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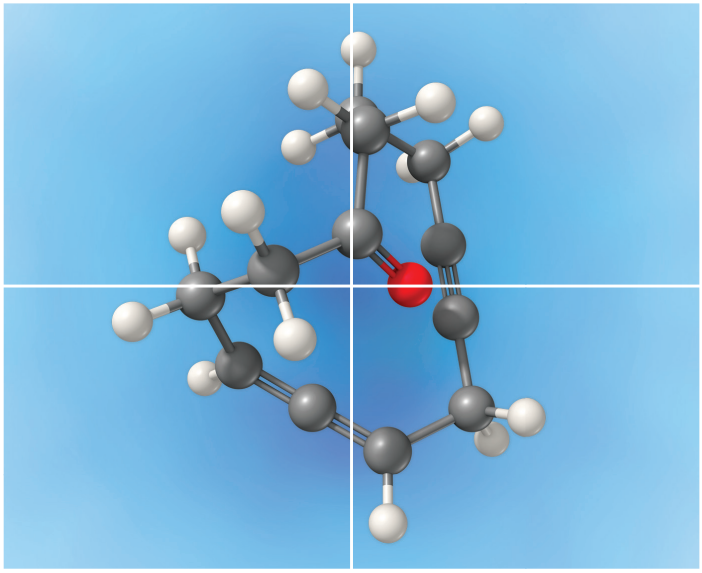

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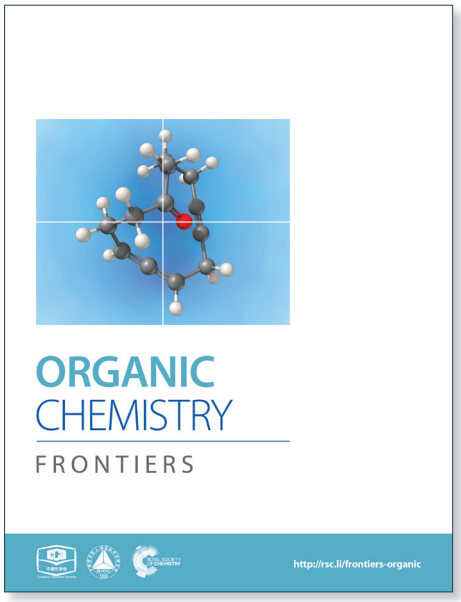

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ARTICLE TYPE

Controllable Mono/Di- Alkenylation of Aryl Alkyl Thioether Tuned by Oxidants via Pd-catalysis

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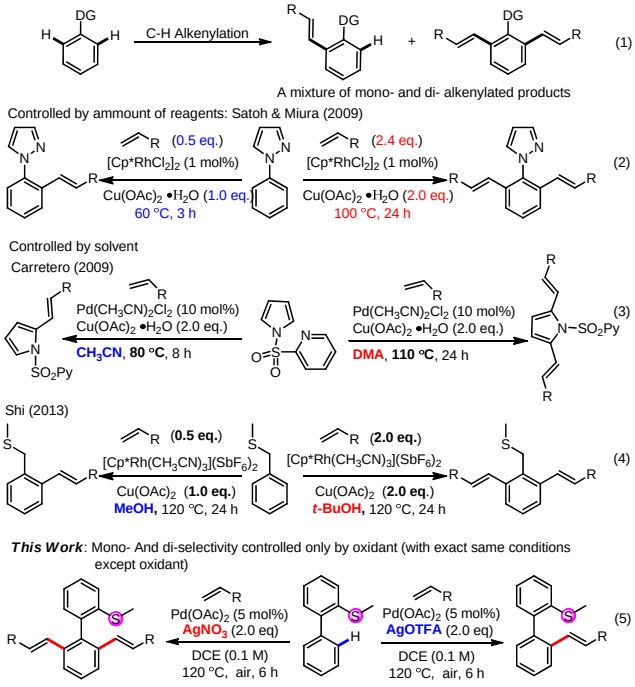
Oxidant-controlled selective mono-/di-alkenylation of aryl C-H bonds via Pd-catalysis were reported. The substrate scopes for both the mono- and di-alkenylation were good. Thioether was used as directing group and the product can be transformed to a useful sulfoxide-olefin ligand by simple oxidation in quantitive yield.

Transion-metal-catalyzed oxidative alkenylation (Fujiwara Reaction) has attracted much attention in recent years[1] due to its high atom-economy, high effeciency, less waste production and potential applications in complex molecules synthesis.[2] To approach the high regio- and chemo-selectivity, directing strategy[3] has been well applied in such alkenylations. While two C-H bonds beside the directing group exist in the molecule, it is alwalys difficult to control the selectivity between mono- and di-alkenyaltion and a mixture of them was usually obtained (Scheme 1, (1)). In past, some successful strategies have been well established to approach high selectivity between mono- and di-alkenylation, such as by the amount of alkenylating reagents, oxidants, reaction time and temperature[4 5], by solvent effects[6 7] and by others[8 9 10 11], although in almost all cases more than more factors were changed to tune the selectivity. Herein, we reported a controllable selective mono- or di-alkenyaltion of aryl C-H bonds by changing only one factor for the first time, with thioether as a new directing group. The oxidants with different anions were found to be crucial to approach high selectivity. Although oxidant has been found to tune the regio-selectivities of C-H activation,[12] no report on the oxidant controlled mono-/di-functionalization selectivity exists.

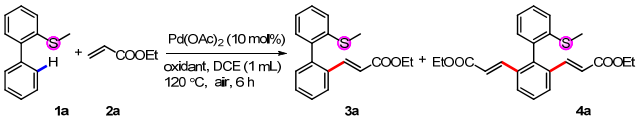
Although *S*-contained groups were considered not to be a good directing group in C-H activation due to its easy oxidation and potential ability to poison the late transition-metal catalysts. Recent advances unveiled the successes to adapt such groups as directing group in C-H activation.[13 14] We recently reported the alkenylation of benzyl methyl sulfide with thioether as a directing group, in which a five-membered rhodacycle was considered as a key intermediate.[6b] The extension of such studies showed that homobenzyl methyl sulfide showed very low reactivity, probably arising from the less rigid 6-membered metallocycle intermediate.[13d] We envisioned that biphenyl-2-yl(methyl)sulfane (**1a**) could be the proper substrate by enhancing the rigidity of the key intermediate to promote the efficiency. Structurally, the desired product is indeed important since the sulfide group can be transformed into different functionalities, for example, the sulfoxide-olefin ligands.[15 16]



Scheme 1. Selectivities of mono-functionalization and di-functionalizaiton in the transition-metal-catalyzed C-H bond activation.

Although initial screenings of rhodium catalysts based on our previous work showed low efficiency (see SI), palladium catalysts showed very good activity. With AgOAc as oxidant, the mono-alkenylated product could be obtained as the major product in 78% NMR yield (Table 1, entry 1). Interestingly and importantly, further screening showed that the selectivity of the mono-alkenylation and di-alkenylation could be controlled by oxidant. When AgOTFA was used as oxidant, the mono-alkenylated product was obtained in 92% NMR yield, while only changing the oxidant to $AgNO_3$ gave di-alkenylated product in 93% NMR yield (table 1, entry 6 and 7). Further investigation revealed that the catalyst loading could be reduced to 5 mol% and the yield was not affected when the reaction was conducted on 0.2 mmol scale. (table 1, entry 12 and 13)

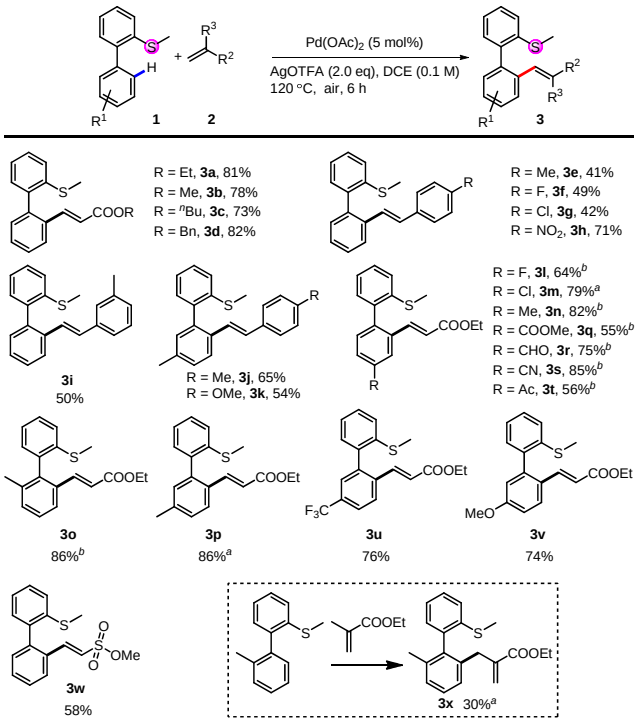
Table 1. Condition screening for the thioether directed selective C-H bond alkenylation



Entry	1	2	Oxidant	Yield of **3** (%)[a]	Yield of **4** (%)[a]	Recover of **1** (%)[a]
1	0.10 mmol	0.20 mmol	AgOAc	78.4	10	8.6
2	0.10 mmol	0.25 mmol	AgOAc	82.5	14	6.9
3	0.10 mmol	0.30 mmol	AgOAc	73.6	21.1	2.5
4	0.10 mmol	0.20 mmol	Ag_2O (1.5 eq)	25.7	--	75.6
5	0.10 mmol	0.20 mmol	Ag_2CO_3 (1.5 eq)	62.9	2.7	32.2
6	0.10 mmol	0.20 mmol	**AgOTFA**	**92.4**	11.4	2.6
7	0.10 mmol	0.20 mmol	**$AgNO_3$**	No	**93.3**	No
8[b]	0.10 mmol	0.20 mmol	AgOTFA	83.2	4.4	17.4
9[b]	0.10 mmol	0.20 mmol	$AgNO_3$	13.0	89.4	6.9
10[c]	0.20 mmol	0.40 mmol	AgOTFA	99.0	11.4	6.6
11[c]	0.20 mmol	0.40 mmol	$AgNO_3$	No	85.0	No
12[b,c]	0.20 mmol	0.40 mmol	**AgOTFA**	**92.4 (80.5)**[d]	11.4	2.6
13[b,c]	0.20 mmol	0.40 mmol	**$AgNO_3$**	No	**91.6**	No

[a] NMR yield with CH_2Br_2 as internal standard. [b] 5 mol% of catalyst. [c] 2 mL DCE. [d] isolated yield.

Table 2. Substrate scope for mono-alkenylation

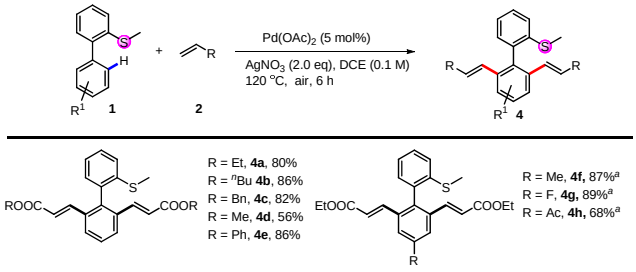


Conditions: **1** (0.1 mmol or 0.2 mmol), **2** (2.0 eq), $Pd(OAc)_2$ (5 mol%) and AgOTFA (2.0 eq) were mixted in DCE (0.1 M) at 120 °C under air for 6 h. a 10 mol% of $Pd(OAc)_2$ was used. b. After the reaction, another **2** (2.0 eq), Pd(OAc)2 (5 mol%) and AgOTFA (1.0 eq) were added to react for further 10 h for full coversion.

We firstly investigated the substrate scope for the mono-alkenylation (Table 2). For the thioethers, both electron rich (**3n**, **3o**, **3p** and **3v**) and electron poor (**3l**, **3m**, **3q-3t**, **3u**) ones are tolerated very well. The group compatability of this monoalkenylation (**3l-3m**, **3q-3v**) showed its wide substrate scope. Notably, methyl ethenesulfonate was also proper alkenylating reagent in this reaction (**3w**), expanding the application of this method. It should be noted that the di-substituted alkene was also applicable coupling partner, and the isomerized product was obtained in relative lower efficiency (**3x**). Apart from a variety of acrylates (**3a-3d**), styrene derivatives also reacted smoothly in moderate to good yields (**3e-3k**). Although the efficiency of electron-rich styrene was low, the yield can be improved by blocking the other ortho- position with methyl group (**3j** and **3k**).

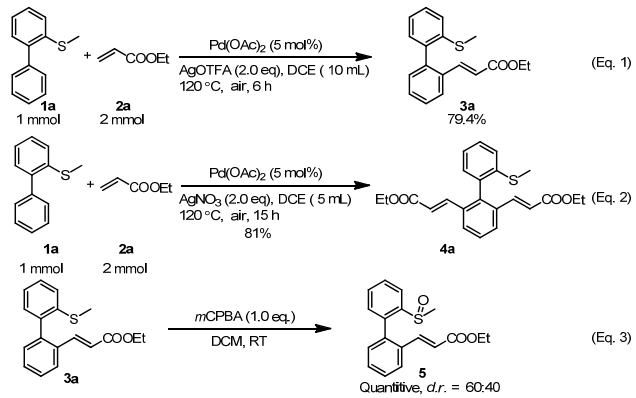
Under the condition for di-alkenylation, with only change of oxidant to $AgNO_3$, a variety of alkenes and bi-phenyl arenes were tolerated very well, providing good to excellent yields (table 3). A variety of acrylates, both alkyl (**4a-4d**) and aryl acrylates (**4e**), reacted smoothly to give the desired products in high yields. For the thioethers, both electron-rich and electron-deficient substituents can be tolerated very well (**4f**, **4g**). Functional groups like acyl was untouched (**4h**).

Table 3. Substrate scope for di-alkenylation



Conditions: **1** (0.1 mmol or 0.2 mmol), **2** (2.0 eq), $Pd(OAc)_2$ (5 mol%) and $AgNO_3$ (2.0 eq) were mixted in DCE (0.1 M) at 120 °C under air for 6 h. [a] 10 mol% of $Pd(OAc)_2$ was used.

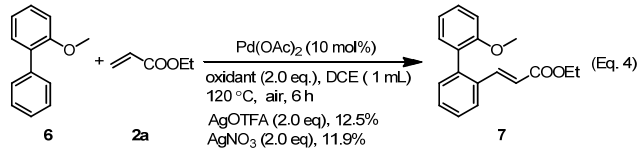
To explore the potential applications, both reactions (mono-alkenylation and di-alkenylation) were scaled up to 1 mmol scale and the yields were not affacted intensively, although for the di-alkenylation longer reaction time was needed (Scheme 2, Eq. 1 and 2). In addition, the mono-alkenylated product can be transformed to the sulfoxide-olefin ligand in quantitive yield by the simple oxidation (*d.r.* = 60:40) (Scheme 2, Eq. 3).



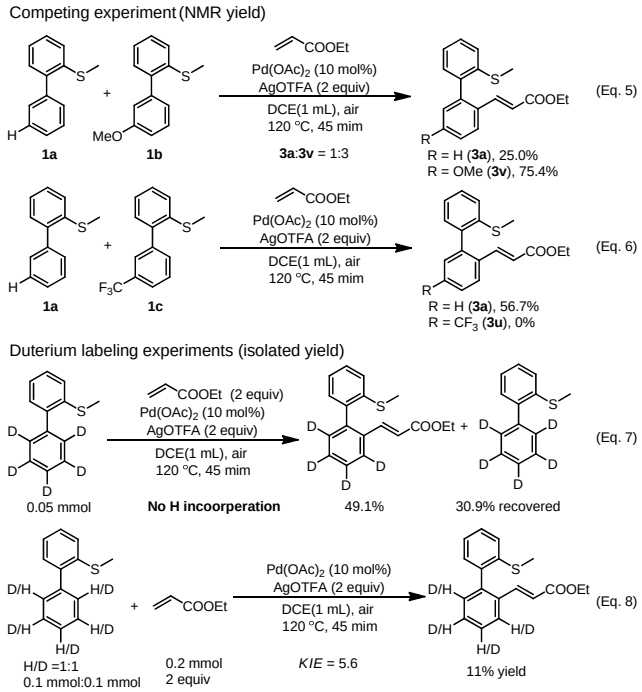
Scheme 2. Large scale reaction and transformation of the product to synthesize ligand.

In order to get some insights into the mechanism, we conducted several control experiments. When the *S*-atom was changed to *O*-atom, the ether directed alkenylation also occured, albeit in a lower yield and low selectivity, showing the importance of *S*-atom (Scheme 3, Eq. 4).[13a, 17] The competing experiments showed that the electron rich arenes reacted much faster (Scheme 4, Eq. 5 and Eq. 6). The deuterium labeling experiment showed that the C-H bond activation was not reversible and gave a KIE value of 5.6, indicating that the C-H activation was possibly involved in the turnover limiting step

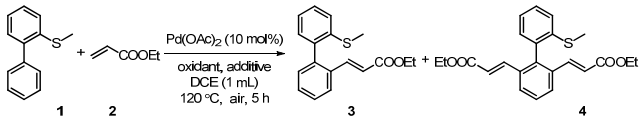
(Scheme 4, Eq. 7 and Eq. 8). As a result, the C-H bond activation was proposed to undergo an electrophilic metalation pathway.



Scheme 3. Ether as directing group.



Scheme 4. Mechanistic studies



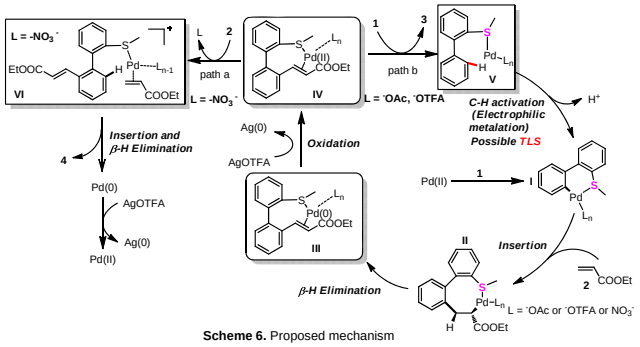
Oxidant	Additive	Yield of **3** (%)[a]	Yield of **4** (%)[a]	Ratio (**3**:**4**)
$AgNO_3$	No	No	99.7	--
$AgNO_3$	NaOTFA (4.0 eq.)	No	87.1	--
$AgNO_3$	NaOTFA (8.0 eq.)	No	83.2	--
$AgNO_3$	NaOAc (4.0 eq.)	16.6	97.9	1:5.9
$AgNO_3$	NaOAc (6.0 eq.)	40.3	73.1	1:1.8
$AgNO_3$	NaOAc (8.0 eq.)	49.0	60.3	1:1.2
AgOTFA	No	88.0	8.7	10.2:1
AgOTFA	$NaNO_3$ (4.0 eq.)	88.0	12.9	6.8:1
AgOTFA	$NaNO_3$ (8.0 eq.)	27.4	72.0	1:2.6

[a] NMR yield with CH_2Br_2 as internal standard.

Scheme 5. The effect of additives on the selectivity

On the other hand, the oxidant controlled selective C-H bond mono- and di-functionalization is interesting and the reason is not clear at this stage. To clarify the reason for the oxidant controlled selectivity, we investigated the additive effect (Scheme 5) by adding some inorganic salts. We found that when $NaNO_3$ was added to the mono-alkenylation system, the ratio of mono-alkenylated product reduced. And when NaOAc was added to the di-alkenylation system, the ratio of di-alkenylated product reduced. However, when NaOTFA was added to the di-alkenylation system, no obvious change in mon-/di- selectivity was observed. Based on these results, we concluded that it is possibly the coordinating ability of the counter anion of the oxidant that affected the selectivity.

Base on the above mentioned experiments and mechanism studies, the detailed mechanism was depicted in Scheme 6. Pd-catalyzed first C-H bond activation formed intermediate **I**, alkene insertion and β-H elimination produced Pd(0) complex **III** with the mono-alkenylated product coordinating as a ligand, which was oxidized to Pd(II) complex **IV**. Weak coordinating NO_3^- can be exchanged by another molecule of alkene (**2**) and further promote the second C-H bond activation (Path a). However, the relatively strong coordinating $^-$OAc could not be exchanged by another molecule of alkene, so the coordination of another molecule of thioether (**1**) released the mono-alkenylated product (**3**) (Path b).



Scheme 6. Proposed mechanism

In summary, with our thioether directing group, we realized the selective mono- and di-alkenylation of aryl C-H bonds in biphenyl framwork controlled by the oxidant, mainly by the coordinating ability of the counter anion of the oxidant. The substrate scope for both the mono-alkenylation and the di-alkenylation are very good. Widely used sulfoxide-olefine ligand was also obtained by simpe transformation of the product. More detailed mechanism studies and other reactions based on the thioether directing group are underway.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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TOC. Oxidant controlled selective C-H bond mono-alkenylation and di-alkenylation of biphenylthioethers to synthesize sulfoxide-olefin ligands with thioether as directing group