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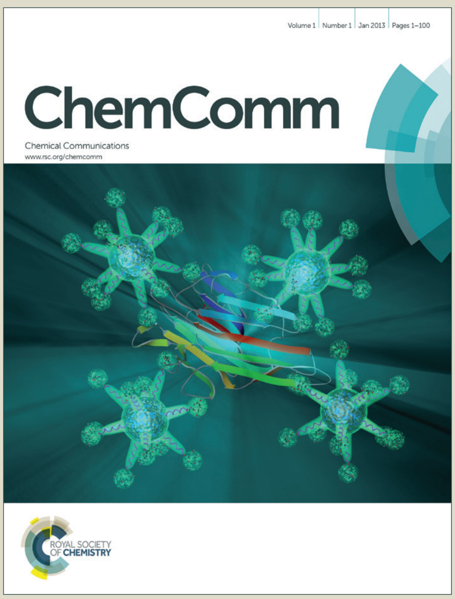

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COMMUNICATION

Iron-Catalyzed Alkylation of *α*-oxo Ketene Dithioacetals

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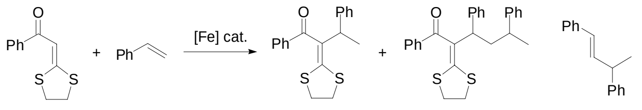
Iron-catalyzed alkylation of internal olefins, that is, *α*-oxo ketene dithioacetals, was successfully realized by means of styrenes as the alkylating reagents. Highly functionalized tetrasubstituted olefins were prepared in moderate to high yields.

Alkylation has been used as a powerful method for the construction of carbon–carbon bonds.[1] Carbon electrophiles such as alkyl alcohols, acetates, halides, ethers, and olefins can be applied for this purpose,[2] among which olefins are considered as the green alkylating reagents to establish an environmentally benign and atom–economical alkylation process.[3] Friedel–Crafts alkylation is well-known for alkylating sp^2 C–H bonds of arenes and heteroarenes,[4] and transition metal–catalyzed insertion of alkenes to these sp^2 C–H bonds have been extensively explored.[5] However, less attention has been paid to the potential alkylation of internal olefinic C–H bonds by alkenes.[6] Dai, et al. reported $In(OTf)_3$–mediated addition of vinylarenes to the internal olefinic C–H bond of 1,1–diarylethenes.[6b] An olefin may be tuned highly polarized to exhibit enhanced reactivity by attaching both the electron–donating functionality, that is, dithioalkyl, and an electron–withdrawing group such as a carbonyl to the two ends of its C=C bond. For example, ketene dithioacetals bearing an *α*–electron–withdrawing group (EWG) are polarized internal olefins which have been shown versatile reactivity towards electrophiles.[7,8] Recently, our group reported transition metal–catalyzed direct trifluoromethylation and alkenylation of the internal olefinic C–H bonds of *α*–EWG ketene dithioacetals.[9] Iron compounds are a promising class of environmentally benign catalysts with advantages such as low cost, nontoxicity, good stability, and easy manner to handle.[10] During our ongoing investigation on iron catalysis,[11] we envisioned that iron salts might promote the alkylation of *α*–EWG ketene dithioacetals by alkenes.[12] Herein, we report $Fe(OTf)_3$ and $FeCl_3$–catalyzed alkylation of *α*–EWG ketene dithioacetals by styrenes.

Initially, the reaction of *α*–benzoyl ketene dithioacetal (**1a**) with styrene (**2a**) was employed to optimize the reaction conditions (Table 1). With 10 mol % $FeCl_3$ as the catalyst in DCE at 100 °C, the target product **3a** was obtained in 26% GC yield with formation of compound **4a** as the minor product, while the dimer of styrene **2a**, i.e., **4b**,[12] was obtained in 28% yield (Table 1, entry 1). Variation of solvents from DCE to CH_3CN, CH_3NO_2, 1,4–dioxane, and THF enhanced the conversion of **1a** as well as slight increase of the selectivity of **3a** (Table 1, entries 2-5). In toluene, the conversion of **1a** was remarkably improved to 88%, and use of cyclohexane further increased the conversion to 92% (Table 1, entries 6 and 7). Due to the difficulty to separate the coalesced **4a**, **3a** was only isolated in 59% yield (Table 1, entry 7). Screening of the iron sources revealed that $Fe(OTf)_3$ could act as the effective catalyst and a mixture of cyclohexane and THF (5:1, v/v) was the suitable solvent (Table 1, entries 8-12), and thus **3a** was obtained in 76% yield under the optimized conditions (Table 1, entry 12). It should be noted that further increasing the styrene loading to 1.5 equiv. did not improve the reaction efficiency (Table 1, entry 13).

Table 1 Screening of the reaction conditions[a]



1a **2a** **3a** **4a** **4b**

Entry	[Fe] cat.	Solvent	Conv. of **3a** (%)[b]	**3a**:**4a**[b]	Yield of **3a** (%)[c]
1	$FeCl_3$	DCE	29	89:11	26 (28)[d]
2	$FeCl_3$	CH_3CN	56	67:33	37
3	$FeCl_3$	CH_3NO_2	60	55:45	33
4	$FeCl_3$	1,4-dioxane	68	90:10	61
5	$FeCl_3$	THF	68	92:8	62
6	$FeCl_3$	toluene	88	79:21	69
7	$FeCl_3$	cyclohexane	92	88:12	81 (59)
8	$FeCl_3{\cdot}6H_2O$	cyclohexane	85	95:5	79
9	$FeBr_3$	cyclohexane	84	95:5	80
10	$Fe(OTf)_3$	cyclohexane	93	95:5	88 (68)
11	$Fe(OTf)_3$	cyclohexane/ dioxane (5:1)	73	98:2	72
12	$Fe(OTf)_3$	cyclohexane/ THF (5:1)	82	98:2	80 (76)
13[e]	$Fe(OTf)_3$	cyclohexane/ THF (5:1)	81	98:2	79

[a] Reaction conditions: **1a**, 0.5 mmol; **2a**, 0.6 mmol; [Fe] cat., 10 mol %; solvent, 2 mL; 0.1 MPa N_2, 100 °C, 18 h. The reaction was performed in a 25–mL sealed tube. [b] Determined by GC analysis. [c] Isolated yield given in parentheses. [d] Isolated yield for **4b**[12] given in parentheses. [e] 1.5 equiv. styrene was used. DCE = 1,2-dichloroethane, THF = tetrahydrofuran.

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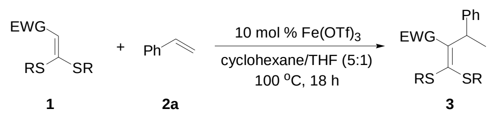
Next, the substrate scope of ketene dithioacetals **1** was explored under the optimal conditions. Substrates **1a**–**1o** reacted smoothly to give the target products, i.e., **3a**–**3o**, in 55-81% yields, exhibiting good tolerance of the structural and electronic variations of *α*–oxo ketene dithioacetals (Table 2, entries 1-15).

Table 2 The substrate scope of ketene dithioacetals (**1**)[a]



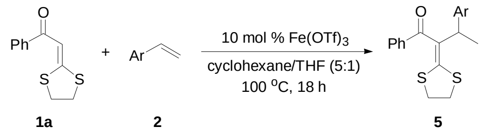
Entry	EWG (**1**)	R, R	**3**	Yield (%)[b]
1	PhCO (**1a**)	$(CH_2)_2$	**3a**	76
2	2-MeC_6H_4CO (**1b**)	$(CH_2)_2$	**3b**	68
3	3-MeC_6H_4CO (**1c**)	$(CH_2)_2$	**3c**	66
4	4-MeC_6H_4CO (**1d**)	$(CH_2)_2$	**3d**	68
5	4-$MeOC_6H_4CO$ (**1e**)	$(CH_2)_2$	**3e**	61
6	2-ClC_6H_4CO (**1f**)	$(CH_2)_2$	**3f**	66
7	3-ClC_6H_4CO (**1g**)	$(CH_2)_2$	**3g**	70
8	4-ClC_6H_4CO (**1h**)	$(CH_2)_2$	**3h**	68
9	2,4-$Cl_2C_6H_3CO$ (**1i**)	$(CH_2)_2$	**3i**	68
10	4-FC_6H_4CO (**1j**)	$(CH_2)_2$	**3j**	66
11	4-BrC_6H_4CO (**1k**)	$(CH_2)_2$	**3k**	80[c]
12	4-$CF_3C_6H_4CO$ (**1l**)	$(CH_2)_2$	**3l**	81
13	2-naphthyl-CO (**1m**)	$(CH_2)_2$	**3m**	77[c]
14	2-furyl-CO (**1n**)	$(CH_2)_2$	**3n**	55[c]
15	2-thienyl-CO (**1o**)	$(CH_2)_2$	**3o**	68
16	PhCO (**1p**)	Et, Et	**3p**	55
17	PhCO (**1q**)	Me, Me	**3q**	58
18	PhCO (**1r**)	$(CH_2)_3$	**3r**	23
19	CN (**1s**)	$(CH_2)_2$	**3s**	75
20	CO_2Et (**1t**)	$(CH_2)_2$	**3t**	80[c]
21	CF_3CO (**1u**)	$(CH_2)_2$	**3u**	33[d]

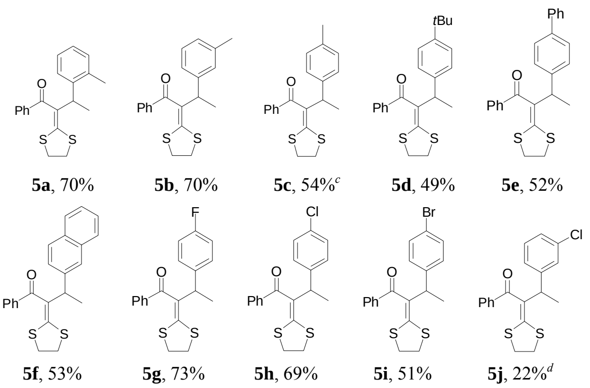
[a] Reaction conditions: **1**, 0.5 mmol; **2a**, 0.6 mmol; $Fe(OTf)_3$, 10 mol %; cyclohexane/THF (5/1, v/v), 2 mL; in a 25-mL sealed tube, 0.1 MPa N_2, 100 ºC, 18 h. [b] Isolated yields. [c] 2 equiv. styrene. [d] 110 ºC.

Electron–donating groups such as methyl and methoxy, and electron–withdrawing substituents F, Cl, Br, and CF_3 in the aroyls of **1** were tolerant, and the steric hindrance from the 2–substituent of the aroyl moiety was negligible (Table 2, entries 1–12). Naphthyl and heteroaryl-substituted α-oxo ketene dithioacetals **1m**–**1o** also reacted with **2a** to form products **3m**–**3o** in 55–77% yields (Table 2, entries 13-15). For acyclic α–oxo ketene dithioacetals **1p** and **1q**, their reactions with styrene afforded **3p** (55%) and **3q** (58%) in relatively lower yields, demonstrating a less effective push–pull effect of the two thioalkyls and benzoyl on the substrate reactivity, and enlargement of the cyclic dithioalkyl ring in **1r** further deteriorated the reaction (Table 2, entries 16–18). It should be noted that under strong basic conditions, only acyclic α–cyano ketene dithioacetals could react with electrophiles to form the alkylation products.[8] α–Cyano and ester ketene dithioacetals **1s** and **1t** also reacted to produce the target products **3s** and **3t** in good yields (Table 2, entries 19 and 20). However, introduction of a strong electron–withdrawing group, that is, CF_3, led to much less formation of **3u** (33%) under the relatively harsh conditions (Table 2, entry 21).

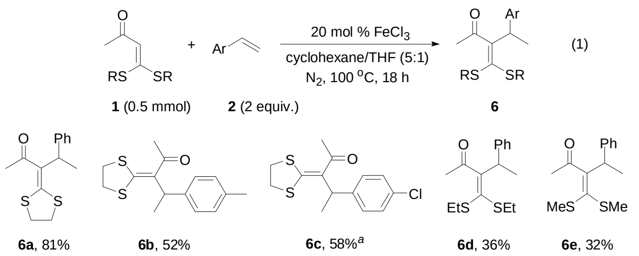
The generality of styrene substrates was then investigated (Table 3). It was found that the steric and electronic effects from styrenes had various impact on the yields of the target products (**5**). 2– and 3–methyls in styrenes slightly improved the reaction to afford **5a** and **5b** in 70% yield, while the reaction of styrene bearing a *para*–Me or *t*Bu group was obviously deteriorated to form **5c** (54%) or **5d** (49%) due to easy dimerization of these styrenes under the reaction conditions. Extension of the π-system in styrenes also lessened formation of **5e** (52%) and **5f** (53%). The styrenes bearing *para*–F or Cl still reacted well, but 4–bromo and 3–chlorostyrenes underwent the reactions less efficiently to give **5i** (51%) and **5j** (22%), respectively.

Table 3 The generality of styrenes (**2**)[a,b]





[a] Reaction conditions: **1a**, 0.5 mmol; **2**, 0.6 mmol; $Fe(OTf)_3$, 10 mol %; cyclohexane/THF (5/1, v/v), 2 mL; in a 25–mL sealed tube, 0.1 MPa N_2, 100 ºC, 18 h. [b] Isolated yields. [c] 2 equiv. styrene. [d] 120 ºC.



Scheme 1 Reactions of *α*–acetyl ketene dithioacetals (**1**) with styrenes (**2**). Conditions: **1**, 0.5 mol; **2**, 1.0 mmol; 20 mol % $FeCl_3$; cyclohexane/THF (5/1, v/v), 2 mL; in a 25–mL sealed tube, 0.1 MPa N_2, 100 ºC, 18 h. Isolated yields. [a] 30 mol % $FeCl_3$, cyclohexane/1,4-dioxane (5/1, v/v), 2 mL; 110 ºC.

α–Acetyl ketene dithioacetals were also employed to react with styrenes (eqn (1)). This type of ketene dithioacetals exhibited a reactivity lower than their benzoyl analogs (Table 2) and the reactions had to be performed in the presence of 20–30 mol % $FeCl_3$. The cyclic ketene dithioacetals gave 52–81% yields, whereas the acyclic substrates reacted slowly to produce **6d** (36%)

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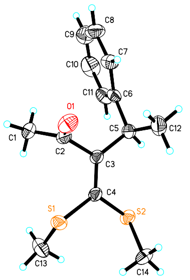
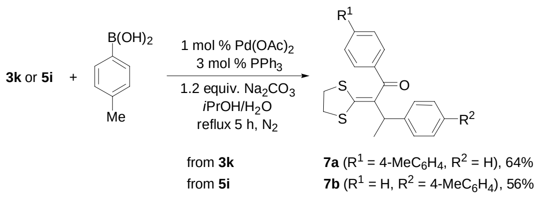


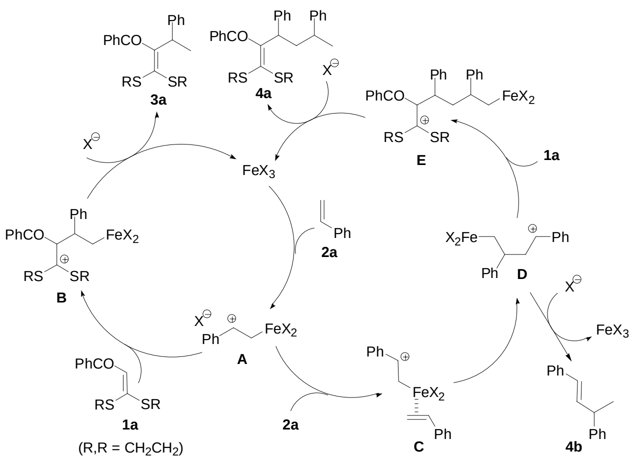
Figure 1 Molecular stucture of compound **6e**.

and **6e** (32%). The molecular structure of **6e** was further confirmed by the X-ray crystallographic determination (Figure 1). Further transformations of the alkylation products were carried out by Suzuki cross–coupling reactions of **3k** and **5i** (eqn (2)). They reacted with *p*–tolylboronic acid to form **7a** (64%) and **7b** (56%), respectively, suggesting a potential application for the preparation of highly functionalized tetrasubstituted olefins.



(2)

A plausible mechanism is proposed in Scheme 2. Initially, interaction of the iron(III) catalyst FeX_3 with styrene (**2a**) forms benzylic carbocation **A**, which is then trapped by *α*–EWG ketene dithioacetal **1a** to form a more stable carbocation species **B** stabilized by the two adjacent thioalkyls.[8d] Regeneration of the catalyst from **B** affords the target product **3a**. Iron(III) species **A** can also activate the soft nucleophile, that is, styrene,[2c] producing carbocation **D** by insertion of the alkene to its C–Fe bond. Subsequent reaction with **1a** gives intermediate **E** which releases the Lewis acid catalyst to yield the minor product **4a**. During the reaction **D** can also be decomposed to **4b**[12] which was successfully isolated and identified.



Scheme 2 Proposed mechanism.

In summary, iron–catalyzed alkylation of *α*–oxo ketene dithioacetals was realized by means of styrenes as the alkylating reagents. Highly functionalized olefin derivatives were prepared in moderate to good yields, demonstrating an alternative route to tetrasubstituted olefins. This work was financially supported by the National Natural Science Foundation of China (21272232).

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