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Communication

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Direct Vicinal Difunctionalization of Thiophenes Enabled by the Palladium/Norbornene Cooperative Catalysis

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Supporting Information Placeholder

ABSTRACT: Herein we report a direct vicinal difunctionalization of thiophenes via the palladium/norbornene (Pd/NBE) cooperative catalysis. A series of mono- and disubstituted thiophenes can be difunctionalized site- and regio-selectively at the C4 and C5 positions in good yields, enabled by an arsine ligand and a unique amide-based NBE. The synthetic utility has been shown in derivatizations of complex bioactive compounds and an open-flask gram-scale preparation. Preliminary results have been obtained in the difunctionalization of furans and a direct C4-selective arylation of 2-substituted thiophenes.

Polysubstituted aromatic heterocycles are commonly found in pharmaceuticals, agrochemicals and organic materials (Figure 1).[1] Site-selective conversion of unactivated C−H bonds directly to new functional groups (FGs) represents an important and straightforward approach for efficient functionalization of heteroarenes.[2] To date, great success has been achieved for site-selectively introducing one FG to heteroarenes without aids of directing groups (DGs);[3] it remains challenging to simultaneously install two *different* FGs,[4] particularly at vicinal positions in a regioselective manner. However, such a transformation would constitute significant interests because it could rapidly increase molecular complexity, thereby facilitating streamlined synthesis of polysubstituted heteroarenes.

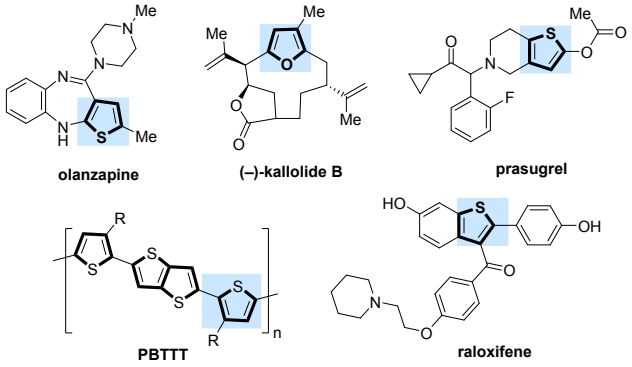
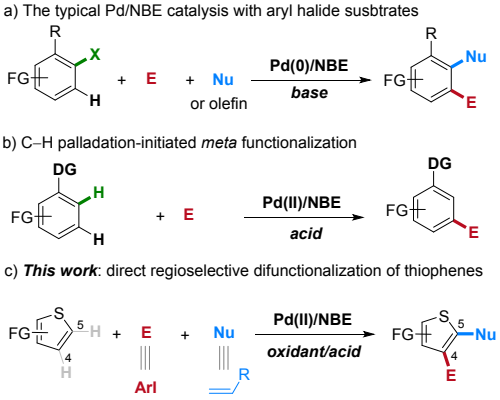


Figure 1. Examples of Polysubstituted Thiophenes and Furans

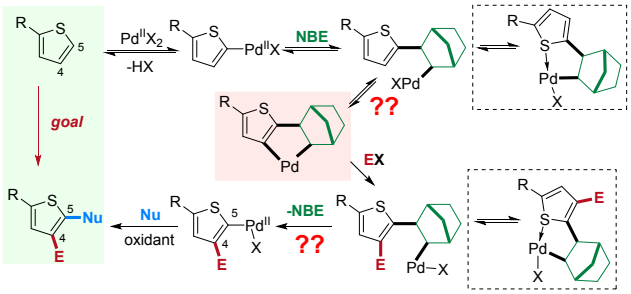
The palladium/norbornene (Pd/NBE) cooperative catalysis, also known as Catellani-type reactions, has emerged as a versatile approach for vicinal difunctionalization of arenes.[5] Seminal efforts led by Catellani[6] and Lautens[7] show that, using aryl halides as substrates, an electrophile and a nucleophile could be coupled simultaneously at arene *ipso* and *ortho* positions, respectively (Scheme 1a). Beyond using aryl halides as substrates,[8] in 2015 the Yu[9a] and our[9b] groups independently disclosed the direct *meta* functionalizations of arenes initiated by a directed *ortho* C−H palladation (Scheme 1b). Very recently, a *meta* arylation of electron-rich alkoxyarenes was developed by Yu through a related approach.[10] However, to the best of our knowledge, vicinal difunctionalization of arenes through the C−H-initiated Pd/NBE catalysis (either directed or non-directed) has not been reported yet. The primary challenge is associated with the fact that, for the proposed difunctionalization, acidic conditions are often beneficial for the C−H palladation step,[11] which could result in an *ipso* protonation process instead of further couplings.[9] Additional difficulties could be envisaged for using heteroarene substrates in the Pd/NBE catalysis, as many aromatic heterocycles can behave as good ligands for Pd and they are often less stable than arenes under oxidative conditions. Herein, stimulated by these challenges and given the therapeutic importance of thiophene derivatives,[12] we describe the initial development of a double C−H functionalization of thiophenes at the C4 and C5 positons via the Pd/NBE catalysis using a unique catalytic system (Scheme 1c).

Scheme 1. Direct C−H Functionalization of Heterocycles



The C5 (or C2) position of thiophene is generally considered to be most electron-rich, and a number of direct C−H metalation methods have been successfully developed.[13] However, directly merging the C5-palladation with the Pd/NBE catalysis would still be nontrivial because of (1) the lack of an *ortho* substituent to promote the NBE extrusion (namely the "*ortho constraint*")[14] and (2) the coordinative ability of the sulfur that could retard the C4 palladation and NBE extrusion (Scheme 2). For example, the use of α-halothiophenes as substrates for the Catellani-type reactions has been elusive.[15] We hypothesized that one key to address the sulfur coordination problem is to use *a weak and π-acidic ligand* that could facilitate dechelation from the sulfur on thiophene but not inhibit the C−H palladation and the Catellani process. In

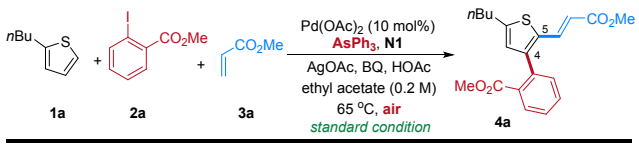
addition, the use of a *bulkier NBE* was also anticipated to be beneficial over simple NBE for assisting the NBE extrusion step via β-carbon elimination.[5c]



Scheme 2. Potential Challenges for the Proposed Approach

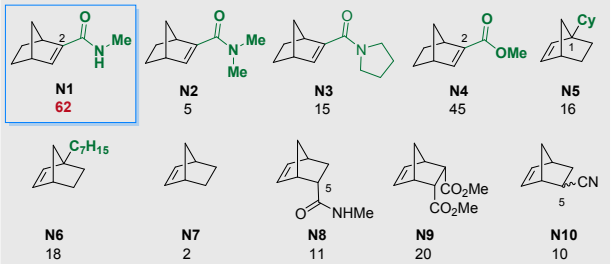
To test the hypothesis, 2-butylthiophene (**1a**) was used as the model substrate, and *ortho* arylation/*ipso* Heck reaction was examined at this initial stage (Table 1). Indeed, $AsPh_3$, previously employed for dechelating the amine directing group in our *meta* arylation reaction,[9b] was found to be superior over phosphine and phosphite ligands (entries 1-4) and delivered the desired C4,5-difunctionalized thiophene product (**4a**) in 82% yield after systematic optimization. Unsurprisingly, no desired product was observed in the absence of Pd or NBE (entries 5 and 6). The C2 methyl amide-substituted NBE (**N1**) proved to be most efficient,[16]

Table 1. Control Experiments



Entry	Change from the *"standard condition"*	yield of **4a** (%)[a]
1	none	82(81)
2	w/o $AsPh_3$	2
3	PPh_3 instead of $AsPh_3$	1
4	$(PhO)_3P$ instead of $AsPh_3$	0
5	w/o $Pd(OAc)_2$	0
6	w/o **N1**	0
7	25 mol% **N1**	72

NBE Effect (15 mol% NBE used instead)[b]

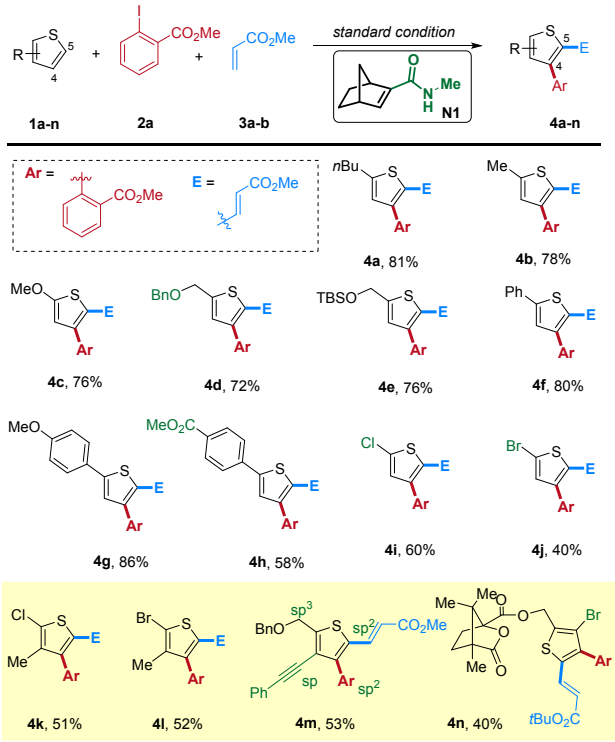


8	w/o BQ	11
9	w/o AgOAc	13
10	w/o HOAc	51
11	0.1 M	72[b]
12	**1a**/**2a** = 1 : 1 (1 equiv)	71[c]

[a]The reaction was run with 0.15 mmol **1a**, 0.1 mmol **2a**, 0.18 mmol **3a**, $Pd(OAc)_2$ (0.01 mmol), **N1** (0.15 mmol), $AsPh_3$ (0.025 mmol), AgOAc (0.3 mmol), BQ (0.1 mmol) and HOAc (0.5 mmol) in 0.5 mL ethyl acetate for 48 h. Yields were determined by ^1H NMR analysis using dibromomethane as the internal standard. [b]1 mL ethyl acetate was used. [c]0.1 mmol **1a** was used.

and 72% yield was still obtained with 25 mol% **N1** (entry 7). Other substituted NBEs were less optimal. For example, tertiary amide-derived NBEs (**N2** and **N3**)[17] showed significantly reduced reactivity likely due to excessive steric hindrance. In addition, the C2 ester-substituted one (**N4**) was slightly less effective.[18] While simple NBE (**N7**) gave almost no desired product, the bulkier bridgehead-substituted NBEs (**N5** and **N6**)[14] or the remotely substituted NBEs (**N8-10**)[18,19] could indeed afford the desired product in higher yields. The difunctionalization reaction requires stoichiometric oxidants to regenerate the Pd(II) catalyst. Both BQ and AgOAc were found necessary (entries 8 and 9); it is likely that BQ could promote fast oxidation of Pd(0) to Pd(II) by acting as a redox active ligand,[20] while AgOAc could assist activation of the C−I bond through forming AgI. Adding HOAc was beneficial, though 51% yield could still be achieved without HOAc (entry 10). The reaction was less efficient at a lower concentration (entry 11). Finally, when substrates **1a** and **2a** were used in an equal molar ratio, the desired product **4a** was afforded in a good yield (entry 12). It is noteworthy that the reaction can be run directly in air at a relatively low reaction temperature (65 °C).

Table 2. Thiophene Derivatives Scope[a]



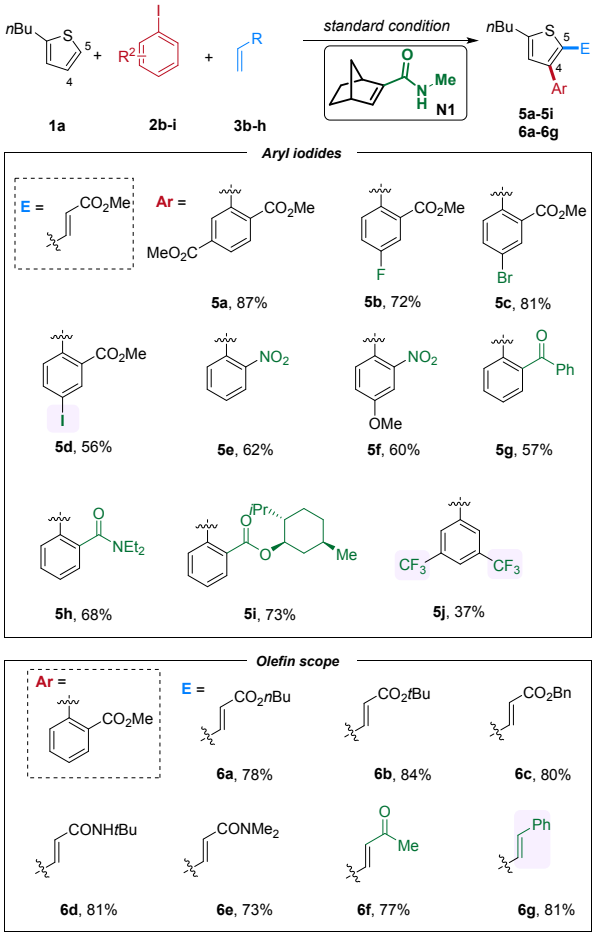
[a]The reaction was run with 0.3 mmol **1**, 0.2 mmol **2** and 0.36 mmol **3** in 1.0 mL ethyl acetate for 48 h.

With the optimized reaction condition in hand, the scope with respect to thiophenes was examined first (Table 2). A range of thiophenes with various substituents at the C2 position were found to be suitable substrates for vicinal difunctionalization. Besides alkyl substitution (**4a-4e**), aryl-derived thiophenes (**4f-4h**) still delivered the desired products in good to excellent yields; both electron-rich (**4g**) and deficient (**4h**) aryl groups were tolerated. Interestingly, for **4g**, the C−H functionalization took place site-selectively at the thiophene site instead of the electron-rich alkoxyarenes. Many FGs were found compatible, including methoxy group (**4c**), benzyl and silyl-protected primary alcohols (**4d** and **4e**) and esters (**4h**). Note that 2-chloro and bromo thiophenes (**4i** and **4j**) were also reactive; the halogen FGs could potentially be used as a handle for further functionalization. The C2 and C3 disubstituted thiophenes also proved to be competent

substrates, giving fully substituted products (**4k-4n**) that are nontrivial to be prepared via conventional approaches. In particular, the reaction can tolerate internal alkyne (**4m**) and generate a tetrasubstituted thiophene bearing all carbon groups with three different hybridizations.

The scope with respect to aryl iodides and olefins was next explored (Table 3). Aryl iodides with an *ortho* electron-withdrawing group (EWG) were found to be most efficient, which is consistent with the preference in the standard Catellani *ortho* arylation[5] and our prior observation[9b]. Ester, amide, ketone and nitro-substituted aryl iodides served as effective electrophiles. Notably, a second iodide moiety (**5d**) not *ortho* to the EWG was compatible. Use of other aryl iodides, particularly the less reactive electron-rich ones, was challenging under the current conditions, though 3,5-bistrifluoromethylphenyl iodide gave the desired difunctionalization product in 37% yield. In addition to methyl acrylate, other Michael acceptors, such as conjugated esters (**6a-c**), amides (**6d**, **6e**) and ketones (**6f**), are also excellent coupling partners for the C5 functionalization. Encouragingly, the more electron-neutral styrene could also be efficiently coupled in 81% yield (**6g**).

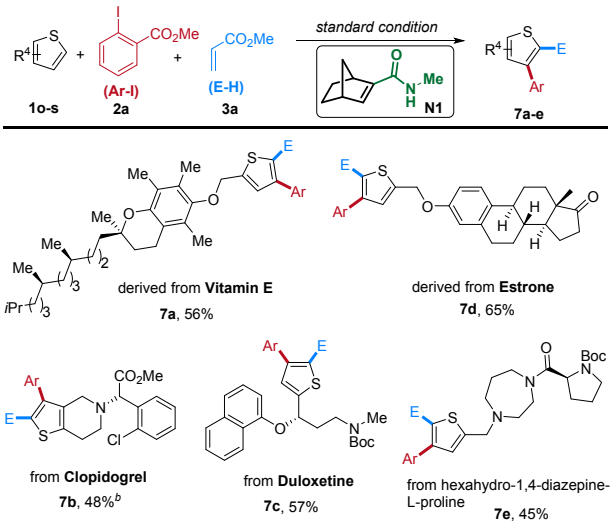
Table 3. Aryl Iodides and Olefin Scope[a]



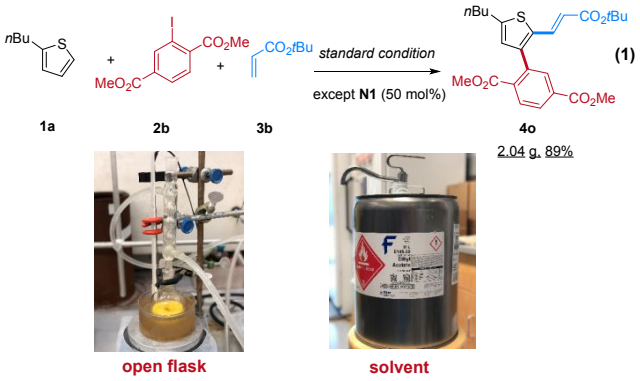
[a]The reaction was run with 0.3 mmol **1a**, 0.2 mmol **2** and 0.36 mmol **3** in 1.0 mL ethyl acetate for 48 h.

The synthetic utility of this method was first tested in the derivatization of complex bioactive compounds that contain thiophenes (Table 4). Reactions with derivatives from vitamin E (**7a**), estrone (**7d**) and hexahydro-1,4-diazepine-L-proline adduct (**7e**), clopidogrel (**7b**) and Boc-protected duloxetine (**7c**) all worked smoothly to afford the desired difunctionalized products in moderate to good yields. Additional chemoselectivity could be observed from the tolerance of electron-rich arenes (**7a**, **7c**, **7d**), ketones (**7d**), tertiary amines (**7b**, **7e**) and epimerizable stereocenters (**7b**, **7e**). In addition, this reaction is robust and scalable: a high yield was obtained on a gram scale in an open-flask operation (Eq. 1). The commercial ethyl acetate can be directly used as solvent without further purification.

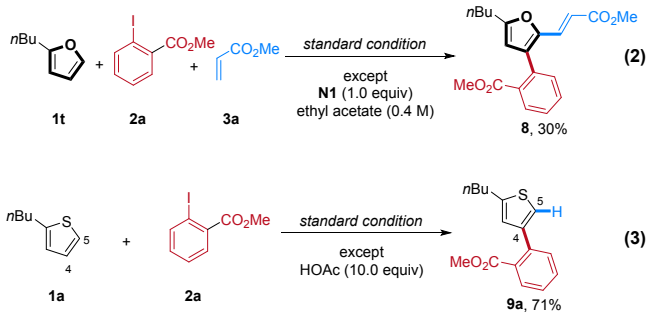
Table 4. Functionalization of Complex Bioactive Compounds[a]



[a]The reaction was run with 0.3 mmol **1**, 0.2 mmol **2a** and 0.36 mmol **3a** in 1.0 mL ethyl acetate for 48 h. [b]A pair of rotational isomers was isolated in a 1:1 ratio.



Beyond thiophenes, preliminary success was achieved using a simple furan substrate. When 2-butylfuran **1t** was subjected to the standard conditions with 1.0 equiv of **N1**, the desired trisubstituted product (**8**) was obtained in 30% yield (Eq. 2). In addition, the direct C4 arylation with protonation at the C5 position was realized with excess HOAc in the absence of acrylate **3a** (Eq. 3).[21]



Regarding the mechanistic pathway, an intriguing question is whether the reaction goes through a "coupled" difunctionalization as a regular Catellani pathway (**path a**) or a sequential stepwise C4/C5 functionalization (**path b**), i.e. C4 arylation followed by an independent C5 C−H/Heck reaction. To address this question, the kinetic profile of the model reaction was obtained (Fig. 2), which indicates that the difunctionalization product (**4a**) was formed immediately at the beginning of the reaction and there was no accumulation of the C4-arylation intermediate (**9a**) during the course of the reaction. A competition experiment further indicated that direct difunctionalization is more favorable than the C5 alkenylation (C−H/Heck) of **9a** (see Supporting Information). Taken together, these results suggest that the Heck quench at the C5 position is preferred compared to the protonation, thus supporting the "coupled" difunctionalization pathway (**path a**).

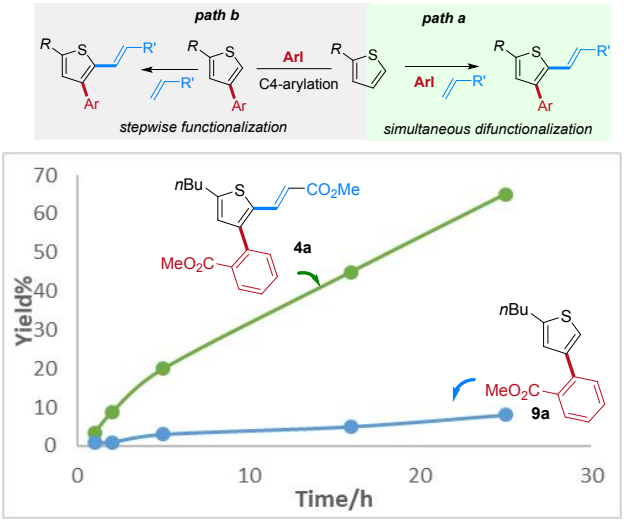


Figure 2. Kinetic Profile of the Model Reaction

In summary, a direct method for vicinal difunctionalizations of thiophenes has been developed through the Pd/NBE cooperative catalysis. The reaction exhibits excellent FG tolerance and complete site- and regio-selectivity. The mild and robust reaction condition should make it attractive for preparing complex poly-substituted thiophenes and late-stage functionalization of bioactive compounds. Efforts on disclosing the detailed mechanism, including the exact role of the amide-derived NBE cofactor, and expanding the reaction scope to other types of difunctionalizations and other electron-rich heterocycles (besides thiophenes and furans) are ongoing.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interests.

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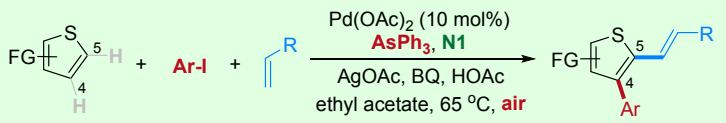
Direct Difunctionalization



* *site- and regio-selective*
* *open flask reaction*
* *broad functional group tolerance*
* *access to fully substituted thiophenes*