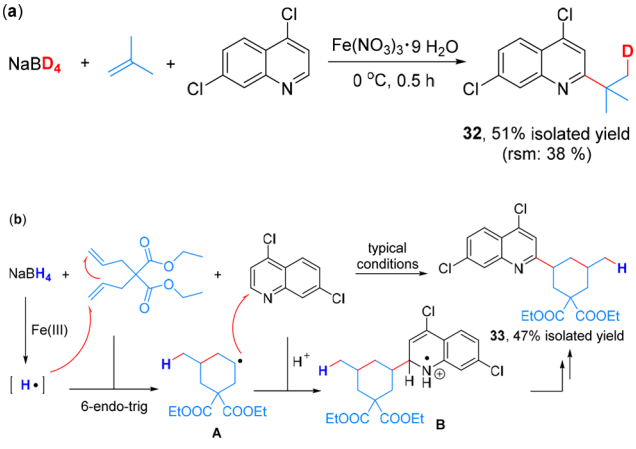


[a]Reaction conditions: 4,7-dichloroquinoline (1 equiv, 0.4 mmol), alkenes (2 equiv, 0.8 mmol), $NaBH_4$ (4 equiv, 1.6 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (6 equiv, 2.4 mmol), CH_3CN/EtOH (1/1, 20 mL), 0 °C, 0.5 h. Unless otherwise noted, for the details, see the SI. Isolated yields. [b]Alkenes (5 equiv), $NaBH_4$ (4 equiv). [c]Alkenes (5 equiv), $NaBH_4$ (8 equiv).

heterocycles such as quinoline, pyridine, benzo[*h*]quinoline, pyrido[2,3-*b*]pyrazine, and benzo[*d*]thiazole were amenable to this reaction (**24**−**31**). It is very interesting that quinoline-4-carbaldehyde gave the corresponding product 2-cyclohexylquinoline-4-carbaldehyde in 69% yield (**27**). In this case, the aldehyde group was not reduced by $NaBH_4$, which suggested that the rate of the radical hydroheteroarylation should be faster than that of the hydride reduction.

Finally, several experiments were carried out to investigate the mechanism for this process (Scheme 4). As demonstrated in Scheme 4a, reaction of 4,7-dichloroquinoline and 2-methylprop-1-ene with sodium borodeuteride ($NaBD_4$) afforded the corresponding 4,7-dichloro-2-(2-methylpropan-2-yl-1-*d*)quinoline (**32**) as the major product in 51% isolated yield with recovery of the heterocycle in 38% yield. We could reach some conclusions from this result. First, the hydrogen

Scheme 4. Mechanistic Studies



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atom comes from $NaBH_4$. Next, the addition of a hydrogen atom to olefin might not be involved in the rate-determining step by comparing reaction **4a** with that producing **11** in Scheme 2. Furthermore, a deuterium atom could be smoothly introduced into organic molecules via this strategy. On the other hand, a radical clock experiment was conducted. The evidence for a radical process can be observed in Scheme 4b. Single-electron oxidation of the hydride by Fe(III) salt would give a formal H radical,[9] which then adds to the C=C double bond of diethyl 2,2-diallylmalonate followed by a 6-endo-trig cyclization affords radical **A**. A radical cation intermediate **B** would be generated by addition of the C-centered radical **A** to the protonated *N*-heterocycle. Subsequently, hydrogen-atom transfer (HAT) followed by deprotonation via workup leads to the final product **33**.

In summary, an Fe(III)-mediated hydroheteroarylation of unactivated alkenes was developed. Through simply mixing heteroarenes and olefins with sodium borohydride together at 0 °C, a wide range of alkylated heterocycles could be obtained within 1 h. In contrast to the previous olefin-based Minisci alkylation reactions, the present method features mild conditions, faster reaction times, and sensitive functional group tolerance. Given the widely found scaffolds of heteroarenes in natural products and drugs, this strategy would be expected to find wide applications in the medicinal chemistry community.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03313.

Experimental procedures, mechanistic studies, and characterization and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liuzhq@lzu.edu.cn.

ORCID

Zhong-Quan Liu: 0000-0001-6961-0585

Notes

The authors declare no competing financial interest.

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