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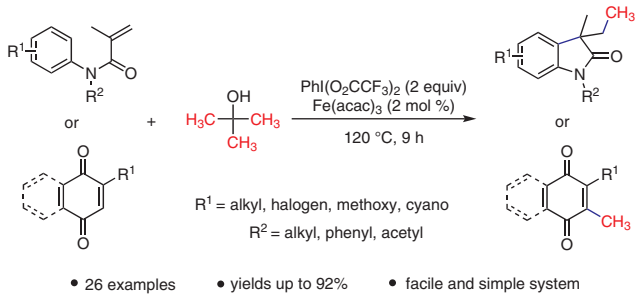
# Iron-Catalyzed Radical Methylation of Activated Alkenes with *tert*-Butanol as the Methyl Source

**Zhengbao Xu**[*a,c◊] **Rui Jia**[b◊] **Zhiwei Ma**[c] **Shouhao Cao**[c] **Liang Shen**[*a,c] **Hongfang Ji**[*a,c]

[a] Institute of Biomedical Research, Shandong University of Technology, Zibo, 255000, Shandong, P. R. of China
1208241003@qq.com
shen@sdut.edu.cn
jhf@sdut.edu.cn
[b] Zibo Meteorological Bureau, Zibo, 255000, Shandong, P. R. of China
[c] Shandong Provincial Research Center for Bioinformatic Engineering and Technique, Zibo Key Laboratory of New Drug Development of Neurodegenerative Diseases, School of Life Sciences, Shandong University of Technology, Zibo, 255000, Shandong, P. R. of China

◊ These authors contributed equally to this work.

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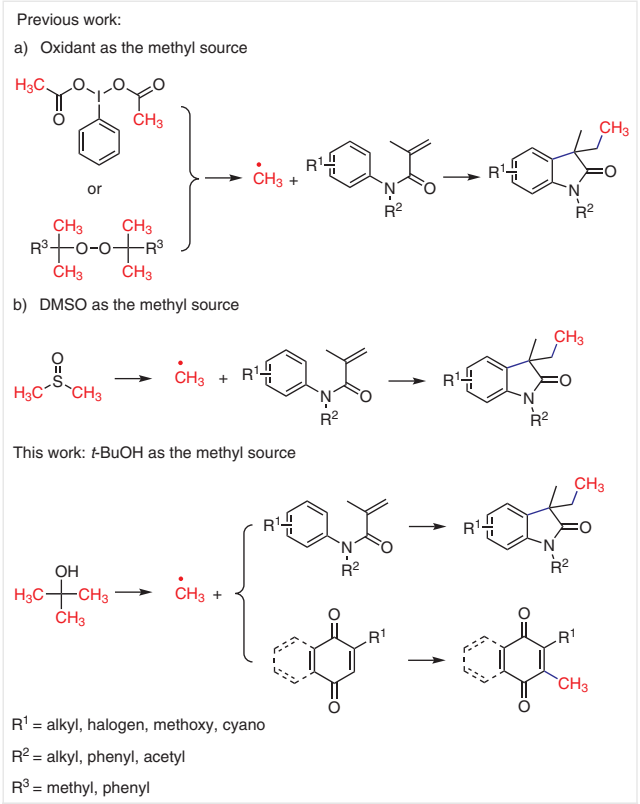
**Abstract** A free-radical-initiated methylation/addition/cyclization of *N*-arylacrylamides and a methylation/addition/elimination of quinines have been developed in which *t*-BuOH is used as a methyl source. These reactions provide effective and selective methods for the synthesis of various methylated oxindoles and quinones in moderate to good yields.

**Key words** methylation, oxinidoles, quinones, arylacrylamides, quinones, cascade reaction

The methyl group is one of the most prevalent functional groups in biologically active molecules.[1] In the field of pharmaceutical chemistry, the so-called 'magic methyl effect' can often improve a molecule's biological activity and physical properties.[2] Therefore, synthetic reactions that install methyl groups onto organic compounds with ease are of value in organic and pharmaceutical chemistry. In recent decades, methylation has been achieved by using various methylated metal reagents,[3] $MeB(OH)_2$,[4] MeI,[5] DMSO,[6] AcOH,[7] peroxides,[8] or $PhI(O_2CMe)_2$[9] as sources of methyl groups. However, most of these methylating reagents are toxic and polluting. Therefore, more-efficient methylation strategies and new methylating reagents are highly desirable.

Oxindoles and quinones are ubiquitous structural motifs that can be found in various natural products and biologically active molecules.[10,11] Recently, many methods have been reported for the construction of alkylated oxindoles and quinones.[12,13] Among these, radical-initiated methylation/addition/cyclizations of *N*-arylacrylamides have been reported by Zhu,[14] Liu,[15] Cheng,[16] Li,[17] and Chen[18] and their respective co-workers (Scheme 1). To the best of our knowledge, radical-initiated methylations of quinones are rare.[19] A longstanding challenging problem is that the methylating reagents are not economical or environmental-




**Scheme 1** Approaches to the methylation of activated alkenes

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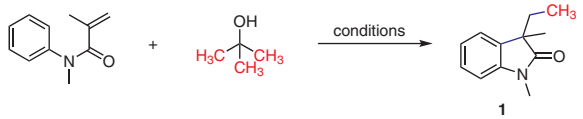
ly friendly. Here, we report the first example of a free-radical methylation of *N*-arylacrylamides or quinones by using *t*-BuOH as a source of methyl radicals.

Initially, the reaction of *N*-methyl-*N*-phenyl(methacrylamide) with *t*-BuOH was chosen as a model reaction to optimize the reaction conditions (Table 1; also see the Supporting Information). The desired product 3-ethyl-1,3-dimethyl-1,3-dihydro-2*H*-indol-2-one (**1**) was obtained in 25% yield (Table 1, entry 1). Encouraged by this result, we tested a series of other catalysts [$Cu_2O$, CuBr, $Cu(OAc)_2$, $Cu(acac)_2$, $AgNO_3$, $Fe(acac)_2$, $Fe(acac)_3$, $Mn(acac)_2$, $Ni(acac)_2$, and $Pd(acac)_2$], and we found that $Fe(acac)_3$ was most efficient (entries 2–13). [Bis(trifluoroacetoxy)iodo]benzene (PIFA) was found to be more efficient than other iodine reagents (entries 14 and 15). The desired product **1** was isolated in 78% yield when 2 mol% of $Fe(acac)_3$ was added (entry 16). Additionally, the yield of the product after nine hours was better than that after six or 12 hours (entries 17 and 18). Finally, the desired product **1** was isolated in 78% yield under the following optimal conditions: *N*-methyl-*N*-phenylmethacrylamide (1 equiv, 0.2 mmol), PIFA (2 equiv, 0.4 mmol), $Fe(acac)_3$ (0.02 equiv, 0.004 mmol), *t*-BuOH (2 mL), 120 °C, nine hours, sealed tube.

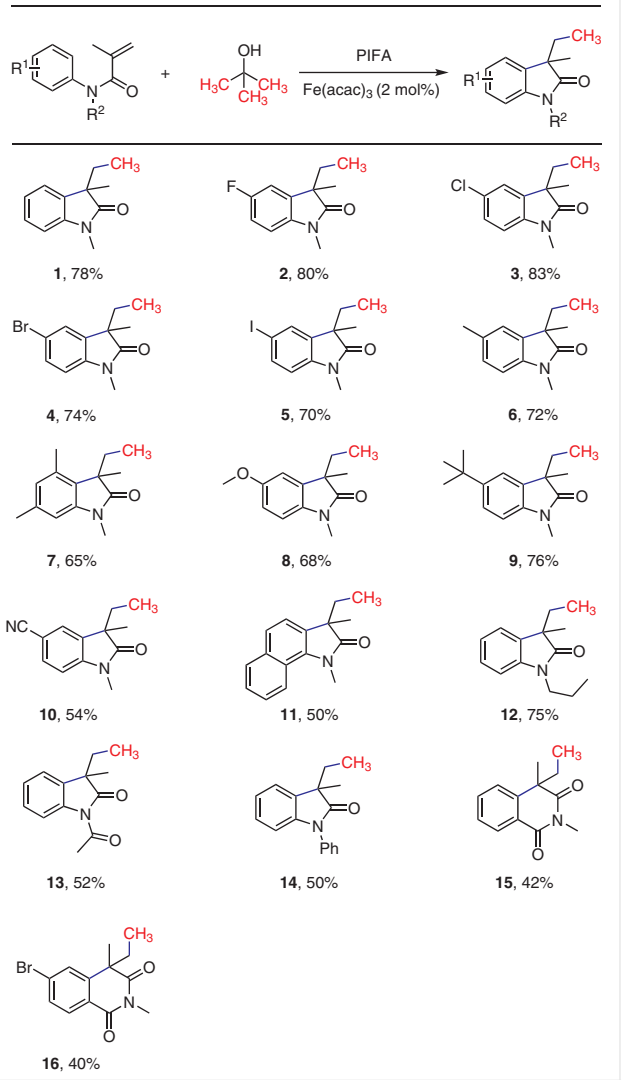
With the optimized conditions in hand, we examined the scope of the substrates (Scheme 2). When various N-protected substrates were employed, the desired products **1** and **12** were obtained in yields of 78 and 75%, respectively. In contrast, *N*-acetyl- and *N*-phenyl-substituted substrates gave the corresponding products **13** and **14** in moderate yields. *N*-Arylmethacrylamides with halo (F, Cl, Br, or I), alkyl, or methoxy substituents in the *para*-position afforded the corresponding products **2**–**9** in moderate to good yields, whereas *N*-(4-cyanophenyl)methacrylamide, containing an

**Table 1** Modification of the Typical Conditions[a]

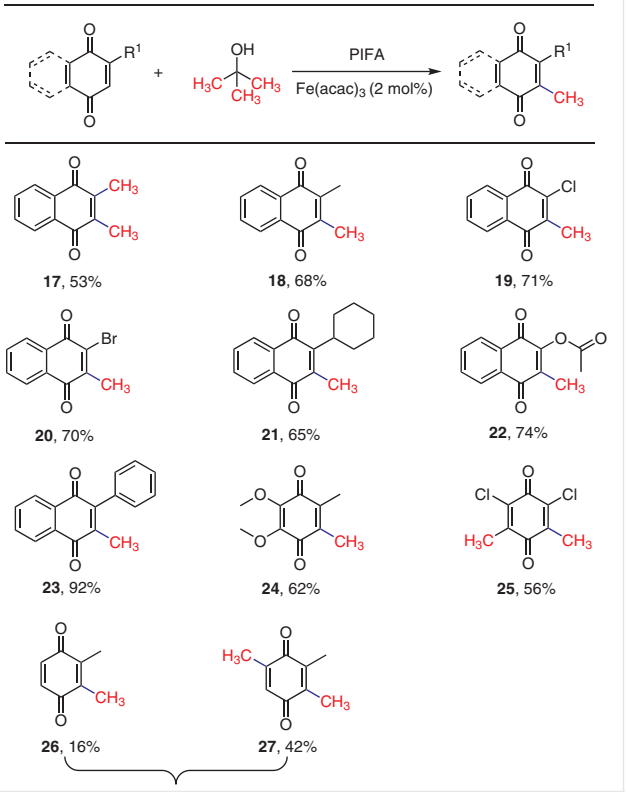



| Entry | Catalyst (mol %) | Iodine reagent | Time (h) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $Cu_2O$ (5) | PIFA | 9 | 25 |
| 2 | CuBr (5) | PIFA | 9 | 13 |
| 3 | $Cu(OAc)_2$ (5) | PIFA | 9 | 12 |
| 4 | $Cu(acac)_2$ (5) | PIFA | 9 | 20 |
| 5 | $AgNO_3$ (5) | PIFA | 9 | trace |
| 6 | $Fe(OTf)_2$ (5) | PIFA | 9 | 50 |
| 7 | $Fe(acac)_2$ (5) | PIFA | 9 | 66 |
| 8 | $FeCl_3{\cdot}6H_2O$ (5) | PIFA | 9 | 70 |
| 9 | $Fe(acac)_3$ (5) | PIFA | 9 | 73 |
| 10 | $Mn(acac)_2$ (5) | PIFA | 9 | 32 |
| 11 | $Ni(acac)_2$ (5) | PIFA | 9 | 51 |
| 12 | $Pd(acac)_2$ (5) | PIFA | 9 | 16 |
| 13 | – | PIFA | 9 | trace |
| 14 | $Fe(acac)_3$ (5) | $I_2$ | 9 | trace |
| 15 | $Fe(acac)_3$ (5) | $I_2O_5$ | 9 | trace |
| 16[c] | $Fe(acac)_3$ (2) | PIFA | 9 | 78 |
| 17[c] | $Fe(acac)_3$ (2) | PIFA | 6 | 63 |
| 18[c] | $Fe(acac)_3$ (2) | PIFA | 12 | 74 |

[a] Typical conditions: *N*-methyl-*N*-phenylmethacrylamide (1 equiv, 0.2 mmol), PIFA (3 equiv, 0.6 mmol), $Fe(acac)_3$ (5 mol%), *t*-BuOH (3 mL), 120 °C, 9 h.
[b] Isolated yield.
[c] Reaction conditions: *N*-methyl-*N*-phenylmethacrylamide (1 equiv, 0.2 mmol), PIFA (2 equiv, 0.4 mmol), $Fe(acac)_3$ (2 mol%), *t*-BuOH (2 mL), 120 °C, 9 h.




**Scheme 2** $Fe(acac)_3$-catalyzed free-radical cascade methylation of *N*-arylmethacrylamides with *t*-BuOH. *Reaction conditions*: *N*-arylmethacrylamide (1 equiv, 0.2 mmol), PIFA (2 equiv, 0.4 mmol), $Fe(acac)_3$ (2 mol%), *t*-BuOH (2 mL), 120 °C, 9 h.

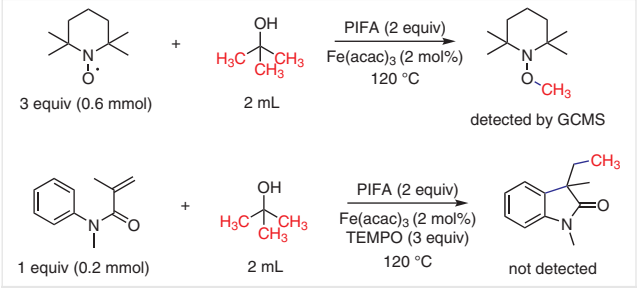



**Scheme 3** $Fe(acac)_3$-catalyzed free-radical cascade methylation of quinones with *t*-BuOH. *Reaction conditions*: quinone (1 equiv, 0.2 mmol), PIFA (2 equiv, 0.4 mmol), $Fe(acac)_3$ (2 mol%), *t*-BuOH (2 mL), 120 °C, 5 h.

electron-withdrawing cyano group, gave product **10** in a moderate yield. *N*-Methyl-*N*-(1-naphthyl)methacrylamide gave the corresponding product **11** in 50% yield. To expand the range of substrates further, this method also was confirmed to be efficient in the synthesis of the methylated isoquinolinediones **15** and **16** in moderate yields.

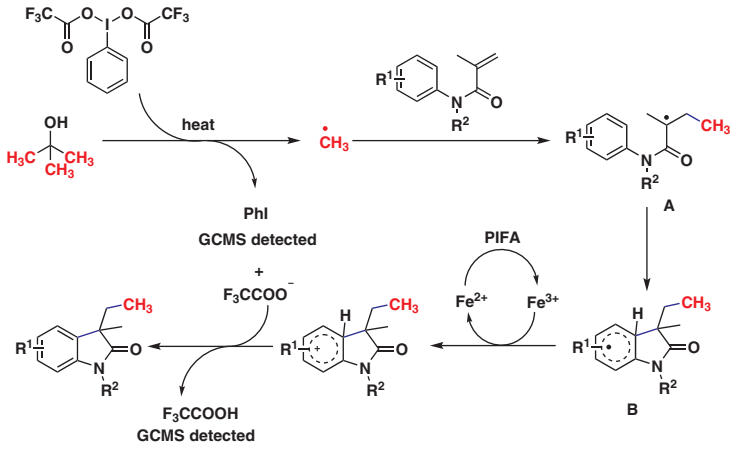
Encouraged by the successful application of this method to the synthesis of methylated oxindoles, we turned our attention to the synthesis of methylated quinones by this strategy. As shown in Scheme 3, we found that a wide range of quinones with either electron-donating or electron-withdrawing groups gave moderate to good yields of the desired products **18**–**24**. Furthermore, naphthoquinone and 2,6-dichlorobenzo-1,4-quinone gave 2,3-dimethylnaphthoquinone (**17**) and 2,6-dichloro-3,5-dimethylbenzo-1,4-quinone, respectively, as major products in yields of 31 and 30%. In the case of 2-methylbenzo-1,4-quinone, two products, **26** and **27**, were obtained.

To verify the reaction mechanism, we performed radical-trapping experiments, and we found that none of the desired product was obtained when TEMPO was added to the system (Scheme 4; see also the Supporting Information); moreover, the coupling product of TEMPO and a methyl radical was detected by GC/MS, indicating that a free-radical process would be involved in this system.




**Scheme 4** Mechanistic study

On the basis of these experiments and reports in the literature, we proposed the mechanism shown in Scheme 5. First, PIFA oxidizes *t*-BuOH to produce a methyl radical, which adds to the double bond in the *N*-arylmethacrylamide to give the radical intermediate **A**. Subsequently, in-




**Scheme 5** Plausible mechanism

tramolecular cyclization of radical intermediate **A** generates radical intermediate **B**, which undergoes single-electron oxidation by Fe(III) and deprotonation by $F_3COO^-$ to generate the target product.

In summary, the Fe-catalyzed methylation of activated alkenes by using *t*-BuOH as a green methylating reagent has been achieved.[20] A sequential methyl-radical methylation/cyclization and methylation/elimination are involved in this strategy, which provides a new method for the construction of methylated oxindoles and quinones. Further studies on the development of novel methylating reagents are currently underway in our laboratory.

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## Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690193.

## Primary Data

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(20) **3-Ethyl-1,3-dimethyl-1,3-dihydro-2*H*-indol-2-one** (**1**); **Typical Procedure**
A mixture of *N*-methyl-*N*-phenylmethacrylamide (1 equiv, 0.2 mmol), $Fe(acac)_3$ (2 mol%, 0.004 mmol), PIFA (2 equiv, 0.4 mmol), and *t*-BuOH (2 mL) was refluxed at 120 °C for 9 h. When the reaction was complete, the mixture was concentrated under vacuum and the residue was purified by flash column chromatography (silica gel) to give a colorless liquid; yield: 78%.
$^1$H NMR (400 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.6 Hz, 1 H), 7.16 (d, *J* = 7.2 Hz, 1 H), 7.07 (t, *J* = 7.6 Hz, 1 H), 6.85 (d, *J* = 7.6 Hz, 1 H), 3.21 (s, 3 H), 1.97–1.88 (m, 1 H), 1.81–1.72 (m, 1 H), 1.34 (s, 3 H), 0.57 (t, *J* = 7.6 Hz, 3 H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ = 181.2, 143.2, 133.8, 127.6, 122.6, 122.4, 108.0, 49.1, 31.3, 26.1, 23.2, 8.7. MS (EI): *m/z* (%) = 189 (51.4), 160 (100.0).
**2-Chloro-3-methylnaphthoquinone** (**19**); **Typical Procedure**
A mixture of 2-chloronaphthoquinone (1 equiv, 0.2 mmol), $Fe(acac)_3$ (2 mol%, 0.004 mmol), PIFA (2 equiv, 0.4 mmol), and *t*-BuOH (2 mL) was refluxed at 120 °C for 5 h. When the reaction was complete, the mixture was concentrated under vacuum and the residue was purified by flash column chromatography (silica gel) to give a yellow solid; yield: 71%.
$^1$H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.07 (m, 2 H), 7.74–7.72 (m, 2 H), 2.32 (s, 3 H). $^{13}$C NMR (101 MHz, $CDCl_3$): δ = 182.5, 177.4, 144.8, 143.2, 134.1, 133.8, 131.5, 131.2, 127.1, 126.9, 14.4. MS (EI): *m/z* (%) = 208 (4.1), 206 (13.3), 171 (100.0).