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PALLADIUM- AND NORBORNENE-CATALYZED SYNTHESIS OF HIGHLY FUNCTIONALIZED THIOPHENES: THE REMARKABLE EFFECT OF ELECTRON-POOR OLEFINS AS LIGAND

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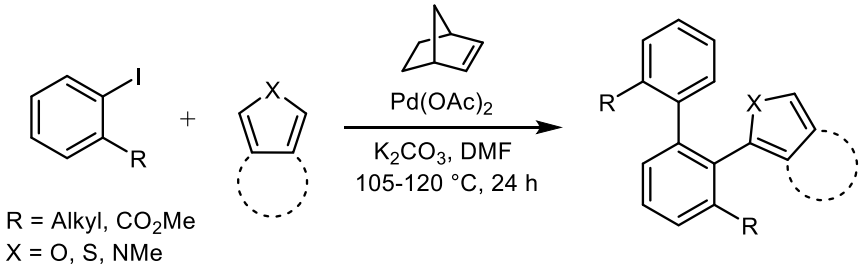
Abstract – Highly functionalized heterocyclic compounds were synthesized by palladium and norbornene catalysis starting from *ortho*-substituted aryl iodides, aryl bromides and 3,4-ethylenedioxythiophene. The addition of methyl cinnamate to the reaction mixture was found to be crucial in order to obtain selectively the unsymmetrical product.

Dedicated with respect to Professor Dr. Masakatsu Shibasaki on the occasion of his 70th birthday

Palladium and norbornene catalysis, the so called Catellani reaction, has been largely employed in the construction of heterocyclic compounds.[1] Carbazoles, phenanthridines, dibenzopyrans and dibenzo[*b,f*]azepines can be effectively synthesized in a one-pot reaction from easily available reagents by exploiting this singular methodology.[2] *ortho*-Teraryls were obtained in satisfactory to high yields from *ortho*-substituted aryl iodides and a five-membered aromatic heterocycle, using palladium acetate and norbornene as catalysts, potassium carbonate as a base in DMF under mild conditions (Scheme 1).[3] Best results were achieved when the electron rich 3,4-ethylenedioxythiophene was employed.

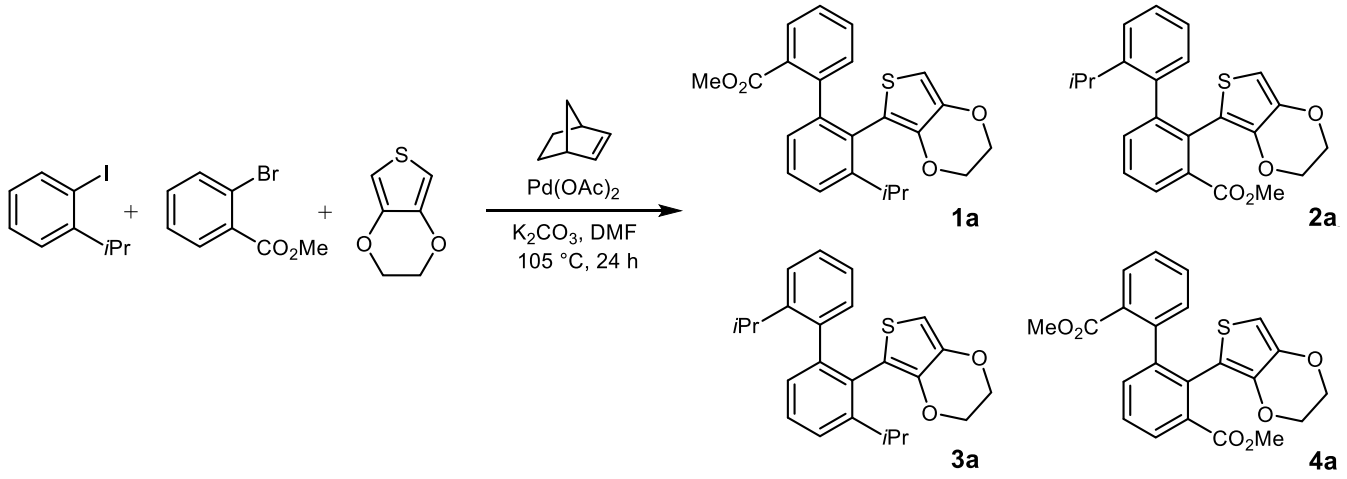
The reaction involves intermolecular aryl–aryl and aryl–heteroaryl bond formation in sequence by double C-H bond activation.[3] Remarkably, the whole process does not need additional ligands. We anticipated that the reaction can be extended to the non-symmetrical case by using an *ortho*-substituted aryl iodide and an aryl bromide, instead of two molecules of aryl iodide. However, yields and selectivities of products containing both the aryl moieties turned out to be unsatisfactory.



Scheme 1. Palladium- and norbornene-catalyzed functionalization of heterocycles

Herein we report an efficient and selective palladium- and norbornene-catalyzed synthesis of highly functionalized thiophenes starting from *ortho*-substituted aryl iodides, aryl bromides and 3,4-ethylenedioxythiophene through the use of a suitable electron poor olefin as ligand.

Our first investigations were carried out employing *ortho*-isopropyliodobenzene, 2-carbomethoxybromobenzene and 3,4-ethylenedioxythiophene as starting reagents, palladium acetate and norbornene as catalysts, potassium carbonate as a base in DMF at 105 °C (Scheme 2 and Table 1). Based on our previous studies, four products can be virtually obtained from these pool of molecules: the compounds **1a** and **2a**, which incorporate one fragment from each halide reagent, and products **3a** and **4a**, resulting from the Catellani-type homocoupling of *ortho*-isopropyliodobenzene and 2-carbomethoxybromobenzene, respectively (Scheme 2).



Scheme 2. Possible products using two different aryl halides

As expected, when the reaction was carried out without additives, a mixture of **1a**, **3a** and **4a** was obtained (in 30, 22 and 29% yield respectively upon warming the mixture for 24 hours). Surprisingly, compound **2a** was not detected. Moreover, product **1a**, analogously to **3a**, was present as a 2:1 mixture of two diastereoisomers as confirmed by NMR analysis (see supporting information).

We next examined the reaction profile through time. Samples were periodically collected, dried in vacuum and analyzed by NMR to determine the relative ratio of **1**-**4a**. Interestingly, at the beginning of the reaction, **4a** only forms. Its concentration increases fairly linearly during the first four hours up to 28%, as estimated by ^{1}H NMR, while key resonances of both **1a** and **3a** remain still barely visible. At this point, the conversion of the aryl bromide is around 45%, while that of the iodide is negligible. During the next four hours of the experiment desired product **1a** forms selectively (28% upon 8 hours), likely owing to concentration effects. Indeed, the amount of **4a** did not change and the aryl bromide is almost completely consumed. Then, the remaining unreacted iodide (40%) can just provide product **3a** (22% upon 24 hours) by continuing to warm the reaction mixture overnight. Taken together, these results show an apparent higher reactivity towards palladium of the aryl bromide compared to its iodide peer (for a possible mechanistic rationale, *vide infra*). To reduce the amount of undesired compounds **3a** and **4a**, we resorted to test the effect of various ligands on the outcome of the reaction (Table 1).

Table 1. Effect of olefins[a]

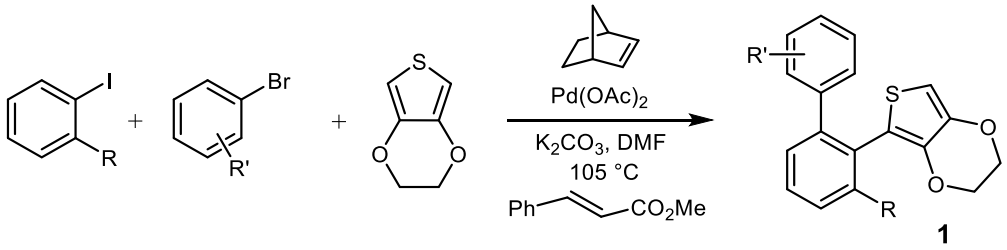
Entry	Olefin (equiv)	Time (h)	Yield[b] (%) of **1a**	Yield[b] (%) of **3a**	Yield[b] (%) of **4a**
1	-	18	30	22	29
2	dimethyl maleate (4)	22	57	2	6
3	**methyl cinnamate (4)**	**19**	**68**	**3**	**7**
4	methyl crotonate (4)	22	26	3	9
5	methyl cinnamate (2)	22	59	5	16
6	methyl cinnamate (8)	22	60	4	6
7[c]	methyl cinnamate (4)	20	63	4	7
8[d]	methyl cinnamate (4)	40	58	6	10
9[e]	methyl cinnamate (4)	64	60	3	6

[a] *Reaction conditions*: 2-isopropyliodobenzene (1 equiv, 0.36 mmol), 2-carbomethoxybromobenzene (1 equiv), 3,4-ethylenedioxythiophene (2.5 equiv), $Pd(OAc)_2$ (5 mol%, 0.018 mmol), norbornene (1 equiv), olefin and K_2CO_3 (2.2 equiv) in DMF (8 mL) at 105 ˚C. [b] NMR yields. [c] 2 equivalents of norbornene were used. [d] 5 equivalents of 3,4-ethylenedioxythiophene were used. [e] 16 mL of DMF were used.

Upon lackluster screening of phosphinic species, we turned to electron poor disubstituted olefins, which recently proved to have a dramatic effect on the selectivity of a similar sequence involving boronic acids.[4] To our delight, the addition of 4 equivalents of dimethyl maleate to the reaction mixture allowed to improve selectivity and, consequently, yield of **1a** increased to 57% (Table 1, entry 2). Even better result was achieved employing methyl cinnamate in place of dimethyl maleate, reaching 68% yield of **1a** (Table 1, entry 3). When methyl crotonate was employed, the reaction resulted in a lower yield and selectivity (Table

1, entry 4). The optimal amount of methyl cinnamate was confirmed to be 4 equivalents (compare entry 3 with entries 5 and 6), in particular with just 2 equivalents, compound **4a** was formed in a considerable amount (16% yield, entry 6). Other reaction parameters were then explored using methyl cinnamate as additive of choice (Table 1, entries 7-9). In all cases the reaction outcome proved to be slightly less efficient.

Table 2. Synthesis of compounds **1**[a]



Entry	R	R'	Time (h)	Yield[b] (%) of **1**
1	*i*Pr	2-CO_2Me	19	**1a** 65
2	*i*Pr	3-CO_2Me	72	**1b** 59
3	*i*Pr	4-CO_2Me	72	**1c** 78
4	*i*Pr	3-CF_3	24	**1d** 74
5	*i*Pr	4-CF_3	19	**1e** 64
6	CF_3	2-CO_2Me	24	**1f** 67
7	CF_3	4-CO_2Me	36	**1g** 62

[a] *Reaction conditions*: *ortho*-substituted aryl iodide (1 equiv, 0.36 mmol), aryl bromide (1 equiv), 3,4-ethylenedioxythiophene (2.5 equiv), $Pd(OAc)_2$ (5 mol%, 0.018 mmol), norbornene (1 equiv), methyl cinnamate (4 equiv), K_2CO_3 (2.2 equiv) in DMF (8 mL) at 105 ˚C. [b] Isolated yields.

With the optimized conditions in hand (Table 1, entry 3), the scope of this multicomponent reaction was then investigated (Table 2). The reaction of *ortho*-substituted aryl iodides with aryl bromides bearing an electron withdrawing group at the *ortho*, *meta* or *para* position of the phenyl ring proceeded smoothly to give the corresponding products **1a-g** in 59-78% yields. An electron-donating or an electron-withdrawing group on the aryl iodide is well tolerated (R = *i*Pr, CF_3), while, on the aryl bromide, only electron-withdrawing substituents such as R' = CO_2Me, CF_3 afforded compound **1** with good yield and selectivity. It is worth noting that the tolerance of an ester group (R' = CO_2Me) on the aromatic ring in this synthesis offers an opportunity for subsequent transformations for the preparation of more complex molecules.

Pivoting on present results and previous mechanistic studies, we propose the following rationale to account the selective formation of **1** in these sequences (Figure 1).[1,2]

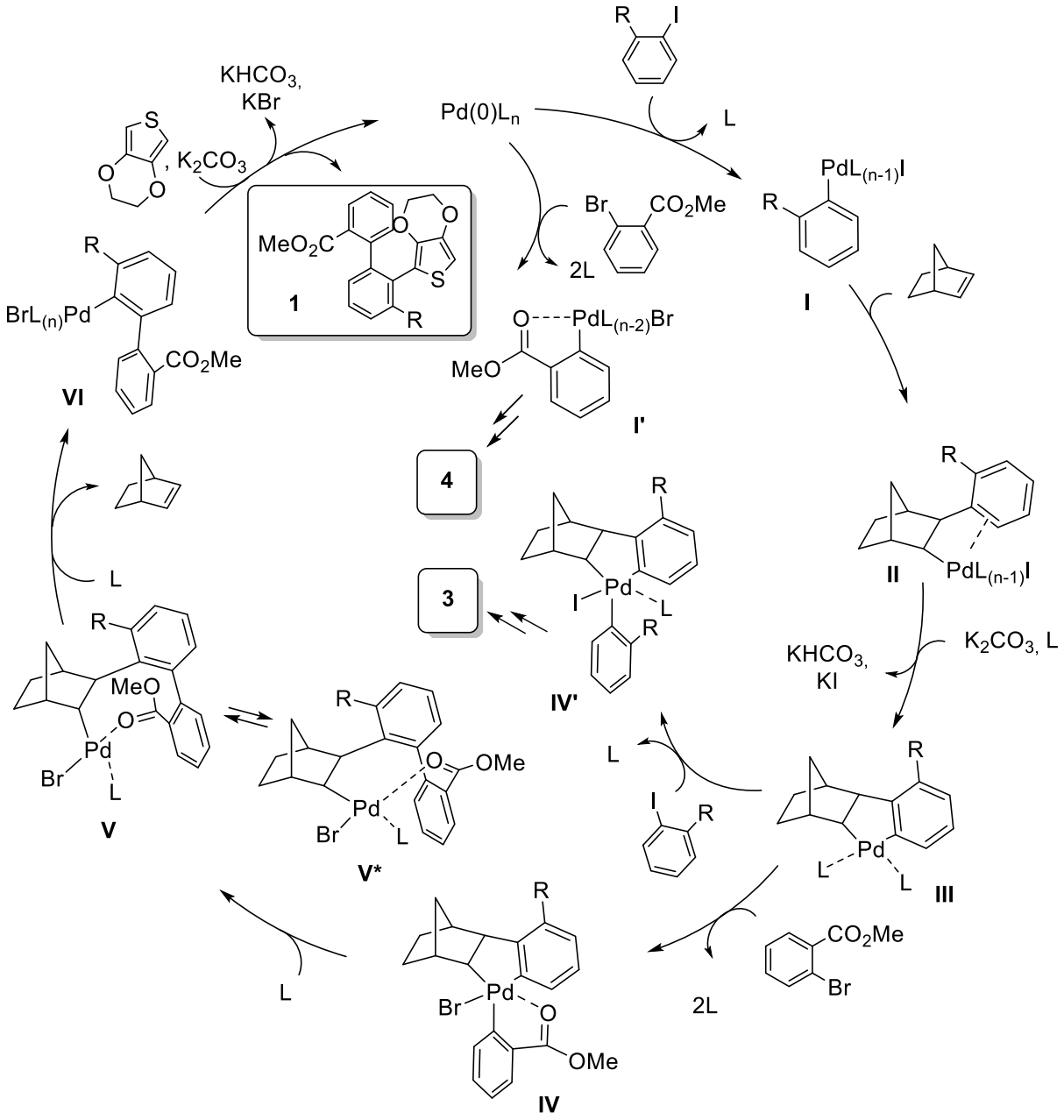


Figure 1. Proposed mechanistic rationale

The reductive environment ensures the reduction of the metal salt to a relatively low-ligated Pd(0) species,[5] which could then oxidatively insert into a C-X bond. Two competitive pathways could then take place, delivering either Pd(II) complex **I** or **I'**. The former exploits the relative lability of the carbon-iodide bond while the latter could take advantage from the presence of heteroatoms, which could favor metal coordination, in its substituent *ortho* to the C-Br bond. This strategy has become a routine tool in Pd(II) catalyzed reactions, involving either C-H or C-X functionalization.[6] In our case, the relative easiness of this

step, which would eventually yield undesired teraryls **2** and **4**, could be smoothened by the presence of an electron poor olefin. Its low-lying LUMO should indeed favor its coordination to electron rich Pd(0) species and thus depress the effect of substituents on aromatic substrates by increasing the metal coordination number.[7] It is worth noting that electron poor olefins are a useful tool to stabilize electron-rich Pd(0) species and could allow the isolation of the corresponding complexes too.[8] This effect depress the relative rate of formation of **I'** and enables the presence in solution of a higher concentrations of **I**. In this scenario, the role of the electron poor olefin evenly correlates with the reaction profile observed without it, which showed a faster reaction of the aryl bromide instead (*vide supra*). Sequential norbornene insertion (**II**) and C-H activation could thus yield selectively metallacycle **III**, likely through the assistance of a sufficiently basic species.[9] Once again, two competitive oxidative additions could then take place, providing either Pd(IV) complex **IV** or **IV'**.[10] In this case, however, the outcome is orthogonal to the previous one. The relative hindrance of **III** compared to **I** together with the higher π-acidic character of Pd(II) species compared to their Pd(0) peers favor the activation of the C-Br bond over that of a C-I one. The aryl bromide takes thus advantage of its reduced size and could benefit from the presence of an ortho-directing group to provide selectively **IV**.[11] Regioselective reductive elimination allows then the formation of the biaryl unit of complex **V**, which releases norbornene thanks to steric congestion.[1,2] The resulting Pd(II) complex **VI** could then react with the heterocycle to eventually provide desired teraryl **1** *via* thiophene C-H activation.[3,12] The relative position of substituents on **1** shrinks its degree of rotational freedom[13] and its two element of axial chirality account for the experimental formation of a mixture of two diastereoisomers (in 2:1 ration for **1**, *vide supra*).[11] Remarkably, complete diastereocontrol is observed instead when stable metal chelation takes place, as a result of atroposelective Pd(IV) reductive elimination that locks the relative configuration of stereogenic centers formed in beyond this step.[14] This confirms the relative lability of interactions between heteroatoms on aryl bromides used herein and the metal center, which could allow the formation of equilibriums between intermediates as, for instance, **V** and **V*** before the non-reversible formation of the C-C bond that ends the sequence, eventually providing a mixture of diastereoisomers of **1**. The role played by the electron poor olefin enables the control of the reactivity of the two aryl halides over the two oxidative addition steps and results thus crucial to control the outcome of the whole sequence.[15] In this case, the cinnamate could be regarded as a competitive ligand that exerts a different force depending on the formal oxidation state of the metal throughout the catalytic cycle.

In summary, we reported a catalytic method for the selective synthesis of highly functionalized polycyclic thiophenes from commercial reagents under relatively mild conditions. The key parameter for the selectivity of the process relies on the choice of a suitable electron poor olefin that mediates the reactivity of the two potentially competing aryl halides used as reagents towards Pd(0) and Pd(II) intermediates involved in the sequence.

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