Synthetic Methods

Deutsche Ausgabe: DOI: 10.1002/ange.201511624
Internationale Ausgabe: DOI: 10.1002/anie.201511624

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

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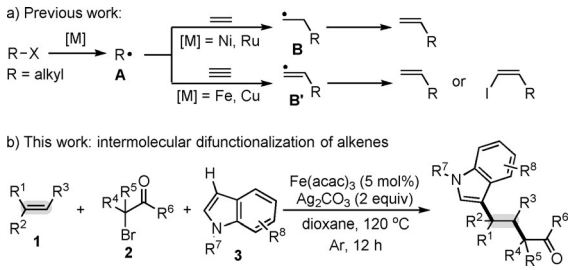
Dedicated to Professor Xue-Long Hou on the occasion of his 60th birthday

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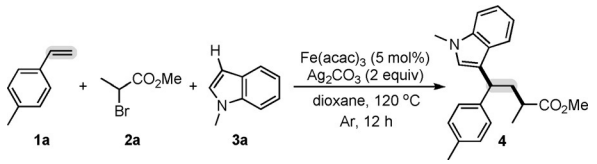
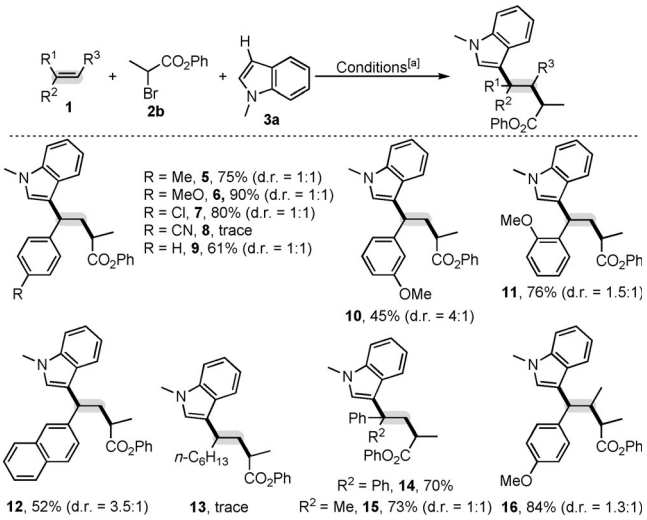
Table 1: Screening of optimal reaction conditions.[a]



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 ^{1}H 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.

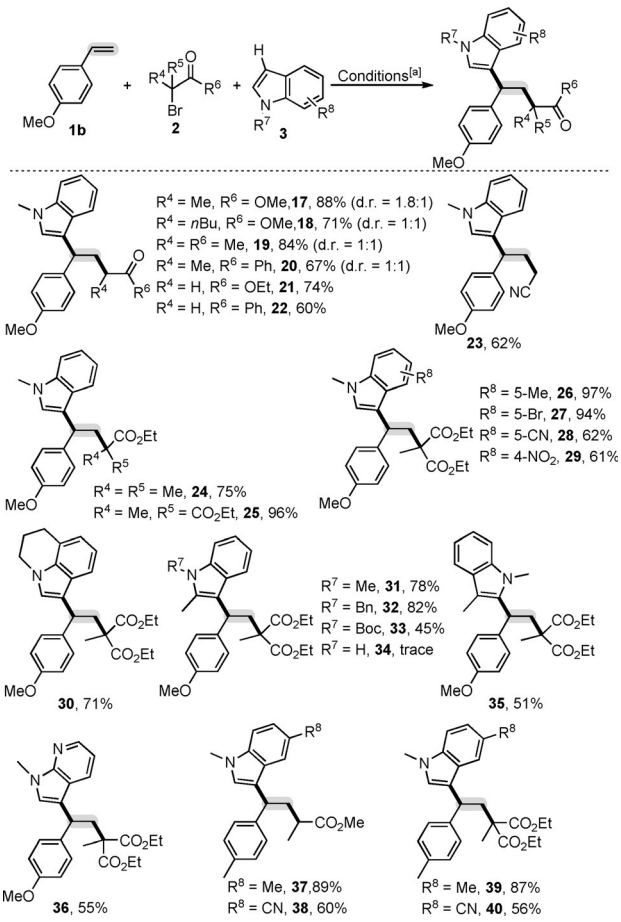


Scheme 2. Variation of the alkenes **1**. [a] Reaction conditions: **1** (0.4 mmol), **2b** (0.4 mmol), **3a** (0.2 mmol), $[Fe(acac)_3]$ (5 mol%), Ag_2CO_3 (2 equiv; 0.4 mmol), and 1,4-dioxane (2 mL) at 120 °C under argon atmosphere for 12 h. Yield of isolated product based on the amount of **3a**.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

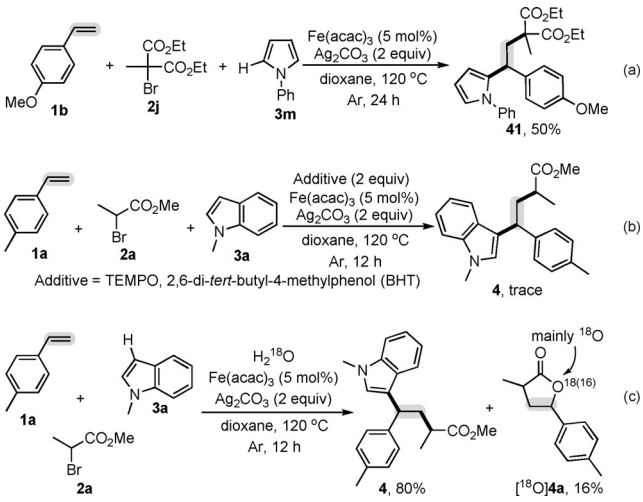
perature (at 130 °C) did not improve the yield compared with the results at 120 °C (entry 12), but lower temperature (at 100 °C) dramatically reduced the yield (entry 11). The reaction proved sensitive to the effect of solvent: While 1,4-dioxane and chlorobenzene were highly effective mediums for the 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.

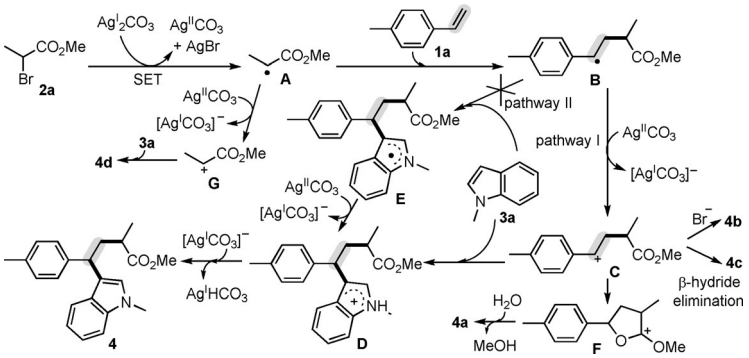


Scheme 4. Reaction with pyrrole (**3m**) and control experiments.

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.

Acknowledgments

We thank the Natural Science Foundation of China (Nos. 21472039 and 21172060) and the Hunan Provincial Natural Science Foundation of China (No. 13JJ2018) for financial support.

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

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 3187–3191
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Received: December 14, 2015
Published online: January 28, 2016

