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Catalyst-Controlled Regiodivergent Dehydrogenative Heck Reaction of 4-Arylthiophene/Furan-3-Carboxylates

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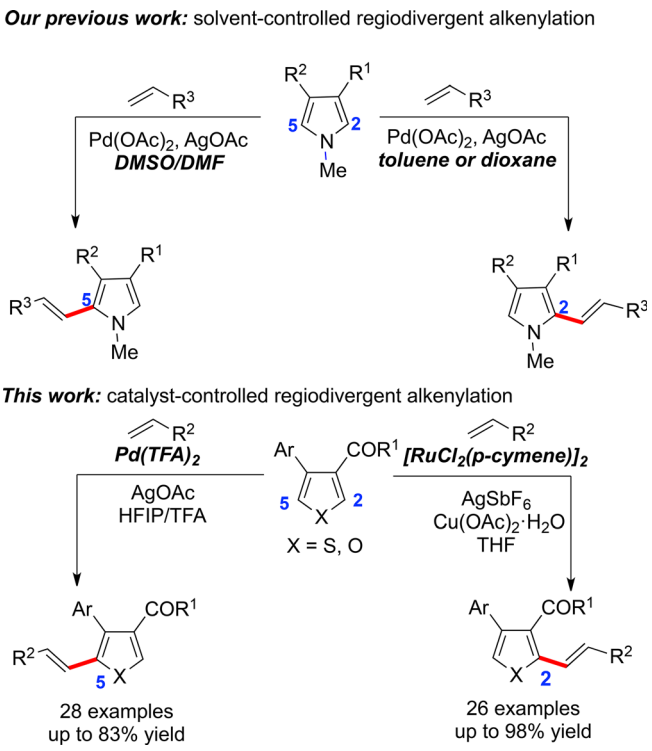
Abstract: A catalyst-controlled regiodivergent dehydrogenative Heck reaction of 4-arylthiophene/furan-3-carboxylates has been realized. Use of a palladium catalyst led to the C-5 alkenylation through electronic palladation, while a ruthenium catalyst favored the C-2 alkenylation with the assistance of a directing group. This reaction exhibited good to excellent regioselectivities.

Keywords: catalyst-control; dehydrogenative Heck reaction; palladium; regiodivergence; ruthenium

Over the past few decades, the transition metal-catalyzed C–H activation strategy has drawn great attention due to its high efficiency and atom economy. However, the ability to functionalize a specific C–H bond regioselectively was still one of the major challenges in transition metal-catalyzed C–H activation when multiple C–H bonds with similar reactivity exist in one molecule.[1] Consequently, improvement of the regioselective C–H functionalization is critically important. Usually, the use of directing groups, ligands, electronic/steric effects and catalyst controlled regioselectivities were adopted to resolve this problem.[2] Although the aforementioned methods were widely investigated, the continuous development of new methods to precisely control the product distribution in C–H activation is still a hot research topic and challenging problem for chemists.

The thiophene and furan scaffolds are key structural motifs widely found in a variety of natural products and bioactive compounds.[3] Recently, much effort has been devoted to functionalize thiophenes and furans through transition metal-catalyzed C–H functionalizations, such as arylation,[4] alkenylation,[5] alkylation,[6] halogenation[7] and borylation,[8] whereas the regiodivergent C–H functionalization of thiophenes and furans in a controllable manner needed to be solved. In 2015, the Glorius group[7a] achieved the C-3 selective halogenation with the aid of an *N*,*N*-dialkylamide directing group at the C-2 position, while C-5 selectivity was realized through the electronic halogenation. In the same year, Ishiyama and co-workers[8c] reported an iridium-catalyzed and ligand-controlled C-3/C-4 regiodivergent borylation of 2,5-disubstituted thiophenes and furans. In 2016, the Larrosa group[9] delivered a palladium-catalyzed selective arylation of benzo[*b*]thiophenes and thiophenes at the C-3 position, and the selective C-2 arylation was obtained through base-mediated intermolecular sp^2 C–H bond arylation *via* a benzyne intermediate by Daugulis's group.[10] Despite the progress of regiodivergent functionalization of thiophenes and furans at C-2/C-3, C-3/C-4 and C-3/C-5 positions, the C-2/C-5 regiodivergent C–H functionalization of thiophenes and furans remained untouched so far due to the very similar electronic properties of the C–H bonds at these two positions. Recently, our group has realized a solvent-controlled C-2/C-5 regiodivergent alkenylation of pyrroles with good regioselectivities (Scheme 1).[11] When applying the solvent-controlled strategy to C-2/C-5 selective alkenylation of 3,4-disubstituted thiophenes and furans, the regioselectivities were unsatisfactory. With our continued interest in exploration of the dehydrogenative Heck reaction,[11,12] herein we wish to report a catalyst-controlled C-2/C-5 selective dehydrogenative Heck reaction of 3,4-disubstituted thiophenes and furans.

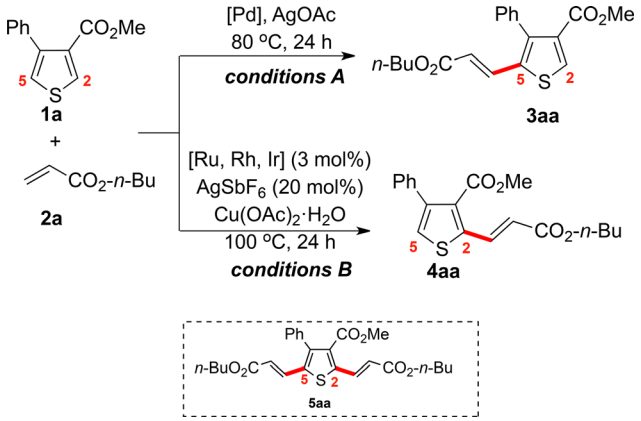
We initiated the study by investigating the dehydrogenative Heck reaction of methyl 4-phenylthiophene-3-carboxylate **1a** and *n*-butyl acrylate **2a** adopting $Pd(OAc)_2$ as catalyst and AgOAc as oxidant with toluene or DMF/DMSO (v/v = 4:1) as solvent following our previous work (Table 1, entries 1 and 2).[11] Toluene or DMF/DMSO afforded the alkenylated products (**3aa** and **4aa**) in 48% and 35% total yields with low regioselectivities. Subsequent solvents screening



Scheme 1. C-2/C-5 Selective alkenylation of pyrroles/thiophenes/furans *via* C–H activation.

(see the Supporting Information for details) revealed that the HFIP (hexafluoroisopropyl alcohol) performed best in the selective C-5-alkenylation, which afforded **3aa** in 66% yield (C-2:C-5 = 7:93). Besides, we found that the C-2,5 dialkenylated by-product **5aa** could be suppressed with TFA as solvent even though the conversion of **1a** was not complete (entry 4). Further screening of the palladium catalysts indicated that the yield and C-5 selectivity could be slightly improved when $Pd(TFA)_2$ was used as the catalyst (entries 5–7). **3aa** could be finally isolated in 79% yield (C-2:C-5 = 4:96) with HFIP and TFA as co-solvent (entry 8). The control experiments indicated that oxygen could be involved in the catalytic procedure (entries 9 and 10). The C-2 selective alkenylation of **1a** could not be well realized under the palladium-catalyzed system even after an elaborate screening of various solvents (see the Supporting Information for details). To achieve the C-2 selective alkenylation, we then turned our attention to screening various metal catalysts (entries 11–14). To our delight, when $[RhCp^*Cl_2]_2$, $[IrCp^*Cl_2]_2$ and $[RuCl_2(p\text{-cymene})]_2$ were used as the catalysts, the C-2 alkenylated product **4aa** could be obtained in moderate yields with excellent regioselectivities. $[RuCl_2(p\text{-cymene})]_2$ was then chosen as the catalyst since it was much cheaper than $[RhCp^*Cl_2]_2$. Screening the solvents revealed that THF was the best choice for the C-2 selective alkeny-

Table 1. Optimization of the reaction conditions.[a,b,c]



Entry	Catalyst	Solvent	Yield [%]	Ratio [C-2:C-5]
1	$Pd(OAc)_2$	toluene	48	27:73
2[d]	$Pd(OAc)_2$	DMF/DMSO	35	38:62
3	$Pd(OAc)_2$	HFIP	66	7:93
4	$Pd(OAc)_2$	TFA	43	12:88
5	$Pd(TFA)_2$	HFIP	72	6:94
6	$Pd(dppf)_2Cl_2$	HFIP	36	14:86
7	$Pd(OOC\text{-}t\text{-}Bu)_2$	HFIP	70	9:91
8[e]	$Pd(TFA)_2$	HFIP	79	4:96
9[e,f]	$Pd(TFA)_2$	HFIP	58	9:91
10[e,g]	$Pd(TFA)_2$	HFIP	80	5:95
11	$[RhCp^*Cl_2]_2$	THF	52	>99:1
12	$[Rh(COD)OH]_2$	THF	trace	–
13	$[IrCp^*Cl_2]_2$	THF	21	>99:1
14	$[RuCl_2(p\text{-cymene})]_2$	THF	54	>99:1
15	$[RuCl_2(p\text{-cymene})]_2$	DCE	46	>99:1
16	$[RuCl_2(p\text{-cymene})]_2$	dioxane	<10	–
17	$[RuCl_2(p\text{-cymene})]_2$	toluene	n.r.	–
18	$[RuCl_2(p\text{-cymene})]_2$	DMF	n.r.	–
19[h]	$[RuCl_2(p\text{-cymene})]_2$	THF	86	>99:1
20[i]	$[RuCl_2(p\text{-cymene})]_2$	THF	90	>99:1
21[f,i]	$[RuCl_2(p\text{-cymene})]_2$	THF	89	>99:1
22[g,i]	$[RuCl_2(p\text{-cymene})]_2$	THF	37	>99:1

[a] *Reaction conditions: Conditions A:* **1a** (0.25 mmol, 1.0 equiv.), butyl acrylate **2a** (0.50 mmol), [Pd] (10 mol%), and AgOAc (0.50 mmol) in solvent (1.0 mL) at 80 °C for 24 h under air. *Conditions B:* **1a** (0.25 mmol, 1.0 equiv.), butyl acrylate **2a** (0.50 mmol), catalyst (3 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (0.50 equiv.) in solvent (1.0 mL) at 100 °C for 24 h under air.

[b] Total isolated yields of **3aa** and **4aa**.

[c] The ratios were determined by ^1H NMR using dibromomethane as the internal standard.

[d] The ratio of DMF/DMSO (v/v) was 4:1.

[e] Using 5.0 equiv. TFA.

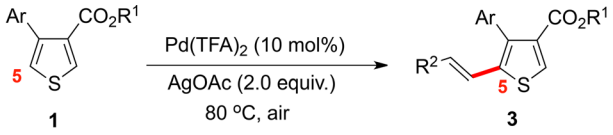
[f] Under an argon atmosphere.

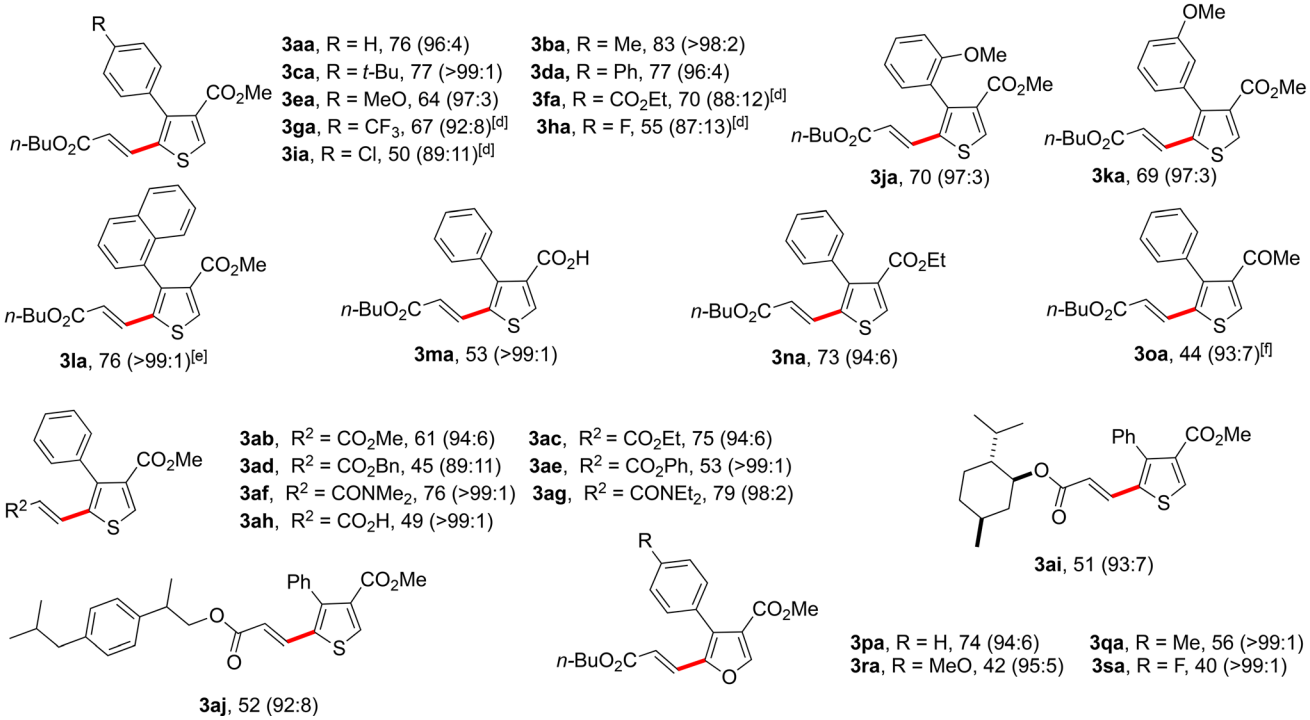
[g] Under an oxygen atmosphere.

[h] $Cu(OAc)_2{\cdot}H_2O$ (1.20 equiv.) was used.

[i] $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (33 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (1.20 equiv.) were used.

Table 2. Substrate scope of the C-5 alkenylation.[a,b,c]



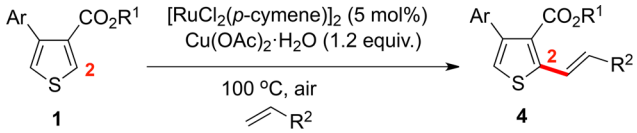


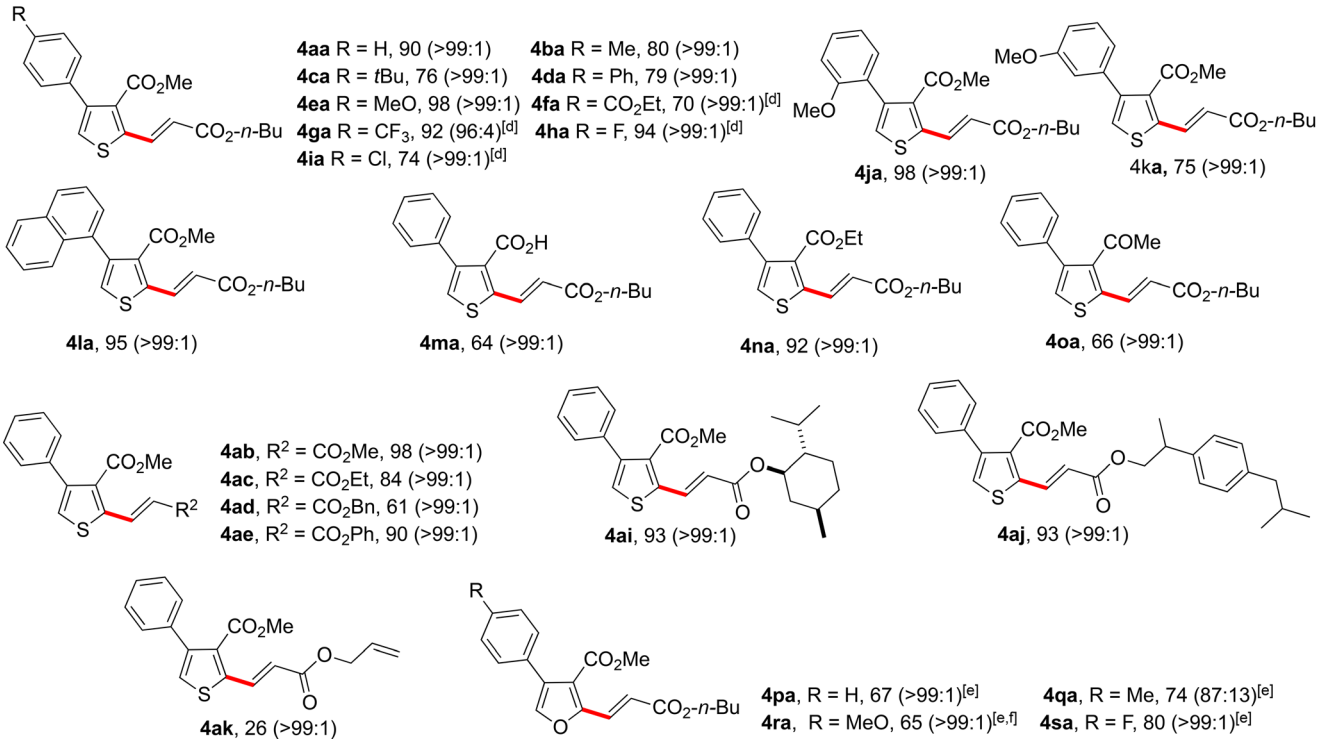
[a] *Reaction conditions:* **1** (0.25 mmol), alkene **2** (0.50 mmol), $Pd(TFA)_2$ (10 mol%), AgOAc (0.50 mmol), and TFA (1.25 mmol) in HFIP (1.0 mL) at 80 °C for 24 h under air.
[b] Isolated yields of the C-5 alkenylated products.
[c] The ratios were determined by ^1H NMR.
[d] For 36 h.
[e] At 65 °C for 36 h.
[f] The TFA was removed.

lation (entries 15–18). By increasing the amount of $Cu(OAc)_2{\cdot}H_2O$ to 1.20 equiv., the yield was further improved to 86% (entry 19). Finally, **4aa** could be isolated in 90% yield with a catalyst loading set to 5 mol% (entry 20). Control experiments indicated that the high concentration of oxygen was harmful to the ruthenium-catalyzed system (entries 21 and 22).

With the optimized conditions in hand, we then examined the scope and generality of the palladium-catalyzed C-5 alkenylation (Table 2). Substrates with electron-donating groups at the C-4 position of phenyl ring, such as methyl, *tert*-butyl, phenyl and methoxy groups, afforded **3ba**–**3ea** in 64–83% yields. Those substrates with electron-withdrawing groups including ester, trifluoromethyl, fluoro and chloro groups at the C-4 position delivered **3fa**–**3ia** in 50–70% yields on prolongation of the reaction time to 36 h. **3ja** and **3ka** could be obtained in 70% yield and 69% yield, which indicated that the position of the substituent at the phenyl ring had no effect on the alkenylation process. Product **3la** with a 1-naphthyl group was obtained in 76% yield. For those substrates bearing a carboxylic group and an ethyl ester group at the C-3 position, the reaction furnished **3ma** in 53% yield and **3na** in 73% yield. 4-Phenyl-3-acetylthiophene afforded **3oa** in moderate yield with good C-5 regioselectivity. The products **3ab**–**3ae** could be isolated in 45–75% yields with C-5/C-2 ratios from 89:11 to >99:1 when methyl, ethyl, benzyl and phenyl acrylates were tested. Acylamides offered **3af** and **3ag** in 76% and 79% yields, respectively. Acrylic acid could also participate to deliver **3ah** in 49% yield. Moreover, the natural molecule (±)-menthol and the non-steroidal anti-inflammatory drug ibuprofen derivative could be introduced at the C-5 position conveniently, providing **3ai** in 51% yield and **3aj** in 52%

Table 3. Substrate scope of the C-2 alkenylation.[a,b,c]



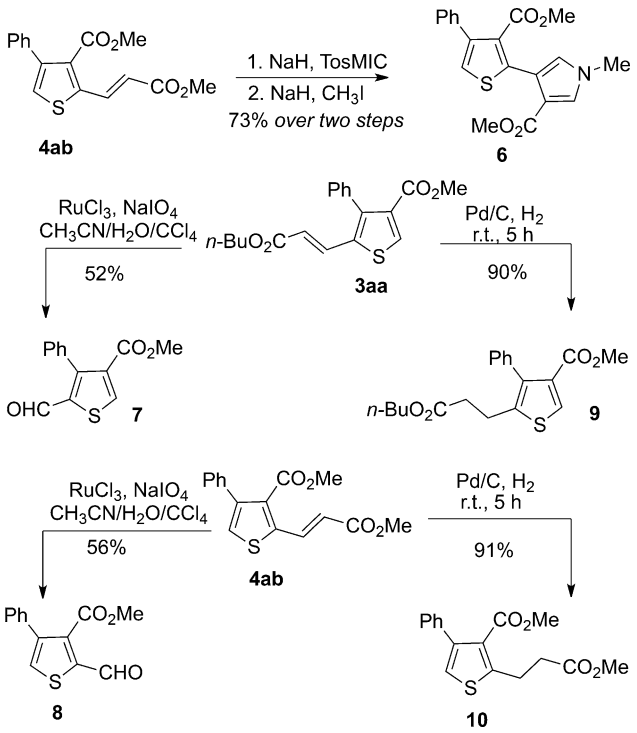


[a] *Reaction conditions:* **1** (0.25 mmol), alkene **2** (0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (33 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (0.30 mmol) in THF (1.0 mL) at 100 °C for 24 h under air.
[b] Isolated yields of the C-2 alkenylated products.
[c] The ratios were determined by ^1H NMR.
[d] For 36 h.
[e] Using **1** (0.25 mmol), **2a** (0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (10 mol%), $AgSbF_6$ (66 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (0.30 mmol) in THF (1.0 mL) at 120 °C for 24 h.
[f] At 100 °C.

yield. It is a pity that non-activated alkenes such as styrene, allylic ether and allylic ester could not afford the corresponding C-5 selective alkenylated products. Gratifyingly, furan derivatives could also work well under this catalytic system and afford **3pa**–**3sa** in 40–74% yields with 94:6 to >99:1 regioselectivities.

After the examination of the scope and generality of the C-5 alkenylation, we then checked the C-2 selective alkenylation of 3,4-disubstituted thiophenes (Table 3). Similar to the C-5 alkenylation procedure, both electron-donating and electron-withdrawing groups at the C-2, C-3, and C-4 positions of the phenyl ring as well as the naphthyl ring were tolerated and afforded **4aa**–**4la** in 74–98% yields. On changing from the methyl ester to the ethyl ester, **4na** was obtained in 92% yield. Moreover, substrates with carboxylic and carbonyl groups also underwent C-2 alkenylation and provided **4ma** and **4oa** in 64% and 66% yields, respectively. Methyl, ethyl, benzyl and phenyl acrylates provided **4ab**–**4ae** in 61–98% yields. Both **4ai** containing (±)-menthyl acrylate and **4aj** with ibuprofen derivative acrylate were isolated in 93% yields. When allyl acrylate **2k** was tested with **1a**,[13] the C-2 selective alkenylated product **4ak** was obtained in 26% yield with excellent regioselectivities. On increasing the loading of catalyst to 10 mol%, C-2 alkenylated furans **4pa**-**4sa** could be obtained in 65–80% yields.

To gain insights into the utility of the reaction, the alkenylated products were further transformed



Scheme 2. Functionalization of the alkenylated products.

(Scheme 2). The thiophene **4ab** could undergo a van Leusen reaction and afford the biheteroaryl compound **6** in 73% yield, which is the core structure of a series of inhibitors of lipoxygenase.[14] The C-2/C-5 alkenylated products **3aa** and **4ab** were oxidized and reduced, affording the formal selective formylated products **7** and **8** in 52% and 56% yields and alkylated products **9** and **10** in 90% and 91% yields.

Based on the previous reports,[15] mechanisms for this catalyst-controlled regiodivergent dehydrogenative Heck reaction are proposed as shown in Scheme 3. Under the palladium-catalyzed system, electronic palladation at the more electron-rich C-5 position gives the intermediate **3a-I**, followed by coordination of **2a** to form a π-complex **3a-II**. Migratory insertion of butyl acrylate affords **3a-III**. β-H elimination of the intermediate **3a-III** delivers the C-5 alkenylated product **3aa** along with a Pd(0) species, which could be oxidized by AgOAc to regenerate Pd(II) to complete the catalytic cycle. Although HFIP is widely used in the transition metal-catalyzed C–H activation reactions, the exact role of HFIP cannot be explained clearly at the present stage.[16] When Ru(II) was selected as the catalyst, the directed cycloruthenation of **1a** at the C-2 position is preferential to form a five-membered cyclic intermediate **4a-I**. Coordination of **4a-I** with butyl acrylate affords **4a-II** and insertion of olefin provides a seven-membered intermediate **4a-III**. β-H elimination of **4a-III** delivers the alkenylated product **4aa** and the active ruthenium catalyst is regenerated by oxidation with $Cu(OAc)_2·H_2O$ to enter the next catalytic cycle.

In summary, we have developed a catalyst-controlled switchable dehydrogenative Heck reaction of 4-arylthiophene/furan-3-carboxylates. When a palladium catalyst used, the dehydrogenative Heck reaction occurred at the more electron-rich C-5 position through electronic palladation. Selective C-2 alkenylation was achieved by employing ruthenium catalyst with the aid of directing groups. The corresponding C-2 and C-5 alkenylated products were obtained in good to excellent yields with high regioselectivities, respectively.

Experimental Section

C-5 Selective Alkenlyation

A sealed tube was charged with thiophene or furan **1** (0.25 mmol, 1.0 equiv.), $Pd(TFA)_2$ (0.025 mmol, 10 mol%), AgOAc (0.5 mmol, 2.0 equiv.), alkene **2** (0.5 mmol, 2.0 equiv.), trifluoroacetic acid (TFA, 1.25 mmol, 5.0 equiv.) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP, 1.0 mL). The reaction mixture was vigorously stirred at 80 °C (oil temperature) under air for the appropriate time, which was detected with TLC. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a plug of Celite. The mixture was concentrated under vacuum and purified by flash chromatography on silica gel to afford the C-5 alkenylated product **3**.

C-2 Selective Alkenlyation

A sealed tube was charged with thiophene or furan **1** (0.25 mmol, 1.0 equiv.), $[RuCl_2(p\text{-cymene})]_2$ (0.0125 mmol, 5 mol%), $AgSbF_6$ (0.0825 mmol, 33 mol%), $Cu(OAc)_2·H_2O$ (0.3 mmol, 1.2 equiv.), alkene **2** (0.50 mmol, 2.0 equiv.) and THF (1.0 mL). The reaction mixture was vigorously stirred at 100 °C (oil temperature) under air for the appropriate time which was detected with TLC. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (20 mL) and filtered through a plug of Celite. The filtrate was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under vacuum to give a dark residue, which was purified by flash chromatography on silica gel to afford the C-2 alkenylated product **4**.

Acknowledgements

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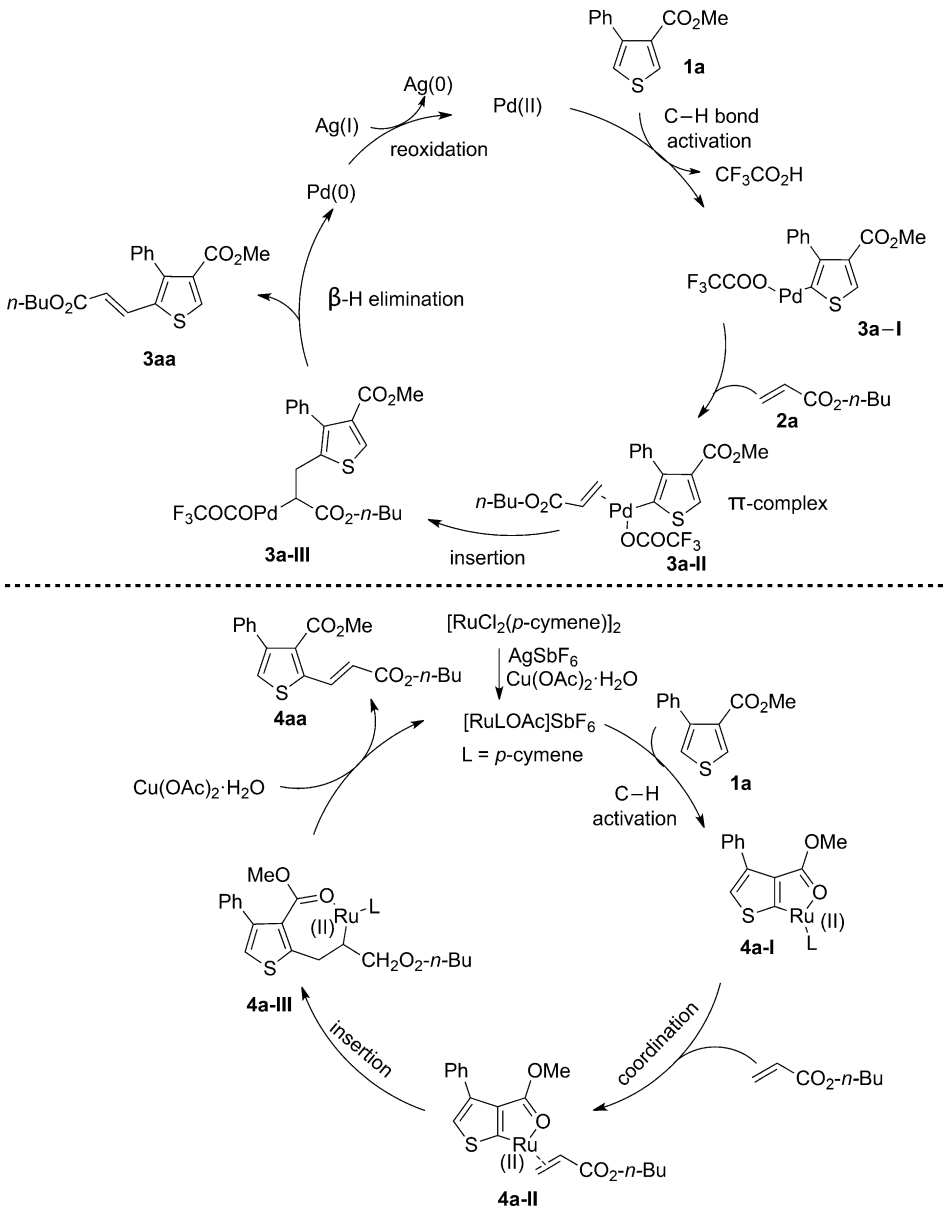

Scheme 3. Proposed mechanism for the selective C-5/C-2 alkenylation.

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8 Catalyst-Controlled Regiodivergent Dehydrogenative Heck Reaction of 4-Arylthiophene/Furan-3-Carboxylates

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