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Ir(III)-catalyzed thioether directed arene C–H alkenylation†

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In this study, we demonstrate an Ir(III)-catalyzed thioether directed alkenylation of arene C–H bonds under mild reaction conditions. The selectivity for mono- or di-alkenylation is controlled by the concentration of alkene and oxidant loading. Various functional groups are tolerated, and moderate to good yields of alkenylated products are achieved.

Transition-metal catalyzed C–H functionalizations of arene compounds have attracted tremendous attention in the development of new synthetic methods, due to their innate step- and atom-economy.[1] In the past decade, the directing-group strategy has witnessed great success;[2] among the achievements, the majority of directing groups use N- or O-atom based directing groups, such as pyridines, oxazolines, amides, imines, carboxylic acids and their derivatives.[3] The sulfur-atom is widely present in medicines and agrochemicals[4] and the direct functionalization of S-containing compounds will significantly benefit the fast diversification of bioactive molecules. Herein we report an Ir(III)-catalyzed thioether directed alkenylation of arene C–H bonds under mild reaction conditions.

Though sulfur atom is strong coordinative to transition metals, and poisonous of catalysts occur in some catalytic processes, recently breakthrough have revealed that thioethers are efficient directing groups for C–H olefinations. In 2012, Zhang reported a Pd-catalyzed C–H alkenylation of thioethers (Fig. 1a). The intermediate in this reaction was isolated, which identified that sulfur was the directing-atom for the first time.[5] In 2013, Shi reported Rh-catalyzed C–H alkenylation of benzylthioether (Fig. 1b).[6] More recently, Miura and co-workers reported Rh-catalyzed selective C4 C–H alkenylation of indoles using 3-thioethers as directing groups (Fig. 1c).[7] Other sulfur-containing functional groups, such as thiocarbonyls[8] and sulfoxides,[9] have also been reported in directing C–H arylations, alkenylations, alkylations, and cyclizations with Pd-, Rh-, and Ru-catalysts.[10] Despite these successes, the demand is still high for S-atom directed C–H functionalization protocol that proceeds with mild reaction conditions, controllable C–H selectivity, diverse functional group tolerance, and generally applicable catalytic system. Herein, we report an Ir(III)-catalyzed thioether directed mono-alkenylation and di-alkenylation of arene C–H bonds that proceeds under mild and controllable conditions (Fig. 1d).

We started to investigate this transformation by examining the reactivity between benzyl *p*-tolyl sulfide (**1a**) and ethyl acrylate (**2a**). When using 1.5 mol% of $[Cp^*IrCl_2]_2$ as the catalyst, 6 mol% of $AgBF_4$ as the activator for the Ir-catalyst, and 1.2 equiv. of $Cu(OAc)_2$ as the oxidant in DCE at 80 °C for 12 h, the desired C–H alkenylation product **3a** was obtained in 38% yield (Table 1, entry 1). After optimizing solvents, HFIP was found a superior solvent over DCE, acetone, diethyl ether, or trifluoromethylbenzene, by giving 80% of isolated yield (entries 2–

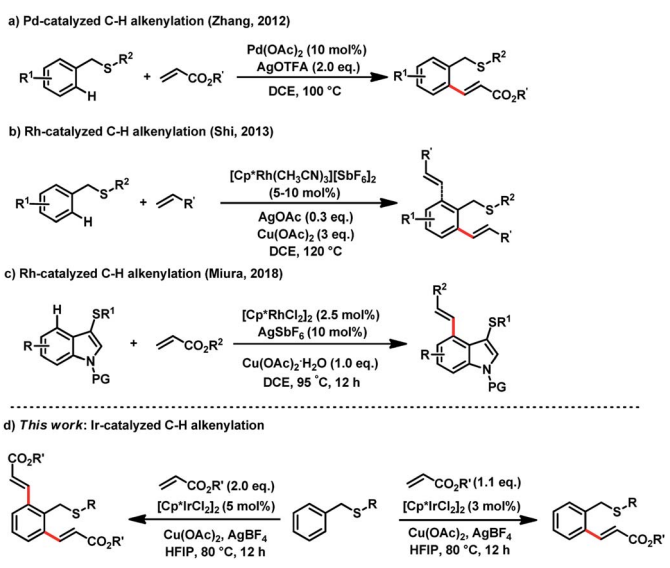

Fig. 1 Thioethers directed *ortho* C–H alkenylation.

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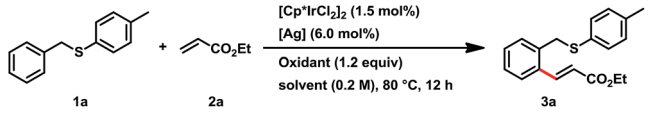
Table 1 Optimization of conditions[a]



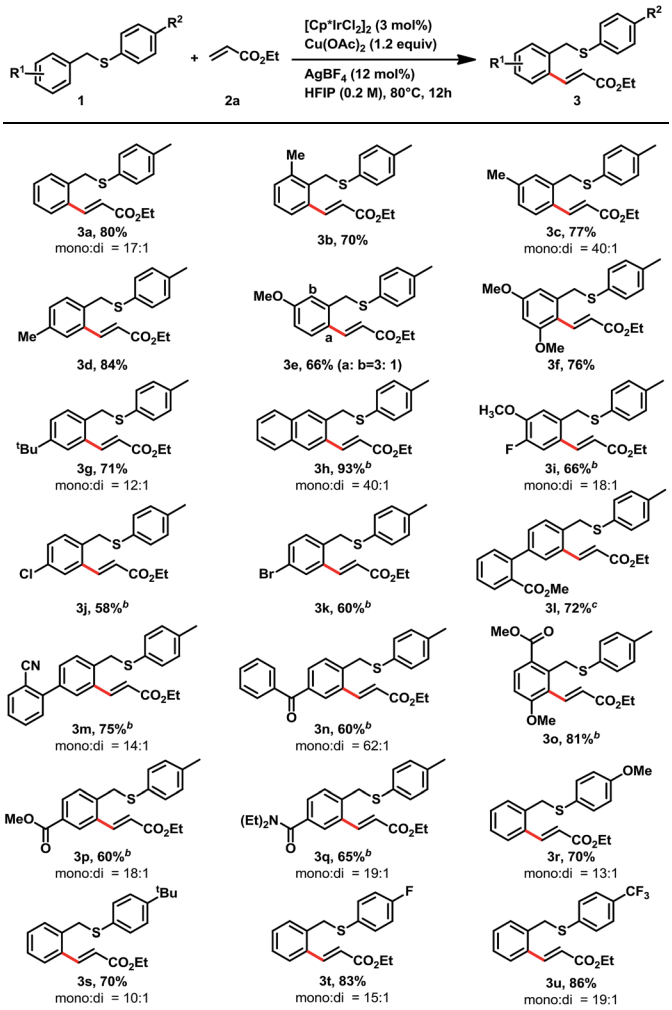
Entry	[Ag]	Oxidant	Solvent	Yield[b] (%)
1	$AgBF_4$	$Cu(OAc)_2$	DCE	38[c]
2	$AgBF_4$	$Cu(OAc)_2$	Acetone	34
3	$AgBF_4$	$Cu(OAc)_2$	Et_20	N.D.
4	$AgBF_4$	$Cu(OAc)_2$	$PhCF_3$	38
5	$AgBF_4$	$Cu(OAc)_2$	HFIP	87 (80)[c]
6	$AgBF_4$	AgOAc (2.2 equiv.)	HFIP	72
7	$AgBF_4$	AgTFA (2.2 equiv.)	HAP	70
8	$AgBF_4$	$Cu(TFA)_2 \cdot XH_2O$	HFIP	12
9	$AgBF_4$	BQ	HFIP	N.D.
10	$AgBF_4$	O_2	HAP	N.D.
11	$AgBF_4$	$Cu(OAc)_2$ (20 mol%)	HFIP	40
12	$AgSbF_6$	$Cu(OAc)_2$	HFIP	62
13	$AgPF_6$	$Cu(OAc)_2$	HFIP	64
14	$AgNTf_2$	$Cu(OAc)_2$	HAP	62

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (2.0 equiv.), $[Cp^*IrCl_2]_2$ (1.5 mol%), [Ag] (6.0 mol%), oxidant (1.2 equiv.), 0.2 M, air, 80 °C, 12 h. [b] Yield was determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. [c] Isolated yield.

5). Next, oxidants were screened. AgOAc and AgTFA provided the desired product in 72% and 70% yields, respectively (entries 6–7). While $Cu(TFA)_2$-hydrate provided only 12% yield of **3a** (entry 8). Benzoquinone (BQ) and O_2 were found inefficient for the reaction, and no desired product was found from these reaction mixtures (entries 9–10). When reducing $Cu(OAc)_2$ loading amount to 20 mol%, the yield of the desired product decreased to 40% (entry 11), which indicated that Cu^{2+} was critical oxidant for this catalytic reaction. Various silver salts, which worked as the activator to promote the Ir-catalyst's efficiency, was also examined, $AgSbF_4$, $AgPF_6$, and $AgNTf_2$ gave the desired product in good yields (entries 12–14), but $AgBF_4$ was superior over the others.

With the optimized conditions in hand, we next examined the substrate scope of thioethers for the mono-alkenylation (Table 2). Various electron-rich substrates provided the desired products in good yields when use 3 mol% of $[Cp^*IrCl_2]_2$ as the catalyst. Sterically bulky substituents on the benzyl ring were well tolerated. For example, benzyl rings containing methyl groups at the *ortho*-, *meta*-, and *para*-positions readily provided the desired products in 70–84% yields (**3b–3d**). 3-Methoxybenzyl *p*-tolyl sulfane provided 66% yield of *ortho*-olefinated products at the 2-, and 6-positions with the ratio of 1 : 3, and the less hindered 6-position was favorable (**3e**). Other electron-donating substituents, such as substrates containing dimethoxy and *tert*-butyl groups offered good yield of the desired products, 76% and 71% yields were achieved, respectively (**3f–3g**). The reaction of 2-naphthylmethyl *p*-tolyl sulfane took place selectively at the less hindered β-position and provided **3h** in 93% yield. For electron-deficient substrates, the transformation showed sluggish reactivity than those electron-rich substrates. When increasing the $[Cp^*IrCl_2]_2$ catalyst loading to 5 mol%, good yields were achieved. For example, halide substituents, such as fluoro-, chloro- and bromo- were compatible with the reaction conditions, and provided the desired alkenylation product in 66%, 58%, and 60% yield, respectively (**3i–3k**). The biaryl substrates that contain electron withdrawing groups, such as ester and cyano substituents, readily afforded the desired mono-olefinated product in 72% and 75% yield (**3l**, and **3m**). Other carbonyl derivatives offered the desired products in good yields, too, which include, a benzoyl (**3n**, 60% yield), esters (**3o**, and **3p**, 81%, and 60% yield, respectively), and an amide (**3q**, 65% yield). The substituents of *p*-tolyl sulfide were also examined. In this event, we found that the electron-deficient substituents provided higher yields of the desired products than those electron-rich ones. For example, when replacing the *para*-methyl group to the methoxy (–OMe, **3r**) or *tert*-butyl (–^{t}Bu, **3s**), the reaction provided

Table 2 Mono-alkenylation of thioethers[a]



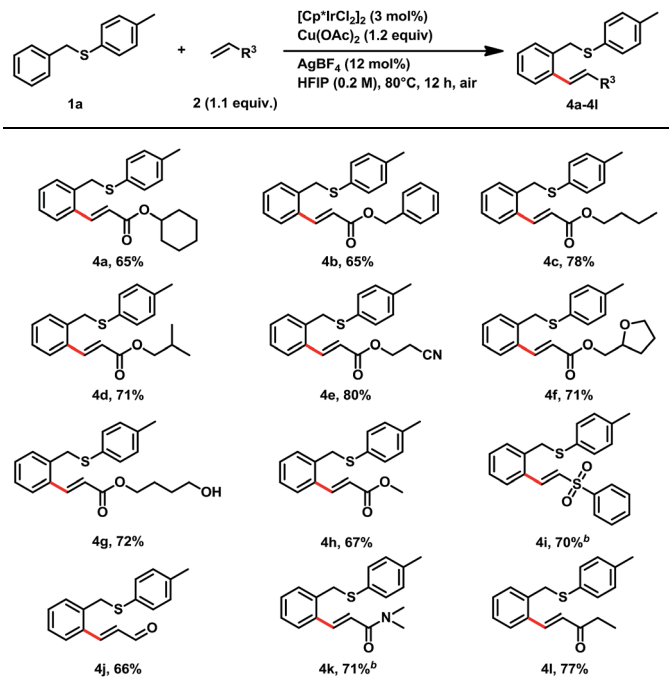
[a] Reaction conditions: **1** (0.4 mmol), **2a** (1.1 equiv.), $[Cp^*IrCl_2]_2$ (3 mol%), $Cu(OAc)_2$ (1.2 equiv.), $AgBF_4$ (12 mol%), HFIP (2 mL), 80 °C, 12 h. [b] 5 mol% Ir-catalyst. [c] 4 mol% Ir-catalyst.

moderate yields (70% for each). While replacement of the *para*-methyl group with fluoro (–F, **3t**) or trifluoromethyl (–CF_3, **3u**) groups, good yields achieved (83% and 86%, respectively). Notably, in all of these samples, only benzyl C–H bonds are active for the olefination, and the arylthiol C–H bonds are inactive.

Next, we investigated the alkene scope for this transformation with benzyl *p*-tolyl sulfane (**1a**) (Table 3). Acrylates were good coupling partners for this reaction, various of alkoxyl groups on acrylate provided C–H alkenylation products in good yields, which included cyclohexyl (**4a**, 65% yield), benzyl (**4b**, 65% yield), *n*-butyl (**4c**, 78% yield), iso-butyl (**4d**, 71% yield), 2-cyanoethyl (**4e**, 80% yield), 2-furanylmethyl (**4f**, 71% yield), and 4-hydroxylbutyl (**4g**, 72% yield). Other electron-deficient alkenes also afforded the desired products in moderate to good yields, such as phenyl vinyl sulfone (**4i**, 70% yield), acrolein (**4j**, 66% yield), *N*,*N*-dimethylacrylamide (**4k**, 71% yield), and ethyl vinyl ketone (**4l**, 77% yield).

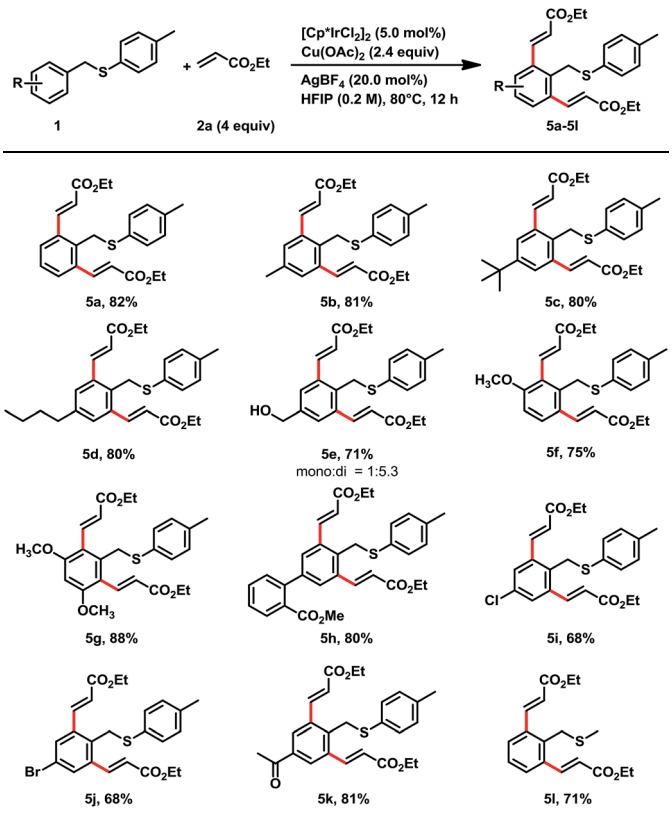
Though a high degree of mono-alkenylation products achieved from these substrates, we occasionally observed some dialkenylation products from reaction mixtures. For example, we have isolated **5a** from the reaction of **1a** and **2a** in 12% yield (entry 6, Table 1). In order to get a high yield of dialkenylation product **5a**, we optimized the reaction conditions. To our delight, when increasing $Cu(OAc)_2$ to 2.4 equiv. and acrylate to 4 equiv., the dialkenylated product **5a** was afforded in 82% yield as a single product. With these conditions, we examined the substrate scope for the dialkenylations (Table 4). Various

Table 3 Substrate scope for alkenes[a]



[a] Reaction conditions: **1a** (0.4 mmol), **2** (1.1 equiv.), $[Cp^*IrCl_2]_2$ (3 mol%), $Cu(OAc)_2$ (1.2 equiv.), $AgBF_4$ (12 mol%), HFIP (2 mL), 80 °C, 12 h. [b] 5 mol% Ir-catalyst.

Table 4 Ir-catalyzed dialkenylation of thioethers[a]



[a] Reaction conditions: **1a** (0.4 mmol), **2a** (4.0 equiv.), $[Cp^*IrCl_2]_2$ (5 mol%), $Cu(OAc)_2$ (2.4 equiv.), $AgBF_4$ (20 mol%), HFIP (2 mL), 80 °C, 12 h.

electron-rich arenes preceded dialkenylation smoothly and provided the desired products in good to high yields. *para*-Methyl, *tert*-butyl, and *n*-butyl substituent arenes delivered the desired products in 81%, 80%, and 80% yields (**5b–5d**), respectively. *para*-Benzyl alcohol was well tolerated and provided the desired product **5e** in 71% yield. *meta*-Methoxy and dimethoxy substituents were good for the transformation and provided the diolefinated products in 75% and 88% yields (**5f** and **5g**). The electron-deficient substrates also provided the dialkenylation products in good yields. For example, ester substituents on the diphenyl substrate offered the desired product **5h** in 80% yield. Chloro-, bromo- and acetal substituents at the *para*-position of arenes delivered the desired products in 68–81% yields (**5i–5k**). It was interesting that the methyl benzyl sulfane provided the desired dialkenylated product **5l** in 71% yield under these conditions.

A plausible mechanism was proposed for this Ir-catalyzed *ortho*-alkenylation (Fig. 2):[11] $[Cp^*IrCl_2]_2$ reacted with $AgBF_4$ to provide the catalytic active Ir(III) species **A**. The coordination of thioether **1** with **A** and followed C–H activation provided iridacycle **B**. The coordination of olefin **2** with iridacycle **B** and followed insertion into Ir–C bond provided the seven-membered iridacycle **C**. Subsequent β-H elimination delivered the desired

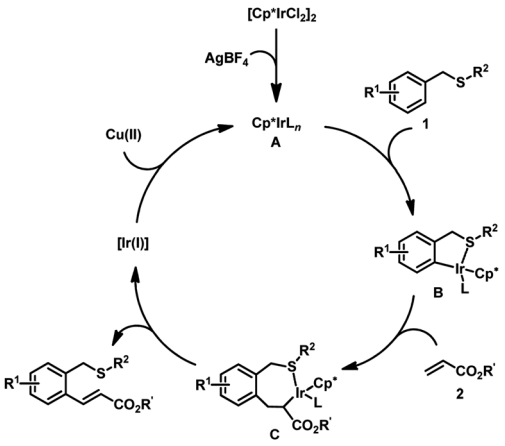


Fig. 2 Plausible mechanism.

product. The regeneration of Ir(III) catalyst with the $Cu(OAc)_2$ finished the catalytic cycle.

In conclusion, we have developed an Ir-catalyzed *ortho*-alkenylation of arene C–H bonds using thioether as the directing group. This protocol undergo under mild and operationally simple conditions. The reaction exhibits broad functional group compatibility, and provides mono- or di-alkenylation products in good to high yields.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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