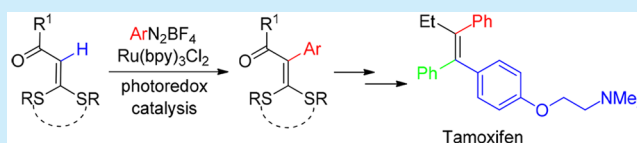# Photoredox-Catalyzed C−H Arylation of Internal Alkenes to Tetrasubstituted Alkenes: Synthesis of Tamoxifen

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S *Supporting Information*

ABSTRACT: Visible-light-induced direct C−H arylation of *S,S*-functionalized internal alkenes, that is, α-oxo ketene dithioacetals and analogues, has been efficiently realized with aryldiazonium salts (ArN_2BF_4) as coupling partners and $Ru(bpy)_3Cl_2 \cdot 6H_2O$ as photosensitizer at ambient temperature. The strategy to activate the internal olefinic C−H bond by both the alkylthio and electron-withdrawing functional groups was investigated. The synthetic protocol was successfully applied to the synthesis of all-carbon tetrasubstituted alkenes including tamoxifen.

Tetrasubstituted alkenes are important structural motifs in many natural products, pharmaceuticals, and functional organic materials[1] and can also be used as versatile organic intermediates.[2] However, their regio- and stereoselective synthesis has remained a great challenge.[3] Although heteroatom-group-substituted tetrasubstituted alkenes have been documented for diverse synthetic applications,[4] all-carbon tetrasubstituted alkenes have demonstrated prominent importance as anticancer agents. For example, tamoxifen[5a] has been the most widely used anticancer drug for clinical treatment of breast cancer. Intrigued by the superior bioactivity of Tamoxifen and its analogs,[5b] construction of all-carbon tetrasubstituted alkenes has recently been paid much attention.[6] Transition-metal catalyzed multicomponent reactions of alkynes[7] and intramolecular carboarylation or tandem cyclization of aryl-tethered alkynes[8] have usually been employed for this purpose. Allenes,[9] diazo reagents,[10a,b] and *N*-tosylhydrazones[10c] could act as the effective building blocks of all-carbon substituted alkenes. In principle, cross-coupling of an activated ethylene or ketene unit can be utilized to synthesize tetrasubstituted alkenes. In this regard, halo-,[11a] oxygen-,[11b] boron-,[11c] and silicon-functionalized[11d] tetrasubstituted alkenes have been used as the substrates. Recently, direct C−H functionalization has attracted much attention due to high atom-economy of the synthetic methods and ready availability of the starting materials.[12] Vinyl(2-pyridyl)silanes have been successfully used to synthesize trisubstituted alkenes by multistep Pd-catalyzed Heck and Hiyama couplings.[6g,13] Tamoxifen was prepared by copper−palladium-catalyzed decarboxylative cross-coupling of 3,3-diarylacrylic acids with aryl halides via triarylethylene-type intermediates.[14] Although C−H functionalization of trisubstituted alkenes seems to be the straightforward route to tetrasubstituted alkenes, only a few examples have been documented[6d,15,16] due to the steric hindrance around the

multisubstituted ketene unit and the low reactivity of the internal olefinic C−H bonds.

Photoredox catalysis is emerging as a promising research area in organic synthesis[17] and has recently been paid much attention to render C−H functionalization under mild, "green" conditions.[18] It has been known that 1,1-diborylalkenes,[19a] 1,1-dihaloalkenes,[6g,19b] and *gem*-silylborylalkenes[19c] can undergo transition-metal-catalyzed cross-coupling with electrophiles to form all-carbon tetrasubstituted alkenes. Liebeskind−Srogl cross-coupling employing the reactions of thioesters with boronic acids has been well explored for C−S cleavage.[20,21a] Featuring the typical structure of *gem*-di(heteroatom)-trisubstituted alkenes, 1,1-di(alkylthio)alkenes, that is, α-oxo ketene dithioacetals,[21b] can be considered as a class of building blocks for all-carbon, tetrasubstituted alkenes.[22]
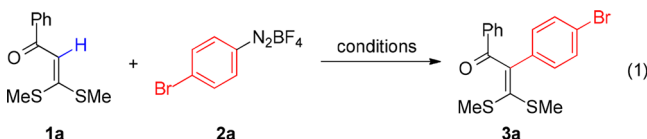
During the ongoing investigation of C−H activation of internal alkenes, we have developed a strategy to activate an internal olefinic C−H bond by introducing two alkylthio groups and one electron-withdrawing group (EWG) to the two ends of an olefinic C═C bond,[21a] which has been successfully applied in the C−H alkylation[15b−f] and alkenylation[16] of trisubstituted α-oxo (cyano) ketene dithioacetals. Unfortunately, C−H arylation of these internal alkenes has not yet been achieved under traditional transition-metal catalysis to date. In our previous work, C−H alkylation and trifluoromethylation of α-oxo ketene dithioacetals could be realized through an iron-[15c] or copper/silver[15f]-catalyzed radical pathway. Thus, we reasonably envisioned that direct C−H arylation of α-oxo ketene dithioacetals might occur throuh a radical pathway under photocatalytic conditions. As radical precursors, aryldiazonium salts have been applied as the coupling partners in photoredox catalysis.[23]

Herein, we report visible light-induced direct C−H arylation of α-oxo ketene dithioacetals as well as construction of all-carbon tetrasubstituted alkenes including tamoxifen.
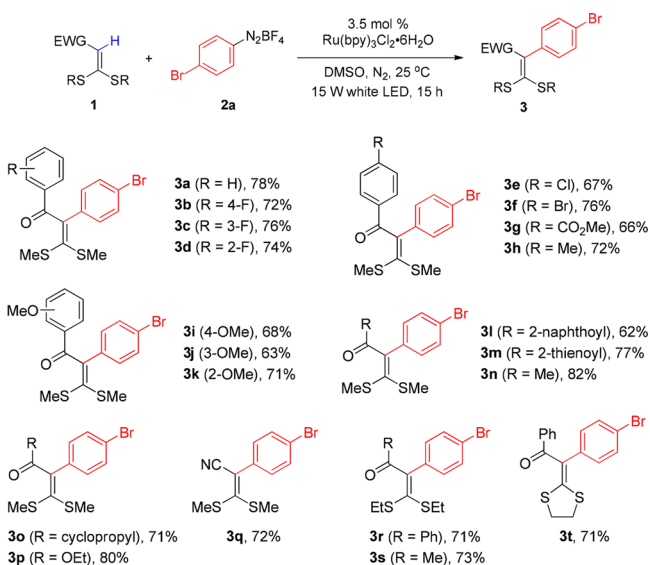
Initially, the reaction of α-benzoyl ketene di(methylthio)acetal (**1a**) with 4-bromophenyldiazonium tetrafluoroborate (**2a**) was conducted to screen the reaction conditions (eq 1). With 3 mol %

Ru(bpy)$_3$Cl$_2$·6H$_2$O as the photosensitizer, the reaction of **1a** with **2a** in a 1:2 molar ratio afforded the target C−H arylation product **3a** in 60% yield in DMSO at ambient temperature under visible-light irridiation of a 15 W white LED bulb. Both the photosensitizer loading and substrate concentrations affected the reaction efficiency. Adding a base such as Na$_2$CO$_3$, K$_2$CO$_3$, or NaHCO$_3$ did not promote the reaction. Shorter reaction times such as 5 and 10 h were applied to the reaction, affording **3a** in 62% and 67% isolated yields, respectively. The highest isolated yield (78%) was obtained at a 1:2.2 molar ratio of **1a/2a** in the presence of 3.5 mol % of Ru(bpy)$_3$Cl$_2$·6H$_2$O. A 4 mmol scale reaction also efficiently afforded **3a** (66%). Notably, the reaction could not occur without either the photosensitizer or visible light irradiation (see the Supporting Information).

Next, the scope of α-oxo ketene dithioacetals (**1**) was investigated under the optimized conditions (Scheme 1). The halo-substituted
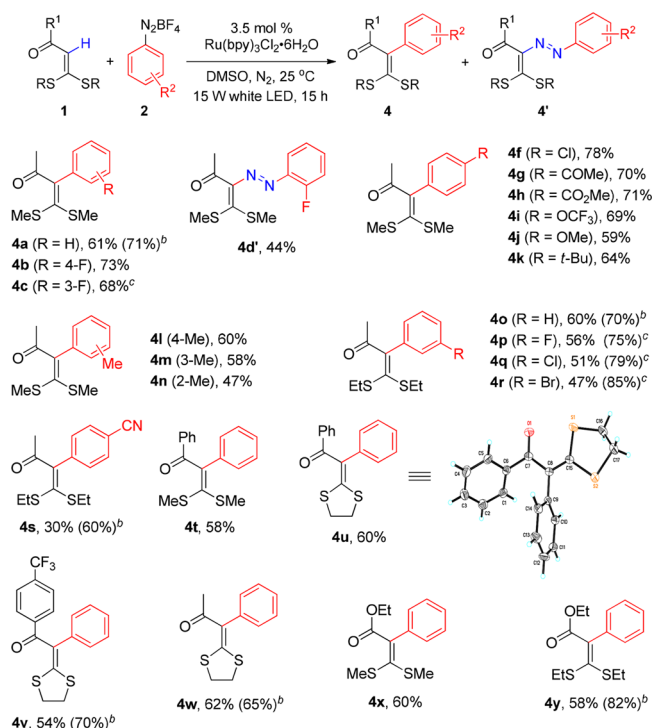
Scheme 1. Scope of α-Oxo Ketene Dithioacetals[a]

[a]Conditions: **1** (0.3 mmol), **2a** (0.66 mmol), Ru(bpy)$_3$Cl$_2$·6H$_2$O (0.0105 mmol), DMSO (3 mL), 0.1 MPa N$_2$, 15 W white LED, 25 °C, 15 h. Yields refer to the isolated products.

α-benzoyl ketene di(methylthio)acetals efficiently underwent the reactions with **2a**, affording the target products **3b−f** in 67−76% yields, while 4-CO$_2$Me as the substituent lessened the yield of **3g** to 66%. Electron-donating methyl and methoxy substituents exhibited different impacts on the formation of **3h−k** (63−72%). 2-Naphthoyl had a negative steric impact on the reaction. Unexpectedly, α-(2-thienoyl)ketene di(methylthio)-acetal reacted efficiently to give **3m** (77%). Moreover, aliphatic α-acetyl-, cyclopropylcarbonyl-, ester-, and cyano-functionalized

ketene di(methylthio)acetals reacted with **2a** to yield **3n−q** in decent yields (71−82%). The di(ethylthio)acetal analogues of **1a** and **1n**, that is, **1r** and **1s**, were reacted with **2a** to give **3r** (71%) and **3s** (73%), respectively, demonstrating a steric effect of the ethylthio group. The cyclic α-benzoyl ketene dithioacetal substrate also reacted well with **2a** to yield **3t** (71%). *tert*-Butyl((1-methoxyvinyl)oxy)dimethylsilane was also tested as the substrate, but it did not react with 4-Br-phenyldiazonium salt (**2a**) to form the target product. In the reaction mixture, only the homo-coupling product of **2a** was detected.
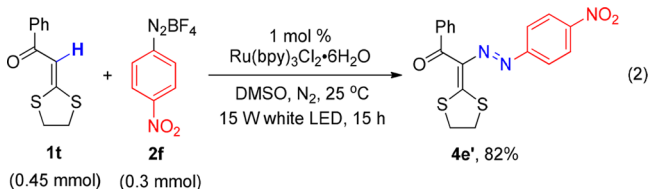
Then the protocol generality was explored by extending the scope of aryldiazonium salts (**2**) (Scheme 2). Because α-acetyl

Scheme 2. Scope of Aryldiazonium Salts 2[a]

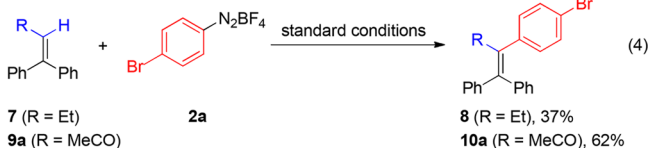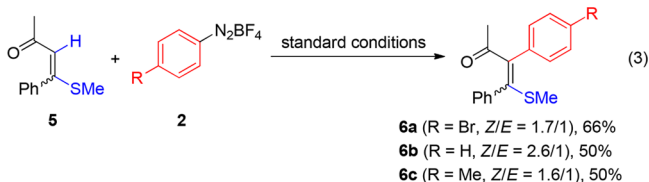[a]Conditions: **1** (0.3 mmol), **2** (0.66 mmol), Ru(bpy)$_3$Cl$_2$·6H$_2$O (0.0105 mmol), DMSO (3 mL), 0.1 MPa N$_2$, 15 W white LED, 25 °C, 15 h. [b]**1** (0.45 mmol), **2** (0.3 mmol), Ru(bpy)$_3$Cl$_2$·6H$_2$O (0.003 mmol). [c]**1** (0.45 mmol), **2** (0.3 mmol), Ru(bpy)$_3$Cl$_2$·6H$_2$O (0.015 mmol). Yields refer to the isolated products.

ketene di(methylthio)acetal (**1n**) could efficiently react with **2a** to form **3n** (82%) which might be easily transformed to a tamoxifen-type alkene, α-acetyl ketene dithioacetals were used as the trisubstituted alkene substrates to react with various aryldiazonium salts. Reacting **1n** with phenyldiazonium tetra-fluoroborate (**2b**) led to **4a** in 61% yield, and the yield was improved to 71% by altering the molar ratio of **1:2** from 1:2.2 to 1.5:1. Both 4-F- and 3-F-phenyldiazonium salts reacted well to give **4b** (73%) and **4c** (68%), respectively. However, the reaction of 2-F-phenyldiazonium salt (**2e**) formed unsymmetrical alkenyl azobenzene **4d′** (44%), exhibiting steric and electronic effects. Further probing of the electron-withdrawing substituent effect revealed that a 4-NO$_2$ substituent led to exclusive formation of alkenyl azobenzene **4e′** (82%) (eq 2), depicting a direct route to unsymmetrical azobenzenes through C−H diazo reaction.[24] Aryldiazonium salts bearing an electron-withdrawing substituent such as 4-Cl, 4-MeCO, or 4-CO$_2$Me reacted with **1n** to afford

(2)

1t (0.45 mmol)   **2f** (0.3 mmol)   **4e′**, 82%

4f−h (70−78%), while the electron-donating groups OCF$_3$, OMe, *t*-Bu, and Me on the aryl functional group of **2** deteriorated the reaction efficiency, leading to **4i−m** in 58−69% yields, and 2-methyl exhibited a negative steric effect on the yield of **4n** (47%). In a similar manner, excess α-acetyl ketene di(ethylthio)acetal reacted with various aryldiazonium salts to yield the target products **4o−s** in decent yields, whereas the same reactions only afforded the products in 30−60% yields under the standard conditions. Phenyldiazonium salt (**2b**) reacted less efficiently with α-benzoyl ketene dithio-acetals to form **4t** (58%) and **4u** (60%) (Scheme 2), while the reactions of the same internal alkenes with **2a** gave **3a** (78%) and **3t** (71%) (Scheme 1), respectively. In the cases of α-(4-CF$_3$-benzoyl), acetyl, and ester ketene dithioacetals, **2b** only showed a moderate reactivity to form **4v−y** (54−62%), but alteration of the reaction conditions by using excessive amounts of the internal alkene substrates led to remarkable yield enhancement for **4v** (54% to 70%) and **4y** (58% to 82%). Heteroaryldiazonium salts such as quinolone-3-diazonium and methyl thiophene-2-carboxylate-3-diazonium salts were also examined, but their reactions with **1a** only afforded the corresponding target products in 21% and 15% yields, respectively. The molecular structures of compounds **4e′** and **4u** were further confirmed by the X-ray single crystal crystallographic determinations (see the SI for details).

To verify the strategy for activating the internal olefinic C−H bond, α-acetyl ketene monothioacetal (**5**)[22a] was applied in the photocatalytic reactions with aryldiazonium salts **2** (eq 3).

(3)

5   **2**

6a (R = Br, *Z/E* = 1.7/1), 66%
6b (R = H, *Z/E* = 2.6/1), 50%
6c (R = Me, *Z/E* = 1.6/1), 50%

(4)

7 (R = Et)   **2a**   **8** (R = Et), 37%
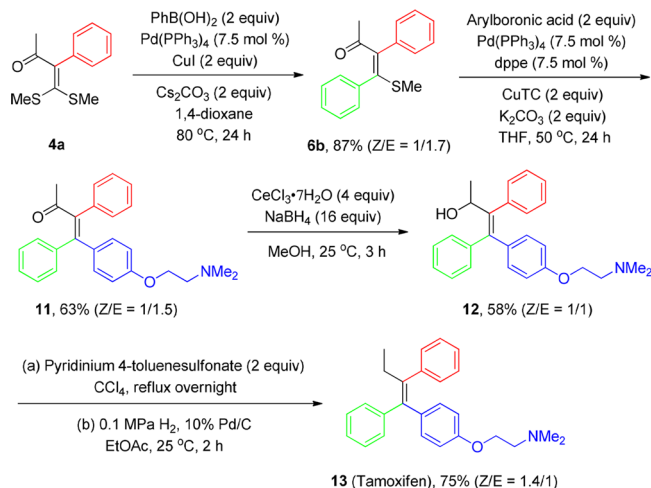**9a** (R = MeCO)   **10a** (R = MeCO), 62%

As compared with the transformations of the corresponding α-acetyl ketene dithioacetals to form **3a** (78%), **4a** (61%), and **4l** (60%), the reaction efficiency to form tetrasubstituted alkenes **6a** (66%), **6b** (50%), and **6c** (50%) was obviously decreased. These results have suggested that the di(alkylthio) functional groups are necessary for internal alkenes **1** to undergo the photocatalytic C−H arylation efficiently with **2**. Under the standard conditions, all-carbon trisubstituted 1,1-diphenyl-1-butene (**7**) reacted with **2a** to give all-carbon tetrasubstituted alkene **8** in 37% yield, while its α-acetyl analog **9a** reacted to form **10a** in a much higher yield (62%), revealing the crucial role of the EWG, that is, α-oxo, in the activation of the internal olefinic C−H bond (eq 4).

Control experiments were conducted to probe the reaction mechanism (see the SI for details). The reaction of **1a** with **2a**
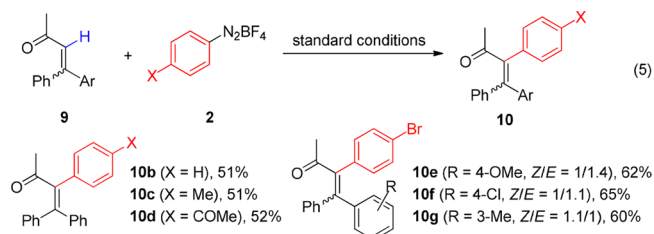
was performed in the presence of 4.0 equiv of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) or 2,6-di-*tert*-butyl-4-methylphenyl (BHT) under the standard conditions. These radical-trapping reagents completely inhibited or deteriorated the reaction, forming no **3a** in the case of using TEMPO or affording **3a** in 24% yield in the presence of BHT, implicating a radical pathway involved in the catalytic cycle. It is noteworthy that the adducts between TEMPO or BHT and the aryl radicals were not detected by HRMS analysis. The kinetic isotope effect (KIE) experiments were carried out by means of the reactions of **1a** and its deuterated form **1a**[D] with **2a**. A secondary isotope effect[25] was observed with k_H/k_D = 1.1, indicating that cleavage of the internal olefinic C−H bond in **1a** was not involved in the rate-determining step in the overall catalytic cycle. Light on/off experiments revealed that the reaction only proceeded with irradiation of the 15 W LED, ruling out the radical-chain propagation mechanism.

Eventually, internal alkenes **1** were applied as the building blocks to prepare tamoxifen-type all-carbon tetrasubstituted alkenes. First, α-acetyl ketene di(methylthio)acetal (**1n**) was transformed to 1,1-*S,S*-functionalized tetrasubstituted alkene **4a** (Scheme 2), which was then successively arylated by PhB(OH)$_2$ and 4-(2-dimethylaminoethoxy)phenylboronic acid through Liebeskind−Srogl cross-coupling,[22a] affording **6b** and **11** in 87% and 63% yields, respectively (Scheme 3). Luche reduction[26]

Scheme 3. Synthesis of Tamoxifen

4a   **6b**, 87% (*Z/E* = 1/1.7)

11, 63% (*Z/E* = 1/1.5)   **12**, 58% (*Z/E* = 1/1)

13 (Tamoxifen), 75% (*Z/E* = 1.4/1)

of **11** gave tamoxifen analogue **12** in 58% yield ((*Z*)-**12**, 29%; (*E*)-**12**, 29%), and subsequent dehydration/hydrogenation[6d] yielded tamoxifen (**13**) in 75% yield (*Z/E* = 1.4/1). An alternative route was also developed for the transformation of alkenes **1** to all-carbon tetrasubstituted alkenes. By means of two successive Liebeskind−Srogl cross-couplings with arylboronic acids, alkenes **1** were first transformed to 1,1-diaryl-trisubstituted alkenes **9**, which were then subject to photocatalytic C−H arylation with **2** to afford the target products **10a−g** in 51−62% yields (eqs 4 and 5).

(5)

9   **2**   **10**

10b (X = H), 51%   **10e** (R = 4-OMe, *Z/E* = 1/1.4), 62%
10c (X = Me), 51%   **10f** (R = 4-Cl, *Z/E* = 1/1.1), 65%
10d (X = COMe), 52%   **10g** (R = 3-Me, *Z/E* = 1.1/1), 60%

In summary, efficient photoredox-catalyzed direct C—H arylation of internal alkene α-oxo ketene dithioacetals with aryldiazonium salts has been realized to form 1,1-S,S-functionalized tetrasubstituted alkenes. Combined with Liebeskind–Srogl cross-coupling, tamoxifen-type alkenes were prepared. The present protocol provides a new route to all-carbon tetrasubstituted alkenes.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental materials and procedures, NMR of compounds, and X-ray crystallographic analysis for compounds **4e′** and **4u**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03223.

> Experimental materials and procedures, NMR of compounds, and X-ray crystallographic analysis for compounds **4e′** and **4u** (PDF)
>
> X-ray crystallographic data for compounds **4e′** and **4u** (CIF)

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Notes

The authors declare no competing financial interest.

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