

Synthetic Methods

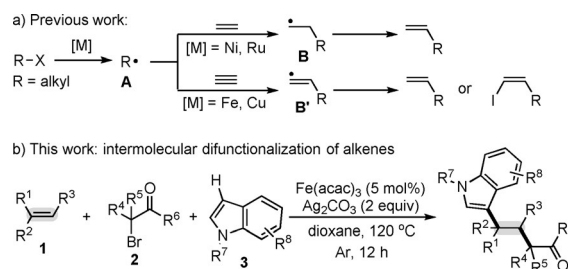
International Edition: DOI: 10.1002/anie.201511624
German Edition: DOI: 10.1002/ange.201511624Silver-Mediated Intermolecular 1,2-Alkylarylation of Styrenes with α -Carbonyl Alkyl Bromides and IndolesXuan-Hui Ouyang⁺, Ren-Jie Song⁺, Ming Hu, Yuan Yang, and Jin-Heng Li*

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(sp³)–Br functionalization and C(sp²)–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,^[2b–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(sp²)–H functionalization are limited to the construction of oxindoles and related heterocycles by a sequence of intramolecular C(sp²)–H functionalization and cyclization.^[2b–l,3] Therefore, the development of new alkene difunctionalization methods, especially an intermolecular C(sp²)–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 monofunctionalization and difunctionalization.^[5] On this basis, we reasoned that arene C(sp²)–H bonds, having the appropriate reactivity, might



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

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(sp²)–H functionalization. Notably, alkyl-functionalized indoles are important structural motifs in natural products and pharmaceuticals, as well as useful intermediates in synthesis.^[8]

We started our investigation with the three-component reaction of *p*-methylstyrene (**1a**) with methyl 2-bromopropionate (**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 Ag₂CO₃ 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 (FeCl₃ and FeCl₂) 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 Ag₂CO₃ had a negative effect (entry 7). Other silver salts, such as AgOAc, Ag₂O, and AgF, had catalytic activity, but they were less efficient than Ag₂CO₃ (entries 8–10). We found that higher reaction tem-

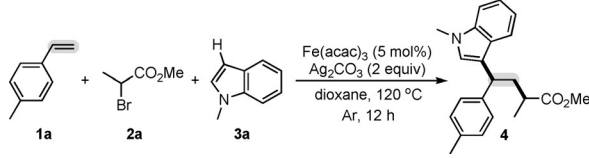
[*] X.-H. Ouyang,^[†] Dr. R.-J. Song,^[†] M. Hu, Y. Yang, Prof. Dr. J.-H. Li
State Key Laboratory of Chemo/Biosensing and Chemometrics
College of Chemistry and Chemical Engineering
Hunan University, Changsha 410082 (China)
E-mail: jhli@hnu.edu.cn

Prof. Dr. J.-H. Li
State Key Laboratory of Applied Organic Chemistry
Lanzhou University, Lanzhou 730000 (China)

[†] These authors contributed equally to this work.

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under <http://dx.doi.org/10.1002/anie.201511624>.

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

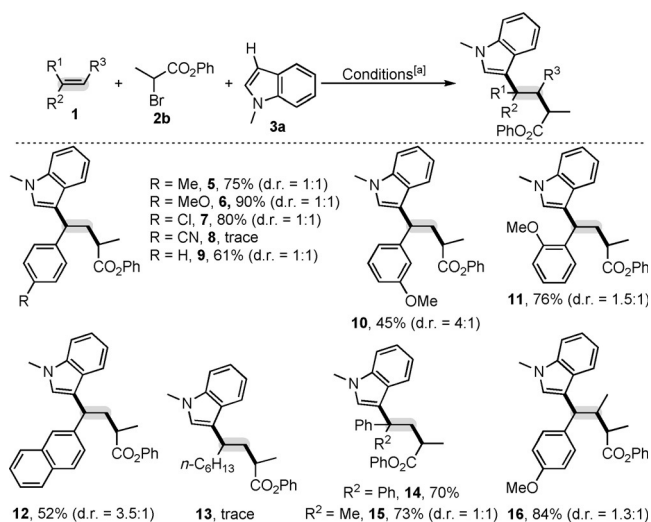


Entry	Variation from the standard reaction conditions	Yield [%] ^[b]
1 ^[c]	none	83
2	[Fe(acac) ₃] (10 mol %)	81
3	without [Fe(acac) ₃]	70
4	FeCl ₃ , FeCl ₂ , or [Cu(acac) ₂] instead of [Fe(acac) ₃]	68
5	without Ag ₂ CO ₃	0
6	K ₂ CO ₃ or Cs ₂ CO ₃ instead of Ag ₂ CO ₃	0
7 ^[d]	Ag ₂ CO ₃ (1 equiv)	42
8	AgOAc instead of Ag ₂ CO ₃	45
9	Ag ₂ O instead of Ag ₂ CO ₃	42
10	AgF instead of Ag ₂ CO 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), Ag₂CO₃ (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 Cs₂CO₃, 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.

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).

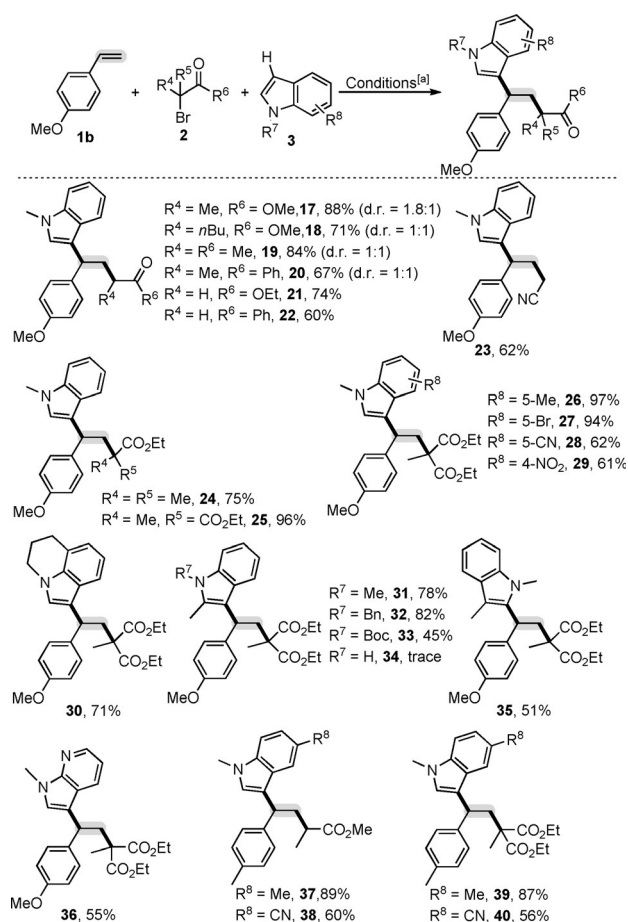
With the optimal reaction conditions in hand, the scope of this [Fe(acac)₃]-facilitated, Ag₂CO₃-mediated 1,2-alkylarylation protocol was investigated with regard to the scope of the alkenes **1**, α -carbonyl alkyl bromides **2**, and indoles **3**. As shown in Scheme 2, the optimal reaction conditions were applicable to a wide range of alkenes. In the presence of phenyl 2-bromopropanoate (**2b**), the indole **3a**, [Fe(acac)₃], and Ag₂CO₃, 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*-MeC₆H₄ group and *p*-ClC₆H₄ group, respec-



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 %), Ag₂CO₃ (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.

tively, 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-disubstituted alkenes **1j,k**, and the reaction delivered **14** and **15**, respectively, with concomitant generation of a quaternary carbon center. Noted that anethole (**1i**), an internal alkene, was viable for constructing **16** in good yield.

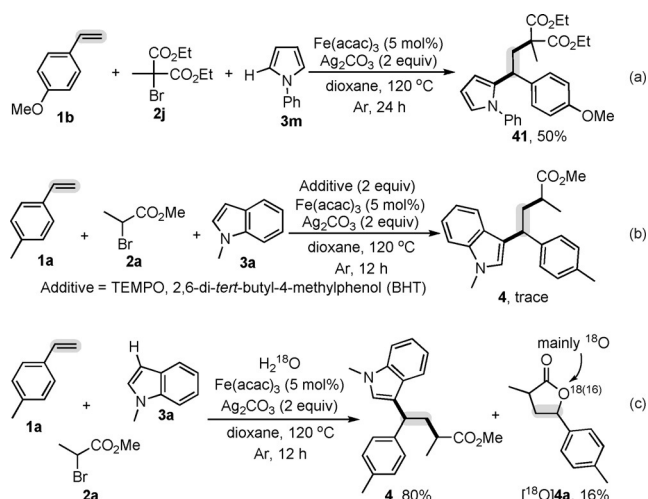
Next, the scope with respect to the α -carbonyl alkyl bromides **2** and indoles **3** were investigated (Scheme 3). We found that this protocol was subjected to various primary, secondary, and tertiary α -carbonyl alkyl bromides (**2**), including α -bromoalkyl esters, ketones, and nitrile (products **17–25**). Using the secondary α -bromoalkyl esters **2a** and **2c**, and ketones **2d,e**, the reaction with **1b**, **3a**, [Fe(acac)₃], and Ag₂CO₃ 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 Ag₂CO₃ (**26–35**). The results showed that electron-rich indoles had higher reactivity than electron-deficient indoles: The reaction tolerated 5-methyl- and 5-bromo-substituted indoles (**3b,c**), thus affording **26** and **27**, respectively, in excellent yields, whereas 5-cyano- and 4-nitro-substituted 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 ^1H NMR analysis of the crude reaction mixture.

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.

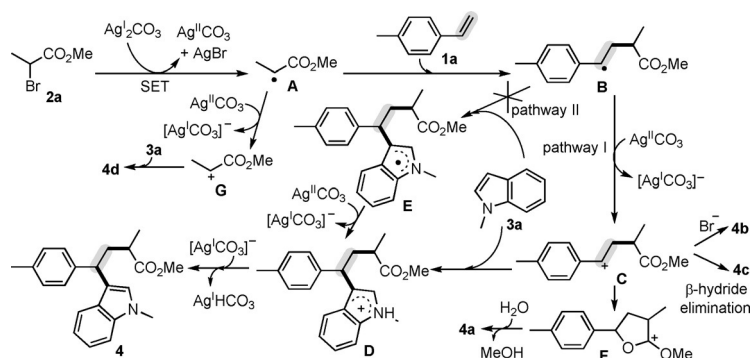
As shown in Scheme 4a, pyrrole (**3m**) was a suitable substrate for the 1,2-alkylarylation reaction, thus generating the product **41** in 50% yield. Notably, the reaction of **1a** with **2a** and **3a** was completely suppressed by a stoichiometric amount of radical inhibitors, including TEMPO and 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



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

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 ($k_{\text{H}}/k_{\text{D}} = 0.7$) 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 $\alpha\text{-C}(\text{sp}^3)\text{-Br}$ 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 $\text{C}=\text{C}$ 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**



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 ¹⁸O-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-alkylation of styrenes with α -carbonyl alkyl bromides and indoles involving intermolecular arene C(sp²)–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 ¹⁸O-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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