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Rapid Synthesis of γ-Arylated Carbonyls Enabled by the Merge of Copper- and Photocatalytic Radical Relay Alkylarylation of Alkenes

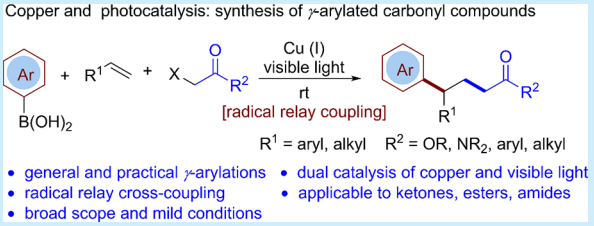
Xu-Lu Lv,[†] Cong Wang,[†] Qiao-Li Wang,[†] and Wei Shu*[,†,‡]

[†]Department of Chemistry and Shenzhen Grubbs Institute, Southern University of Science and Technology, 518055 Shenzhen, China

[‡]State Key Laboratory of Elemento-Organic Chemistry, Nankai University, 300071 Tianjin, China

Supporting Information

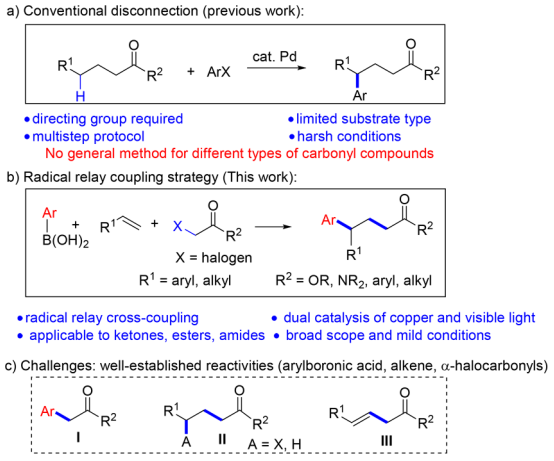
ABSTRACT: The development of mild and practical methods for the γ-arylation of carbonyl compounds is an ongoing challenge in organic synthesis. The first formal γ-arylation of carbonyl compounds via radical relay cross-coupling of α-bromocarbonyl precursors with boronic acids in the presence of alkenes is reported. This directing-group-free protocol allows for the rapid and straightforward access to a wide range of γ-arylated esters, ketones, and amides under ambient conditions with excellent functional group tolerance.



Carbonyl derivatives are ubiquitous in pharmaceuticals, biologically active natural products, and key intermediates in chemical synthesis.[1] Methods for the functionalization at the *ipso*- and α-positions of carbonyl groups have been well established.[2] The β-functionalization of aliphatic carbonyl compounds relying on C−H cleavage has been extensively developed over the past decade.[3,4] In contrast, corresponding γ-functionalization of aliphatic carbonyl compounds remains largely underdeveloped.[4] A few examples of γ-functionalizations of carbonyl compounds thus far are limited to Pd-catalyzed carboxylic acid derivatives containing a quaternary carbon center facilitated by a directing group (Scheme 1a).[5,6] Recently, Yu developed an elegant Pd-catalyzed γ-arylation of ketones enabled by a carboxylic directing group.[7] Significant limitations associated with these methods, such as additional steps required for the preconstruction of substrates and for the removal of directing groups, harsh reaction conditions, and the employment of precious metal, diminish the efficiency and compatibility of the reactions. To date, direct γ-arylation of carbonyl compounds is still a formidable challenge. However, to develop strategies that functionalize abundant and easily available starting materials to construct common and synthetically useful synthons has been emerging as an attractive goal.[8] A promising approach for γ-arylated carbonyl compounds is to introduce the aryl substituent along with the assembly of the carbon skeleton. To this end, we envision to realize the γ-arylation of carbonyl compounds through a new disconnection strategy by simultaneously formation of two C−C bonds, which circumvents the difficulties associated with the cleavage of C−H bond at γ-position of carbonyls, and has the potential to be applied to different types of carbonyl functional groups, such as ketones, esters, and amides. Herein, we report the copper- and photocatalytic[9,10] sequential alkylarylation of alkenes[11] to afford γ-arylated carbonyl compounds under mild conditions (Scheme 1b). This radical relay coupling reaction of α-halogencarbonyl precursors, alkenes, and aryl boronic acids represents the first example of general and practical γ-arylation of broad types of carbonyl functionalities, such as esters, ketones, and amides. This operationally simple strategy allows for the rapid synthesis of a wide range of γ-arylated carbonyl compounds, including ketones, esters, and amides, from inexpensive, readily available starting materials at room temperature.

An extensive literature survey revealed two potential challenges for this proposal (Scheme 1c). First, α-halogen carbonyl precursor may undergo direct cross-coupling with aryl

Scheme 1. Strategies and Challenges for the Synthesis of γ-Arylated Carbonyl Compounds



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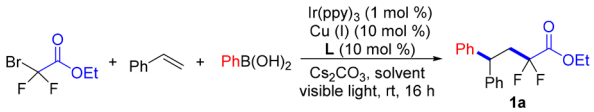
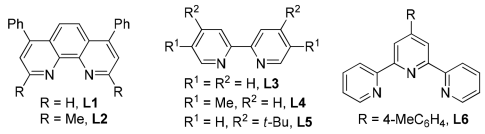
metallic species to afford α-arylated carbonyl compounds **I**.[12] Second, the resulting radical intermediate from addition of α-halogen carbonyl precursor with alkene may undergo atom transfer (halogen or hydrogen)[13] or oxidation[14] to terminate the reaction with formation of **II** or **III**. With these concerns in mind, we started the investigation using ethyl bromodifluoroacetate, styrene, and phenylboronic acid as the stereotype substrates. First trials with Cu(I) and ligand (**L1**−**L5**) as catalyst failed to deliver the radical relay cross-coupling product **1a**, and only the byproducts of bromoalkylation (**II**) or/and Heck-type reaction (**III**) were detected. When the reaction was carried out with $Ir(ppy)_3$ (1 mol %) in the assistance of visible light irradiation, the desired γ-arylated ester **1a** was formed in 20% yield using Cs_2CO_3 as base (Table 1, entry 1).[15] No desired product was observed in the absence of light or $[Cu(MeCN)_4]PF_6$ (Table 1, entry 2). Ligand evaluation revealed that bipyridyl ligand **L5** or tridentate ligand **L6** could increase the yield to 39% and 30%, respectively (Table 1, entries 3−7). The trial of other solvents did not give better result (Table 1, entries 8−10). The use of more cost-effective CuI or $CuBr{\cdot}Me_2S$ further improved the reactivity to afford **1a** in 45% yield (Table 1, entries 11−13). When the reaction was conducted under more dilute concentration (Table 1, entry 14), 50% of **1a** was obtained. When a combination of **L5** and **L6** was used, the reaction delivered the desired product **1a** in 86% yield (Table 1, entry 15).

Table 1. Conditions Evaluation for the Reaction[a]



entry	ligand	Cu (I) cat.	solvent	yield of **1a**[b]
1	**L1**	$[Cu(MeCN)_4]PF_6$	DCM	20%
2	**L1**	$[Cu(MeCN)_4]PF_6$	DCM	0%[c]
3	**L2**	$[Cu(MeCN)_4]PF_6$	DCM	9%
4	**L3**	$[Cu(MeCN)_4]PF_6$	DCM	15%
5	**L4**	$[Cu(MeCN)_4]PF_6$	DCM	13%
6	**L5**	$[Cu(MeCN)_4]PF_6$	DCM	39%
7	**L6**	$[Cu(MeCN)_4]PF_6$	DCM	30%
8	**L5**	$[Cu(MeCN)_4]PF_6$	$CHCl_3$	13%
9	**L5**	$[Cu(MeCN)_4]PF_6$	DCE	32%
10	**L5**	$[Cu(MeCN)_4]PF_6$	PhCl	30%
11	**L5**	CuI	DCM	45%
12	**L5**	CuTC	DCM	30%
13	**L5**	$CuBr{\cdot}Me_2S$	DCM	45%
14	**L5**	CuI	DCM	50%[d]
15	**L5**	CuI	DCM	86% (77%)[e,f]



[a]The reaction was conducted using styrene (0.1 mmol), ethyl bromodifluoroacetate (0.2 mmol), $PhB(OH)_2$ (0.2 mmol), Cs_2CO_3 (2 equiv) in solvent (0.2 M) under 30 W blue LED at room temperature unless otherwise stated. [b]GC yield using dodecane as internal standard. [c]No light or no $[Cu(MeCN)_4]PF_6$. [d]The reaction was conducted in 0.033 M. [e]5 mol % of **L5** and 5 mol % of **L6** were used. [f]Isolated yield after chromatography.

With the optimal conditions in hand, we evaluated the scope of this copper- and photocatalytic three-component relay coupling reactions. This strategy proved to be amenable to a myriad of aryl boronic acids, providing access to a wide range of γ-arylated esters. As shown in Figure 1, different types of aryl

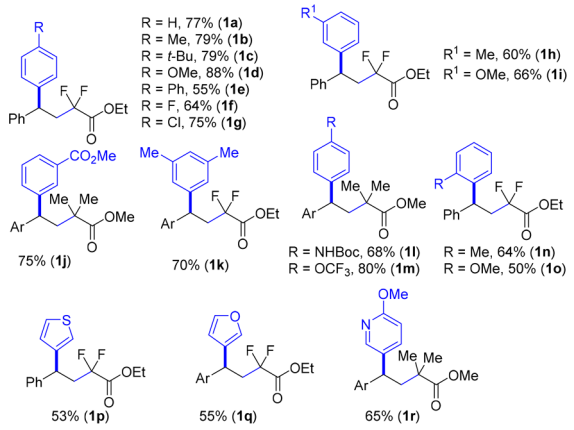


Figure 1. Scope of aryl group at γ-position. For reaction conditions, see Table 1, entry 15. Ar = 4-methoxylphenyl.

group could be installed at γ-position. Phenyl group with electron-donating or -withdrawing substituents could be tolerated, delivering the desired product in good yields (**1a**−**1m**). Aniline with free N−H is compatible in this dual catalytic process (**1l**). *ortho*-Substituted aryl group is also a good substrate under the reaction conditions (**1n** and **1o**). This protocol is also applicable to heteroaromatics, such as thiophene, furan, and pyridine, affording the desired γ-heteroarylated esters in synthetic useful yields (**1p**−**1r**).

Next, we examined the substituents at γ- and β-positions of the alkyl chain (Figure 2). Different styrene with electron-rich or -poor substituents could be applied to this reaction, providing different biaryl substituents at γ-position (**2a**−**2o**). Notably, vinylpyridines could be tolerated in this reaction (**2p** and **2q**). It is noteworthy to observe the good reactivity of alkyl alkene under the standard conditions to furnish alkyl substituent at γ-position (**2r** and **2s**). This reaction provides a complementary γ-arylation protocol to transition-metal catalyzed γ-C−H functionalization pathways, which always restrict the reactivity to the primary methyl group.[8] Internal alkene was successfully applied to the transformation, delivering corresponding β-substituted γ-arylated esters in good yields with *trans*-selectivity (**2t** and **2u**).

Then we tested precursors bearing different carbonyl functional groups (Figure 3), which led to different types of γ-arylated carbonyl compounds. This reaction proved to be a general γ-arylation method, providing rapid access to various types of γ-arylated carbonyl functionalities, including esters (**3a**−**3g**), alkyl and aryl ketones (**3h**−**3j**), and secondary and tertiary amides (**3k** and **3l**), which are always problematic for existing γ-arylation protocols of C−H bonds. It is known that α-

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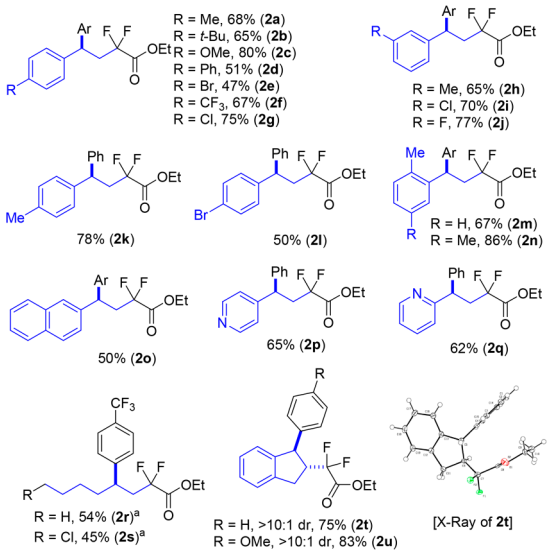


Figure 2. Scope for alkenes (β- and γ-position of the alkyl chain). For reaction conditions, see Table 1, entry 15. Ar = 4-methoxylphenyl. [a]The reaction was run for 24 h.

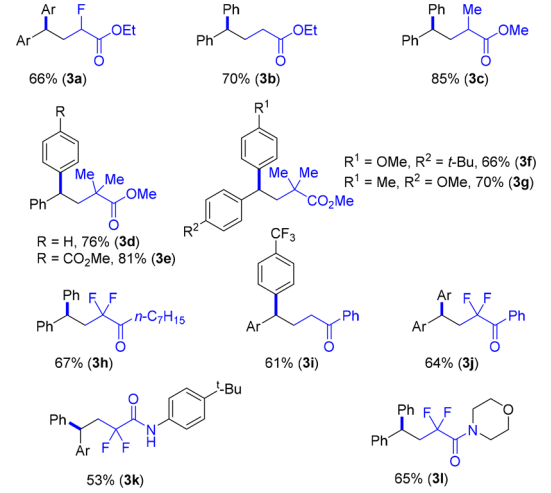


Figure 3. Scope of different carbonyl-containing functional groups. For reaction conditions, see Table 1, entry 15. Ar = 4-methoxylphenyl.

substitution is always necessary in metal-catalyzed γ-arylation via C−H cleavage due to the configuration requirement of metallacycle intermediate.[6,8] This reaction is also applicable to carbonyl compounds with different substitution patterns at α-position (Figure 3). Besides α,α-disubstituted carbonyl functional groups (**3d**−**3g**), α-monosubstituted (**3a** and **3c**) and α-nonsubstituted carbonyl functional groups (**3b** and**3i**) are also tolerated, giving the desired γ-arylated product in good yields.

To further demonstrate the potential utility of this reaction, late-stage functionalization of the complex system and natural products was examined (Figure 4). Amino acid derivative was successfully transformed into corresponding γ-arylated ester **4a** in 57% yield. γ-Tocopherol-containing alkene was successfully incorporated in the reaction to give γ-arylated ester **4b** in 75% yield.

Control experiments were designed to probe the mechanism of this reaction (Scheme 2a). First, when 2 equiv of radical scavenger TEMPO was added into the reaction under standard conditions, no desired product **1a** was detected. This indicates

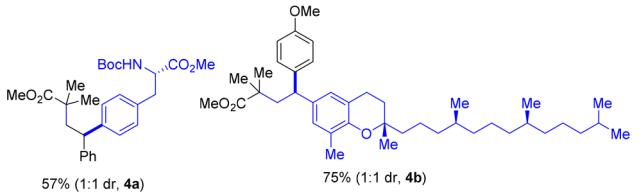
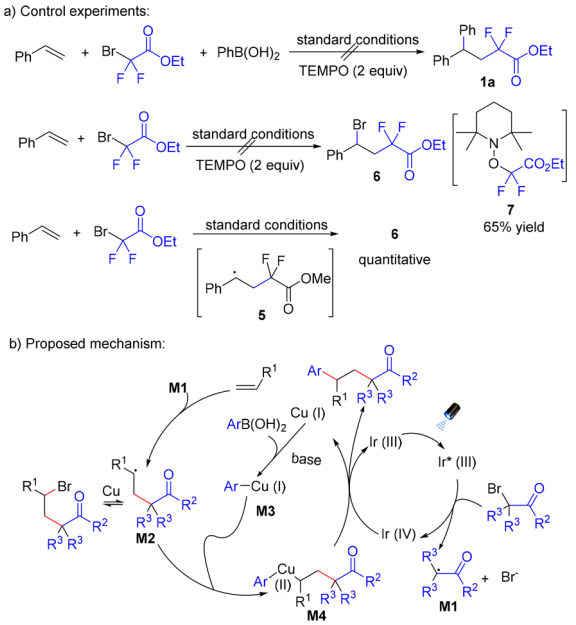


Figure 4. Late-stage functionalization. For reaction conditions, see Table 1, entry 15.

Scheme 2. Control Experiments and Proposed Mechanism for the Reaction



that radical intermediate may be involved in the reaction. When TEMPO was added into the reaction in the absence of phenylboronic acid, no addition product **6** was detected. Instead, the TEMPO and difluoroacetate adduct **7** was isolated in 65% yield, proving the presence of ethyl difluoroacetate radical in the process. Second, when the reaction was carried out in the absence of phenyl boronic acid under standard conditions, bromoalkylation product **6** was observed in quantitative yield, suggesting the presence of benzyl radical intermediate **5** in the catalytic cycle. Based on the results and the literature,[13,16] we proposed the following mechanism for this reaction (Scheme 2b). The interaction of α-bromocarbonyl precursor with excited Ir*(III) photocatalyst would furnish a reactive radical intermediate **M1** and the oxidized photocatalyst Ir(IV) by single electron transfer. **M1** would be trapped by alkene to generate a new alkyl radical intermediate **M2**. Then, the reaction of Cu(I) with aryl boronic acid would deliver the arylcopper intermediate **M3** in the presence of base, which could further recombine with **M2** to give **M4**. **M4** would reduce Ir(IV) to form Ir(III) and undergo reductive elimination to give the final product and regenerate Cu(I) species.

In summary, we have demonstrated the first formal γ-(hetero)arylation of carbonyl compounds via the radical relay alkylarylation of alkenes under mild conditions. The employment of copper and visible-light catalysis is essential for the success of this transformation, which allows for the sequential formation of $C_{sp3}-C_{sp3}$ and $C_{sp3}-C_{sp2}$ bonds, providing a rapid and straightforward access to γ-arylated carbonyl compounds.

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This relay coupling strategy tolerates a wide variety of functional groups, furnishing diverse γ-(hetero)arylated esters, ketones, and amides, in the absence of any directing groups or preactivation. The investigations on the asymmetric version of this reaction and application of this strategy are ongoing in our lab and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03485.

Experimental details for all the reactions and characterization of all new compounds (PDF)

Accession Codes

CCDC 1883036 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: shuw@sustc.edu.cn.

ORCID

Wei Shu: 0000-0003-0890-2634

Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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