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COMMUNICATION

A Free Radical Alkylation of Quinones with Olefins

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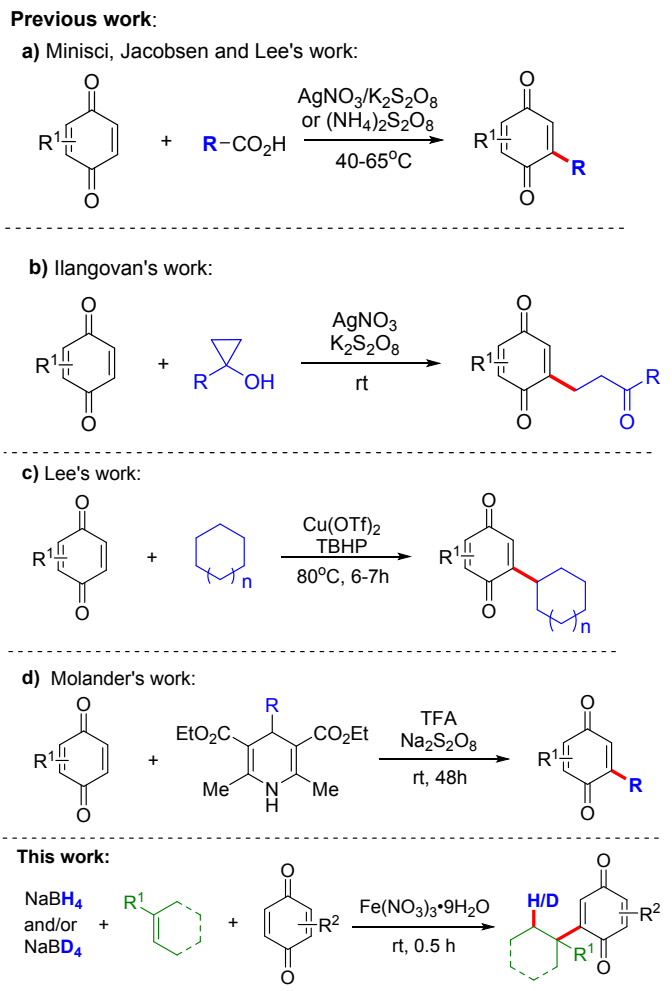
We demonstrated herein an Fe(III)-mediated radical alkylation of quinones. A wide range of bioactive molecules with quinone motifs can be rapidly synthesized by using readily available and inexpensive $NaBH_4$/$NaBD_4$ with alkenes at room temperature under open flask conditions.

Quinone frameworks belong to a highly important class of building blocks which are widely distributed in natural products and pharmaceuticals.[1] Due to the unique structure of quinones, they have many desirable properties for applications in chemistry, materials, medicine and biology.[2] For instance, many quinones have excellent antimicrobial,[3a] anti-tumor,[3b] anti-cancer[3c] and anti-diabetes[3d] properties. In addition, they also play a crucial role in cell respiration and cell metabolism,[4] and have great attraction to the dye industry.[5] However, efficient and economical strategies for direct functionalization of quinones are rare.

Heck coupling is a well-known and efficient method for construction of C-C but it is not suitable for quinones. As quinones are good ligands and oxidants, interacting with transition metal such as Pd presents a huge challenge to this type of coupling.[6] Several optional strategies have been proposed through the efforts of chemists, one of which is Lewis acid-promoted nucleophilic addition of electron-rich arenes to quinones.[7] The other is transition-metal-catalyzed addition of boric acid or borate to quinones[8] and Pd-catalyzed cross-coupling of halogenated quinones.[9] But these approaches usually require a re-oxidation step to convert hydroquinone to quinone. Besides, halogenated quinones are usually not commercially available. Alternatively, free radical alkylation of quinones represents an attractive protocol to overcome these disadvantages in part (Scheme 1). For example, $AgNO_3/K_2S_2O_8$ and $(NH_4)_2S_2O_8$-promoted decarboxylative alkylation of *N*-heterocycles and quinones with carboxylic acids was achieved by Minisci, Jacobsen and Lee (Scheme 1a).[10]



Scheme 1 Approaches to C-H alkylation of quinones.

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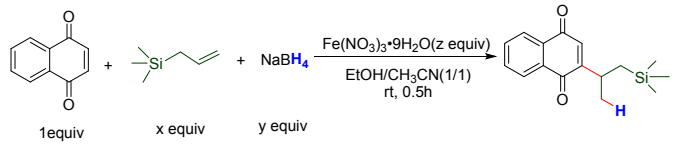
Under similar conditions, Ilangovan[11] showed that cyclopropanols were oxidized to open the ring to obtain alkyl radicals, which were then added to quinones to generate alkylated quinones (Scheme 1b). In 2016, Lee's group[12] reported a copper-catalyzed quinones alkylation with cyclic alkanes in the presence of *tert*-butyl hydroperoxide (Scheme 1c). Later Molander[13] found that 1,4-quinones could be alkylated with 1,4-dihydropyridines under oxidative conditions without metal or photocatalysts (Scheme 1d). Nevertheless, these radial strategies also have limitations such as limited substrate scope, less efficiency and harsh reaction conditions. Hence, more efficient and novel synthesis strategies are still highly desirable. Herein, we developed an Fe(III)/$NaBH_4$-mediated direct C-H functionalization of quinones by utilizing olefin as the alkyl radical source (Scheme 1).

In recent several years, a series of highly efficient C-C bond formation systems using alkene as the alkyl radical precursor have been explored by Boger, and others.[14] Inspired by these previous works and ours,[15] we began to hypothesize that a radical alkylation of quinones with olefins as the radical precursors would be possible. Initially, we focused on the optimization of reaction conditions with naphthalene-1,4-dione and allyltrimethylsilane as the model compounds (Table 1; see also the Supporting Information). When the reaction was carried out without Fe(III) salt (entry 1), no target product was observed. With the increase of the load of iron salts, the yields improved (entries 2-4). We found the yield also depended on the amount of $NaBH_4$ and olefins (entries 5-8).

Table 1 Modification of the typical reaction conditions. [a]

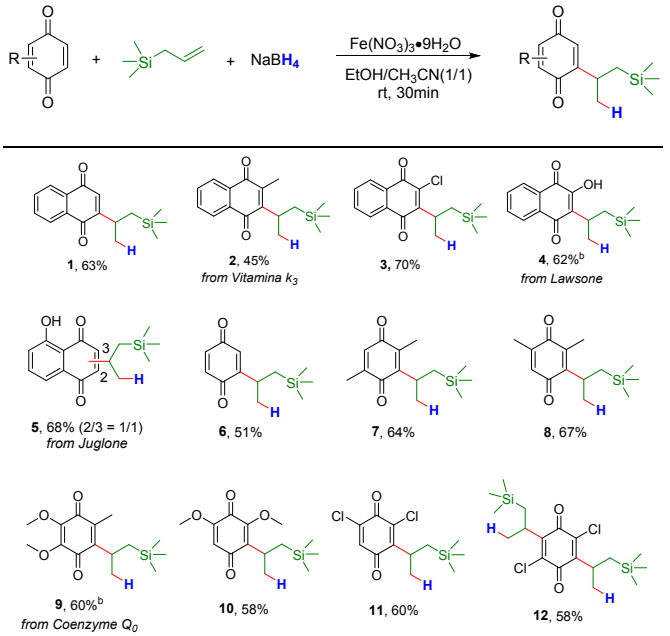


entry	x (equiv.)	Y (equiv.)	Z (equiv.)	yield (%)[b]
1	5	4	0	0
2	5	4	2	20
3	5	4	4	53
4	5	4	5	65
5	4	4	5	63
6	2	4	5	37
7	5	5	5	68
8	5	3	5	45

[a] Reaction conditions: naphthalene-1,4-dione (1 equiv, 0.2 mmol), CH_3CN/EtOH (1/1, 4mL), rt, 0.5 h. [b] Isolated yields.

Since we have established the optimal reaction conditions, the general applicability of the reaction needed to be investigated. As portrayed in Table 2, the reaction was performed with a wide range of quinones. Firstly, a variety of substituted naphthoquinones were found to provide the corresponding products in moderate to good yields (**1**-**5**). Interestingly, Vitamin K_3 (**2**), Lawsone reagent (**4**) and Juglone (**5**) can react efficiently and smoothly. To our delight, very sensitive phenolic hydroxyl groups can also be tolerated in this system (**5**). Next, a series of substituted benzoquinones were investigated, and they were also compatible with this reaction (**6**-**12**). Gratifyingly, the benzoquinones bearing either electron-donating or withdrawing groups all resulted in good yields. Notably, the product **9** was also obtained from the apoptosis inducer Coenzyme Q_0 in 60% yield. To our surprise, 2,5-dichlorocyclohexa-2, 5-diene-1,4-dione gave a dialkylated quinone (**12**) while mono-alkylated quinones were isolated as the major product in most cases.

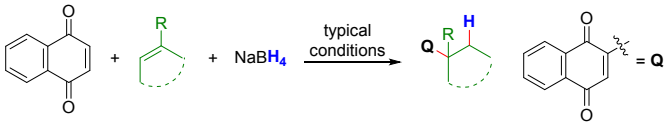
Table 2 Examination of the quinones substrates.[a]

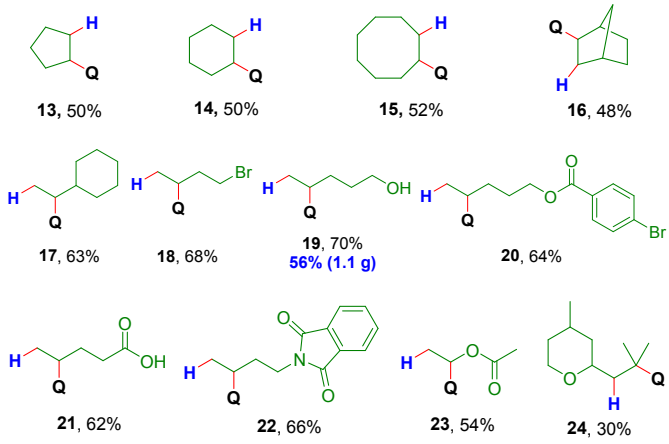


[a] Reaction conditions: quinones (1 equiv, 0.2 mmol), allyltrimethylsilane (4 equiv, 0.8 mmol), $NaBH_4$ (4 equiv, 0.8 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (5 equiv, 1 mmol), CH_3CN/EtOH (1/1, 4 mL), rt, 0.5 h. Isolated yields. [b] $NaBH_4$ (6 equiv, 1.2 mmol, add in two portions), unless otherwise noted, for details, see the SI.

In an attempt to have a further understanding of the versatility of this reaction, a series of olefins were examined. As demonstrated in Table 3, a variety of alkenes were screened to be effective substrates. An array of cyclic alkenes afforded the desired alkylation products in moderate yields (**13**-**16**). Then, a broad range of linear olefins were examined (**17**-**24**). It is worth mentioning that various functional groups such as hydroxyl, carboxylic acid, epoxy, silyl, aryl, ester, amide, etc. could be tolerated in the process. Natural product rose oxide (racemate) enabled a quaternary carbon center to be formed in 30% yield (**24**). The relative low yield might be due to the steric effect. Notably, this reaction could be amplified to grams and maintained its efficiency (**19**).

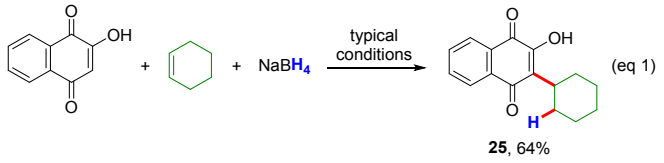
Table 3 Examination of the olefins[a]





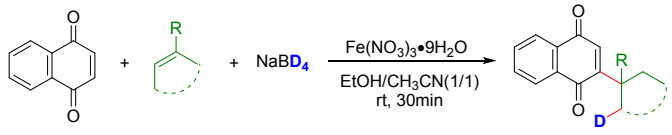
[a] Reaction conditions: naphthalene-1,4-dione (1 equiv, 0.2 mmol), alkenes (4 equiv, 0.8 mmol), $NaBH_4$ (4 equiv, 0.8 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (5 equiv, 1 mmol), CH_3CN/EtOH (1/1, 4 mL), rt, 0.5 h. Isolated yields.

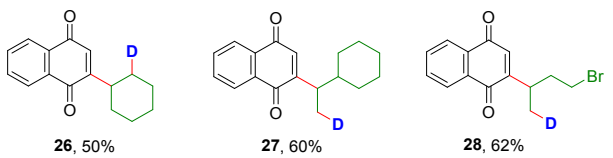
This strategy can also be applied to the synthesis of drug molecules, such as the antimalarial drug, parvaquone, which can be synthesized in one step with high efficiency and good yield (Eq 1).

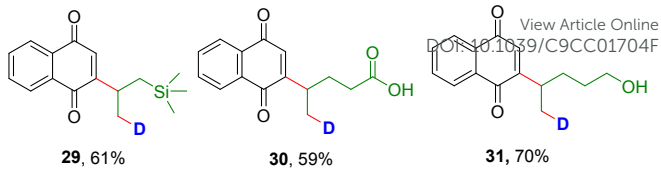


In recent years, the strategy of deuterium substitution has been widely used in drug research[16]. Substitution of hydrogen in drug molecules with deuterium may screen metabolic sites and reduce the production of toxic metabolite[17]. Additionally, it can prolong the half-life of drugs in the body[17]. Hence, we hope to introduce deuterium atoms into organic molecules through this strategy. Fortunately, deuterium atoms can be smoothly installed into quinones by using $NaBD_4$ as the deuterium source (Table 4). We found that various olefins are compatible with this system (**26**-**31**). In all cases, the D-atom was introduced into the molecules at the least hindered position since the more stable C-centered radical intermediate could be formed. These results not only allow a convenient access to deuterized compounds, but also confirm that the H- and/or D-atoms do come from $NaBH_4$ and/or $NaBD_4$.

Table 4 Introduction of deuterium atom into molecules.[a]

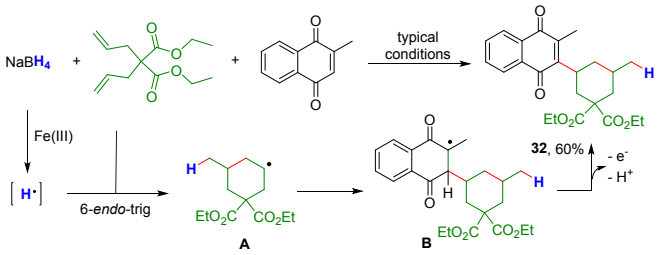






[a] Reaction conditions: naphthalene-1,4-dione (1 equiv, 0.2 mmol), alkenes (4 equiv, 0.8 mmol), $NaBD_4$ (4 equiv, 0.8 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (5 equiv, 1 mmol), CH_3CN/EtOH (1/1, 4 mL), rt, 0.5 h. Isolated yields.

Finally, a radical clock experiment was carried out to verify the reaction mechanism further. Scheme 2 supports that this reaction underwent a radical process. First of all, a formal H radical would be formed via single-electron oxidation of the hydride by Fe(III) salt. Subsequently, radical **A** was generated by addition of H-atom to the 1,6-diene followed by a radical 6-*endo*-trig cyclization. The usual 5-*exo*-trig cyclization was not observed, which might be due to the stability of the radical intermediate. Then addition of **A** to quinone would afford radical intermediate **B**. Ultimately, single-electron oxidation again followed by deprotonation leads to the corresponding product **32**.



Scheme 2 Mechanistic studies.

In conclusion, we developed a simple and practical Fe(III)-mediated C-H conversion of quinones with unactivated alkenes. This protocol provides a mild, rapid, and step-economic access to a broad range of functionalized quinones, which could be converted into various bioactive molecules and drugs via late stage transformation. Furthermore, deuterium atom can also be conveniently installed into organic molecules through this method. Hence broad application of this strategy in drug synthesis would be expected.

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Notes and references

1 (a) R. H. Thomson, *Naturally Occurring Quinones IV*; Blackie Academic: London, 1997; (b) O. M. Demchuk, K. M. Pietrusiewicz, *Synlett.* 2009, **7**, 1149; (c) Z. Shuai, J. S. Fei, B. Z. Dong, and S. Y. Jing, *Chem. Commun.* 2013, **49**, 4558; (d) E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* 2014, **57,** 10257; (e) H. Miyamura, M. Shiramizu, R. Matsubara and S. Kobayashi, *Angew. Chem. Int. Ed.* 2008, **47**, 8093.
2 R. A. Morton, *Biochemistry of Quinones*; Academic Press: New York, 1965.
3 (a) A. Sendl, J. L. Chen, S. D. Jolad, C. Stoddart, E. Rozhon and M. Kernan, *J. Nat. Prod.* 1996, **59**, 808; (b) M. M.

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DOI: 10.1039/C9CC01704F

Alhamadsheh, N. C. Waters, S. Sachdeva, *et al*., *Bioorg. Med. Chem. Lett*. 2008, **18**, 6402; (c) R. P. Verma, *Anti-Cancer Agents Med. Chem.* 2006, **6**, 489; (d) B. Zhang, G. Salituro, D. Szalkowski, Z. Li, Y. Zhang, I. Royo, D. Vilella, M. T. Diez, F. Pelaez, C. Ruby, R. L. Kendall, X. Mao, P. Griffin, J. Calaycay, J. R. Zierath, A. V. Heck, R. G. Smith, D. E. Moller, *Science* 1999, **284,** 974.

4 C. E. Price, A. J. M. Driessen, *Biochim. Biophys. Acta* 2010, **1803,** 748.

5 T. Bechtold, *In Handbook of Natural Colorants*; ed. T. Bechtold and R. Mussak, Wiley, New York, 2009; pp 151.

6 (a) T. W. Lysons, M. S. Sanford, *Chem. Rev.,* 2010, **110**, 677; (b) C. Liu, H. Zhang, W. Shi and A. Lei, *Chem. Rev.,* 2011, **111**, 1780.

7 (a) T. A. Engler and J. P. Reddy, *J. Org. Chem.,* 1991, **56**, 6491; (b) M. C. Pirrung, Y. Liu, D. Deng, D. K. Halstead, Z. Li, J. F. May, M. Wedel, D. A. Austin, N. J. G. Webster, *J. Am. Chem. Soc.,* 2005, **127**, 4609; (c) H.-B. Zhang, L. Liu, Y.-J. Chen, D. Wang,
C.-J. Li, *Adv. Synth. Catal.,* 2006, **348**, 229.

8 (a) M. T. Molina, C. Navarro, A. Moreno, and A. G. Csákÿ, *Org. Lett.,* 2009, **11**, 4938; (b) Y. Fujiwara, V. Domingo, I. B. Seiple, R. Gianatassio, M. D. Bel and P. S. Baran, *J. Am. Chem. Soc.,* 2011, **133**, 3292.

9 A. M. Echavarren, ó. Frutos, N. Tamayo, P. Noheda and P. Calle, *J. Org. Chem.,* 1997, **62**, 4524; (b) X.-W. Gan, W. Jiang, W. Wang and L.-H. Hu, *Org. Lett.,* 2009, **11**, 589.

10 (a) F. Minisci, R. Bernardi, F. Bertini, R. Galli, M. Perchinummo, *Tetrahedron* 1971, **27**, 3575; (b) T. Caronna, A. Crrterio, L. Grossi, F. Minisci and K. Ogawa, *Tetrahedron* 1976, **32**, 2741; (c) N. Jacobsen, K. Torssell, *Acta Chem. Scand.,* 1973, **27**, 3211; (d) D. R. Sutherland, M. Veguillas, C. L. Oates and A.-L. Lee, *Org. Lett.,* 2018, **20**, 6863.

11 A. Ilangovan, S. Saravanakumar and S. Malayappasamy, *Org. Lett.,* 2013, **15**, 4968.

12 E. R. Baral, S. H. Kim and Y. R. Lee, *Asian J. Org. Chem.* 2016, **5**, 1134.

13 Á. Gutiérrez-Bonet, C. Remeur, J. K. Matsui, G. A. Molander, *J. Am. Chem. Soc.,* 2017, **139**, 12251.

14 (a) H. Ishikawa, D. A. Colby, D. L. Boger, *J. Am. Chem. Soc.,* 2008, **130**, 420; (b) T. J. Barker, D. L. Boger, *J. Am. Chem. Soc.,* 2012, **134**, 13588; (c) A. Ekomié, G. Lefévre, L. Fensterbank, E. Lacôte, M. Malacria, C. Ollivier, A. Jutand, *Angew. Chem. Int. Ed.,* 2012, **51**, 6942; (d) T. Hashimoto, D. Hirose, T. Taniguchi, *Angew. Chem. Int. Ed.,* 2014, **53**, 2730; (e) C. Obradors, R. M. Martinez, R. Shenvi, *J. Am. Chem. Soc.,* 2016, **138**, 4962; (f) Z.-L. Li, X.-H. Li, N. Wang, N.-Y. Yang, X.-Y. Liu, *Angew. Chem. Int. Ed.,* 2016, **55**, 15100; (g) X. Ma, H. Dang, J. A. Rose, P. Rablen, S. B. Herzon, *J. Am. Chem. Soc.* 2017, **139**, 5998; (h) J. C. Lo, D. Kim, C.-M. Pan, J. T. Edwards, Y. Yabe, J. Gui, T. Qin, S. Gutiérrez, J. Giacoboni, M. W. Smith, P. L. Holland, P. S. Baran, *J. Am. Chem. Soc.,* 2017, **139**, 2484; (i) G. Feng, S. Sun, G. Liu, H. Long, L. Liu, *Org. Lett.,* 2018, **20**, 7522.

15 (a) B. Liang, Q. Wang, Z.-Q. Liu, *Org. Lett.,* 2017, **19**, 6463; (b) Z. Liu, Z.-Q. Liu, *Org. Lett.* 2017, **19**, 5649; (c) A. Ling, L. Zhang, R. X. Tan, Z.-Q. Liu, *J. Org. Chem.* 2018, **83**, 14489.

16 (a) B. Belleau, J. Burba, M. Pindell, et al., *Science*, 1961,**133**, 102; (b) J. I. Manchester, J. P. Dinnocenzo, *J. Am. Chem. Soc.,* 1997, **119**, 5069; (c) R. Sharma, T. J. Strelevitz, H. Gao, *et al., Drug. Metab. Dispos.* 2013, **40**, 625.

17 (a) R. P. Bell, *Chem. Soc. Rev.* 1974, **3**, 513; (b) M.I. Blake, H. L. Crespi, J. J. Katz, *J. Pharma. Sci.* 1975, **64**, 367.

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Graphical Abstract

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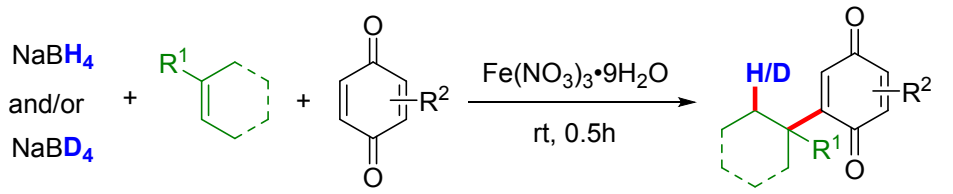

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