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Silver-Mediated Intermolecular 1,2-Alkylarylation of Styrenes with α-Carbonyl Alkyl Bromides and Indoles

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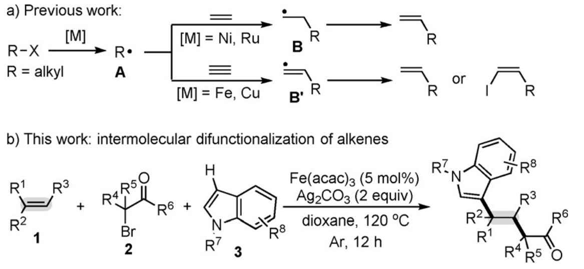
Dedicated to Professor Xue-Long Hou on the occasion of his 60th birthday

***Abstract:** A new iron-facilitated silver-mediated radical 1,2-alkylarylation of styrenes with α-carbonyl alkyl bromides and indoles is described, and two new C–C bonds were generated in a single step through a sequence of intermolecular $C(sp^3)$–Br functionalization and $C(sp^2)$–H functionalization across the alkenes. This method provides an efficient access to alkylated indoles with broad substrate scope and excellent selectivity.*

Functionalization of alkenes has emerged as a powerful method to prepare highly functionalized backbones in chemical synthesis, thus it continues to attract the attention of the synthetic chemists for the development of new functionalization strategies.[1,2] Difunctionalization of alkenes is unarguably a fascinating route to rapidly increase molecular complexity.[2] Despite significant progress in this field, the search for alternatives which allow the simultaneous formation of two C–C bonds in a single step,[2h–l] particularly involving a C–H functionalization,[3,4] still remains a formidable challenge. Further, available examples of the alkene difunctionalization involving an arene $C(sp^2)$–H functionalization are limited to the construction of oxindoles and related heterocycles by a sequence of intramolecular $C(sp^2)$–H functionalization and cyclization.[2h–l,3] Therefore, the development of new alkene difunctionalization methods, especially an intermolecular $C(sp^2)$–H functionalization strategy, beyond oxindole synthesis, for generating two C–C bonds in one step is highly desirable.

In recent years, a few papers have reported that alkyl halides were converted into alkyl radicals (**A;** Scheme 1 a) to initiate the coupling with unsaturated compounds (e.g., alkenes and alkynes) to produce either the intermediate **B** or **B′**, thus selectively achieving monofunctionalizaition and difunctionalizaition.[5] On this basis, we reasoned that arene $C(sp^2)$–H bonds, having the appropriate reactivity, might intermolecularly trap the radical intermediates **B**, thus enabling the simultaneous formation of two C–C bonds across the alkenes and the incorporation of diverse synthetically versatile functional groups. Herein, we report a new iron-facilitated silver-mediated radical 1,2-alkylarylation of styrenes (**1**) with α-carbonyl alkyl bromides (**2**), and indoles (**3**) for producing alkylated indoles (Scheme 1 b).[6,7] This reaction allows a one-step construction of two C–C bonds, and represents the first example of silver-mediated alkene difunctionalization through intermolecular arene $C(sp^2)$–H functionalization. Notably, alkyl-functionalized indoles are important structural motifs in natural products and pharmaceuticals, as well as useful intermediates in synthesis.[8]



Scheme 1. Functionalization by radical reactions. acac = acetylacetonate.

We started our investigation with the three-component reaction of *p*-methylstyrene (**1a**) with methyl 2-bromopropanoate (**2a**) and 1-methyl-1*H*-indole (**3a**) for optimization of the reaction conditions (Table 1).[9] The alkene **1a** was treated with **2a**, **3a**, [Fe(acac)$_3$], and Ag_2CO_3 and led to the formation of the desired 1,2-alkylarylation product **4** in 83 % yield (entry 1). Further screening revealed that [Fe(acac)$_3$] only served to improve the reaction (entries 2 and 3). Identical results to those obtained with 5 mol % [Fe(acac)$_3$] were observed when using a higher amount of [Fe(acac)$_3$] (entry 2). It was noted that in the absence of [Fe(acac)$_3$] the reaction could also furnish product **4** in 70 % yield (entry 3). However, other iron salts ($FeCl_3$ and $FeCl_2$) as well as [Cu(acac)$_2$] had no effect compared with the results obtained in the absence of [Fe(acac)$_3$] (entry 4 versus entry 2). The results demonstrated that silver salts are the real catalysts for the three-component reaction (entries 5–9): the reaction did not proceed without the silver salts, even in the presence of a base (entries 5 and 6), and a lower amount of Ag_2CO_3 had a negative effect (entry 7). Other silver salts, such as AgOAc, Ag_2O, and AgF, had catalytic activity, but they were less efficient than Ag_2CO_3 (entries 8–10). We found that higher reaction tem-

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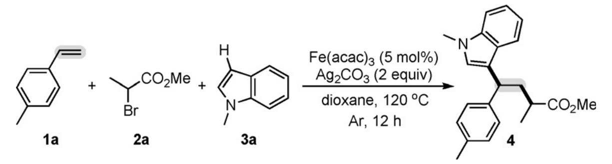
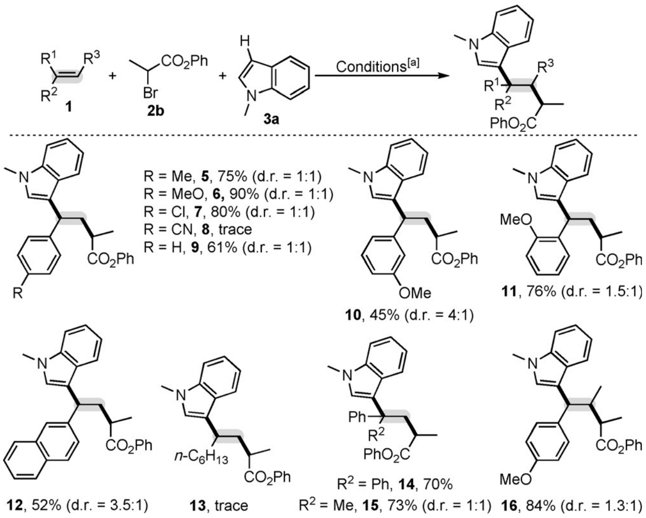
Table 1: Screening of optimal reaction conditions.[a]



Entry	Variation from the standard reaction conditions	Yield [%][b]
1[c]	none	83
2	[Fe(acac)$_3$] (10 mol%)	81
3	without [Fe(acac)$_3$]	70
4	$FeCl_3$, $FeCl_2$, or [Cu(acac)$_2$] instead of [Fe(acac)$_3$]	68
5	without Ag_2CO_3	0
6	K_2CO_3 or Cs_2CO_3 instead of Ag_2CO_3	0
7[d]	Ag_2CO_3 (1 equiv)	42
8	AgOAc instead of Ag_2CO_3	45
9	Ag_2O instead of Ag_2CO_3	42
10	AgF instead of Ag_2CO_3	55
11	at 100 °C	20
12	at 130 °C	84
13	PhCl instead of 1,4-dioxane	82
14[e]	MeCN instead of 1,4-dioxane	61
15[f]	none	81

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.4 mmol), **3a** (0.2 mmol), [Fe(acac)$_3$] (5 mol%; 0.01 mmol), Ag_2CO_3 (2 equiv; 0.4 mmol), and MeCN (2 mL) at 120 °C under argon atmosphere for 12 h. The d.r. value is 1.6:1, as determined by ^1H NMR analysis of the crude reaction mixture. [b] Some side-products, including 3-methyl-5-(*p*-tolyl)dihydrofuran-2(3*H*)-one (**4a**; 16% yield), methyl 4-bromo-2-methyl-4-(*p*-tolyl)-butanoate (**4b**; < 5% yield), and ethyl 2-methyl-4-(*p*-tolyl)but-3-enoate (**4c**; < 5% yield) from the reaction of **1a** with **2a**, and ethyl 2-(1-methyl-1*H*-indol-3-yl)propanoate (**4d**; 12% yield) from the reaction of **2a** with **3a**, were detected by GC-MS analysis. [c] Yield of isolated product based on the amount of **3a**. [d] In the presence or absence of Cs_2CO_3, identical results were observed. [e] For 36 h. [f] Used **3a** (1 g; 7.634 mmol) and 1,4-dioxane (10 mL) for 48 h.

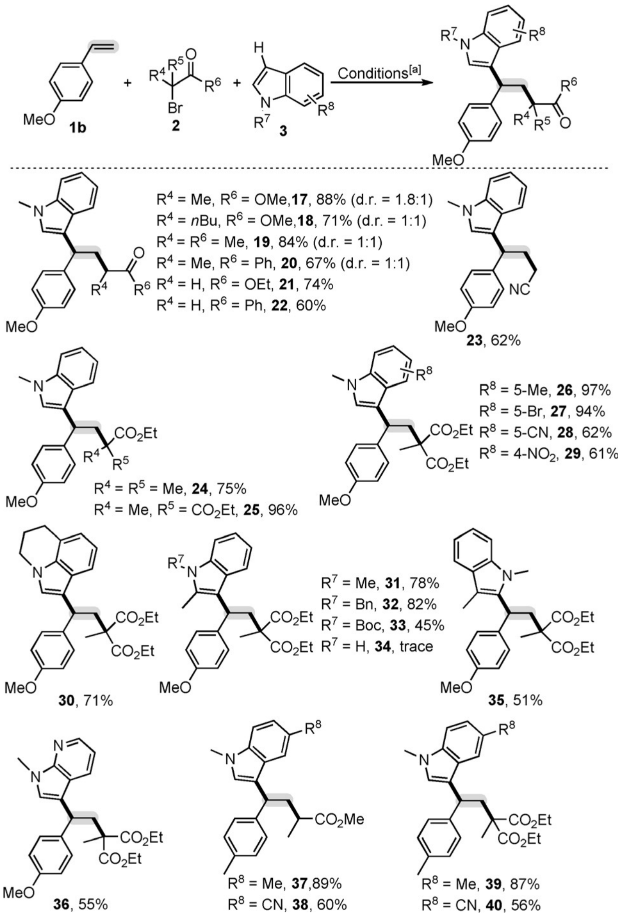


Scheme 2. Variation of the alkenes **1**. [a] Reaction conditions: **1** (0.4 mmol), **2b** (0.4 mmol), **3a** (0.2 mmol), [Fe(acac)$_3$] (5 mol%), Ag_2CO_3 (2 equiv; 0.4 mmol), and 1,4-dioxane (2 mL) at 120 °C under argon atmosphere for 12 h. Yield of isolated product based on the amount of **3a**. The d.r. value is given within the parenthesis and was determined by ^1H NMR analysis of the crude reaction mixture.

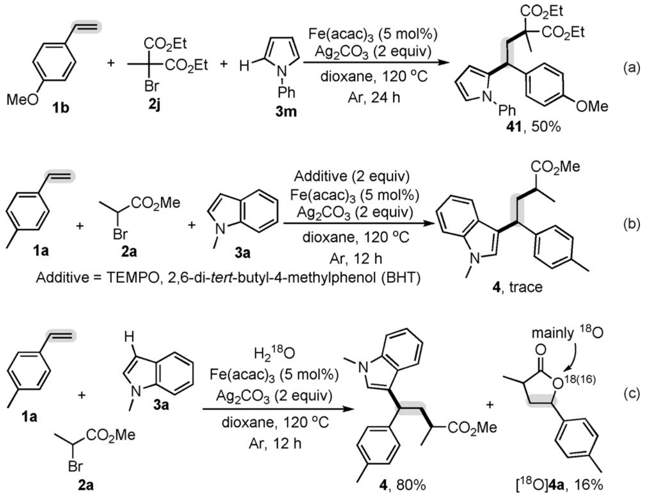
perature (at 130 °C) did not improve the yield compared with the results at 120 °C (entry 12), but lower temperature (at 100 °C) dramatically reduced the yield (entry 11). The reaction proved sensitive to the effect of solvent: While 1,4-dioxane and chlorobenzene were highly effective mediums for the reaction (entries 1 and 13), acetonitrile showed lower reactivity (entry 14). Notably, the reaction is applicable to a 1 gram scale of **3a**, thus giving **4** in good yield (entry 15).

With the optimal reaction conditions in hand, the scope of this [Fe(acac)$_3$]-facilitated, Ag_2CO_3-mediated 1,2-alkylarylation protocol was investigated with regard to the scope of the alkenes **1**, α-carbonyl alkyl bromides **2**, and indoles **3**. As shown in Scheme 2, the optimal reaction conditions were applicable to a wide range of alkenes. In the presence of phenyl 2-bromopropanoate (**2b**), the indole **3a**, [Fe(acac)$_3$], and Ag_2CO_3, a variety of terminal aryl alkenes (**1a**–**c** and **1e**–**h**) were successfully converted into the corresponding 1,2-alkylarylation products (**5**–**7** and **9**–**12**) with moderate to good yields, but the strongly electron-deficient aryl alkene **1d** and aliphatic alkene **1i** were not suitable substrates (products **8** and **13**). We found that both the electronic nature of the aryl group and the substituent position on the aryl group had a fundamental influence on the reactivity. The alkenes **1a** and **1c**, bearing a *p*-MeC_6H_4 group and *p*-ClC_6H_4 group, respectively, furnished the corresponding **5** and **7** with consistent yields. However, the alkene **1d**, with a CN group, had no reactivity (**8**). While the reaction of **1c** enabled the synthesis of **6** in 90% yield, the reaction of *m*- and *o*-methyl-substituted aryl alkenes **1f**,**g** afforded **10** and **11**, respectively, in lower yields. 2-Vinylnaphthalene (**1h**) was transformed into **12** smoothly, albeit with a diminished yield. Gratifyingly, the optimal reaction conditions were compatible with the 1,1-disubstutited alkenes **1j**,**k**, and the reaction delivered **14** and **15**, respectively, with concomitant generation of a quaternary carbon center. Noted that anethole (**1l**), an internal alkene, was viable for constructing **16** in good yield.

Next, the scope with respect to the α-carbonyl alkyl bromides **2** and indoles **3** were investigated (Scheme 3). We found that this protocol was subjected to various primary, secondary, and tertiary α-carbonyl alkyl bromides (**2**), including α-bromoalkyl esters, ketones, and nitrile (products **17**–**25**). Using the secondary α-bromoalkyl esters **2a** and **2c**, and ketones **2d**,**e**, the reaction with **1b**, **3a**, [Fe(acac)$_3$], and Ag_2CO_3 selectively furnished **17**–**20** with high yields. Gratifyingly, the current reaction was not limited to the primary bromoalkyl ester **2f** and ketone **2g** (**21** and **22**), but 2-bromoacetonitrile **2h** could be converted into **23** in 62% yield. Tertiary α-bromoalkyl esters, namely ethyl 2-bromo-2-methylpropanoate (**2i**) and diethyl 2-bromo-2-methylmalonate (**2j**), also showed high reactivity, thus leading to **24** and **25**,[9] respectively, in high yields. Subsequently, we set out to study the generality of the indoles **3** in the presence of **1b**, **2j**, [Fe(acac)$_3$], and Ag_2CO_3 (**26**–**35**). The results showed that electron-rich indoles had higher reactivity than electron-deficient indoles: The reaction tolerated 5-methyl- and 5-bromo-substitued indoles (**3b**,**c**), thus affording **26** and **27**, respectively, in excellent yields, whereas 5-cyano- and 4-nitro-substitued indoles (**3d**,**e**) were transformed into the corre-



Scheme 3. Variation of the α-carbonyl alkyl bromides **2** and indoles (**3**). [a] See Table 1 and Scheme 2. Yield of isolated product based on the amount of **3**. The d.r. value is given within the parenthesis and was determined by ^{1}H NMR analysis of the crude reaction mixture.

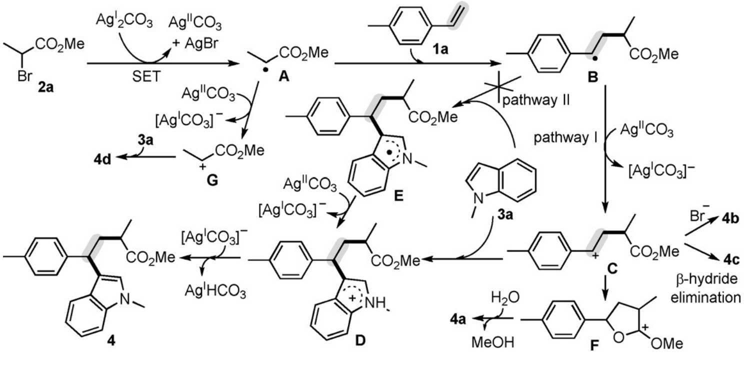


Scheme 4. Reaction with pyrrole (**3m**) and control experiments.

sponding **28** and **29** in moderate yields. For the 6-substituted indole **3f**, the reaction enabled the synthesis of **30** in 71% yield. We found that only N-protected indoles had reactivity: While the reaction of the indoles **3g–i**, having an N-methyl, N-benzyl, and N-Boc (Boc = *tert*-butoxycarbonyl) group, respectively, were successfully performed to furnish **31–33**, the substrate **3j**, having a free NH group, failed to undergo reaction (**34**). By using the 3-substituted indole **3k**, the reaction occurred at the C2-position (**35**). Gratifyingly, the reaction was applicable to 1*H*-pyrrolo[2,3-*b*]pyridine (**3l**) and gave **36** in 55% yield. We found that both **3b** and **3d** were successfully reacted with different alkenes (**1**) and bromides (**2**) to afford **37–40** in good yield.

As shown in Scheme 4a, pyrrole (**3m**) was a suitable substrate for the 1,2-alkylarylation reaction, thus generating the product **41** in 50% yield. Notably, the reaction of **1a** with **2a** and **3a** was completely suppressed by a stoichiometric amount of radical inhibitors, including TEMPO and 2,6-di-*tert*-butyl-4-methylphenol (BHT; Scheme 4b), thus implying that this current reaction involves a free-radical process. In addition, the results of entries 6 and 7 in Table 1 indicated that the bases had no effect on the reaction, and thus support the role of Ag_2CO_3 as a one-electron oxidation. Notably, the ^{18}O-labelled furan-2(3*H*)-one [^{18}O]**4a** was isolated from the reaction of **1a** with **2a**, **3a**, and $H_2{}^{18}O$ (Scheme 4c).[5p] The reaction profiles of competitive reactions showed that electron-rich **3b** is more reactive than electron-deficient **3d**, thus suggesting that the radical addition is not the main process in the indole trapping step [see Figures S1 and S2 in Supporting Information]. To verify the results, the kinetic isotope effect (KIE) experiments of 3-deuterated 1-methylindole ([D]**3a**) were carried out: a small KIE value ($k_H/k_D = 0.7$) was observed, and rules out a hydrogen atom abstraction (radical) process in the indole trapping step (see the Supporting Information).[10]

The possible mechanisms for this Ag_2CO_3-mediated 1,2-alkylarylation reaction are proposed (Scheme 5).[3–7,10] Initially, cleavage of an α-C(sp^3)–Br bond in substrate **2a** with the active Ag^I species under heating produces the alkyl radical **A** and the Ag^{II} species by single-electron transfer (SET).[5,7] Addition of **A** across a C=C bond in **1a** affords the new alkyl radical intermediate **B**, which is also supported by the formation of the side-products **4a–c** (entry 1 in Table 1). Oxidation of **B** by the active Ag^{II} species generates the cation intermediate **C**,[3,7] followed by electrophilic alkylation of **3a**



Scheme 5. Possible mechanisms.

to give the product **4** (pathway I). Within this process, excess **C** can selectively undergo cyclization (side-product **4a**),[5p] atom-transfer reaction (side-product **4b**),[5e–i] and β-hydride elimination (side-product **4c**).[5a–d] [Fe(acac)$_3$] may play a Lewis acid to stabilize the radicals and improve the yields. Notably, the possible pathway II which involves the direct reaction of the **B** with the **3a** is ruled out according to the ^{18}O-labelling experiment,[5p] the reaction profiles of competitive reactions, and the kinetic isotope effect experiments.[10]

In summary, we have developed the first example of silver-mediated radical 1,2-alkylarylation of styrenes with α-carbonyl alkyl bromides and indoles involving intermolecular arene C(sp^2)–H functionalization, in which [Fe(acac)$_3$] was found to improve the yield. The reaction selectively enables the formation of two C–C bonds in a single step, and provides a shortcut to produce 2- and 3-alkylated indoles with broad substrate scope. Furthermore, an electrophilic alkylation process for trapping indoles is supported by the ^{18}O-labelling experiment, the reaction profiles of competitive reactions and the KIE experiments. Work on application of this alkene difunctionalization strategy is currently in progress in our laboratory.

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Keywords: alkenes · C–H functionalization · heterocycles · iron · silver

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