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C–H Functionalization

S,O-Ligand-Promoted Pd-Catalyzed C–H Olefination of Thiophenes

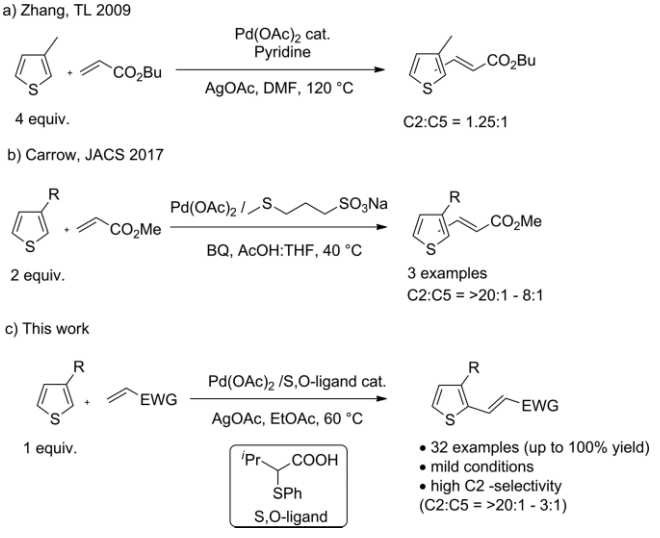
Yolanda Álvarez-Casao[a] and M. Ángeles Fernández-Ibáñez*[a]

Dedicated to Professor Henk Hiemstra on the occasion of his retirement from the University of Amsterdam.

Abstract: An efficient Pd^{II} catalyzed C–H olefination of thiophenes has been developed using an easily accessible bidentate S,O-ligand. The catalytic system promotes the C-2 olefination of a wide range of thiophenes bearing both, electron donating and withdrawing groups under mild conditions. This methodology provides a direct path towards the synthesis of 2,3-disubstituted thiophenes, which are difficult to obtain via other C–H functionalization routes. The S,O-ligand is responsible for the broad substrate scope and high levels of C-2 selectivity in 3-substituted thiophenes.

Introduction

Thiophenes are important motifs in biologically active molecules and functional materials.[1] Common methods to alkenylate 5-membered aromatic heterocycles involve formylation and subsequent Wittig reaction[2] or the Mizoroki–Heck cross coupling.[3] However, these protocols suffer from the disadvantage of requiring prefuntionalized starting materials. In the last decades, metal-catalyzed C–H functionalization reactions has become an attractive and synthetically powerful alternative to functionalize 5-membered aromatic heterocycles.[4,5] In the particular case of palladium-catalyzed C–H functionalization of thiophenes, the vast majority of the reported reactions take place at the most acidic C-2 position. However, when 3-substituted thiophenes are used, addressing selective C–H functionalization at the more hindered C-2 position remain challenging.[6–8] For instance, the C–H olefination of 3-methylthiophene with butyl acrylate have been reported to preferentially occur at the C-2 position albeit with low selectivity (C2/C5 = 1.25:1) (Scheme 1a).[7a] Recently, high levels of C-2 selectivity in the C–H olefination of three different 3-substituted thiophenes with methyl acrylate in the presence of a monodentate anionic thioether ligand have been reported (Scheme 1b).[7b] Herein, we report an efficient C-2 olefination of thiophenes promoted by a Pd/S,O-ligand based catalyst (Scheme 1c). The reaction proceeds under mild conditions with a broad range of thiophenes bearing electron donating and withdrawing groups. Remarkably, good levels of C-2 selectivity are achieved using 3-substituted thiophenes (Scheme 1c).



Scheme 1. Pd-catalyzed C-2 C–H olefination of thiophenes.

Recently, our group has discovered a new family of S,O-bidentate ligands that are capable of promoting Pd-catalyzed C–H olefination reactions of non-directed arenes.[9] We found out that besides accelerating the reaction, the S,O-ligand influences the site-selectivity of the process with preferential functionalization at the most electronrich position of the arene. Then, we hypothesized that using our Pd/S,O-ligand catalyst in the C–H olefination of thiophenes, high levels of C-2 selectivity and a broad substrate scope could be achieved.

Results and Discussion

We started our investigations using 3-methylthiophene as a model substrate in the reaction with butyl acrylate in the presence of 5 mol-% of $Pd(OAc)_2$/3-methyl-2-(phenylthio)butanoic acid (**L1**). After screening different oxidants, temperatures and

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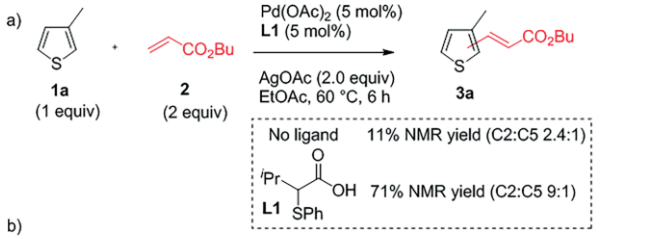
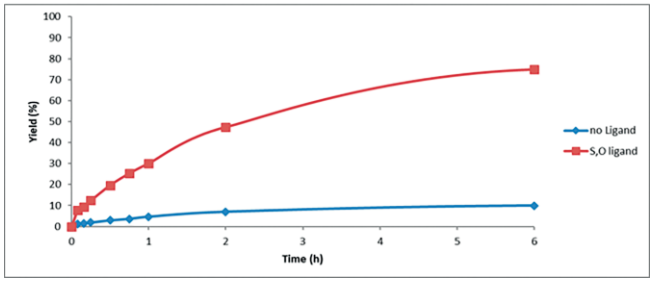
solvents (see Supporting Information) we established as optimal reaction conditions the use of AgOAc as oxidant in EtOAc and stirring the reaction at 60 °C. Under these conditions, we were pleased to find out that the C–H olefination of 3-methylthiophene furnished the desired olefinated product **3a** in 71 % NMR yield with high C-2 selectivity (9:1) (Scheme 2a). We also observed the formation of the di-olefinated product **3a′** in 25 % NMR yield (see Supporting Information for further details). In contrast, the reaction without ligand provided the olefinated product in low yield and C-2 selectivity (C2/C5 = 2.4:1). The kinetic profile of both, the reaction with and without ligand, further proved that the S,O-ligand accelerated the reaction rate dramatically (Scheme 2b).

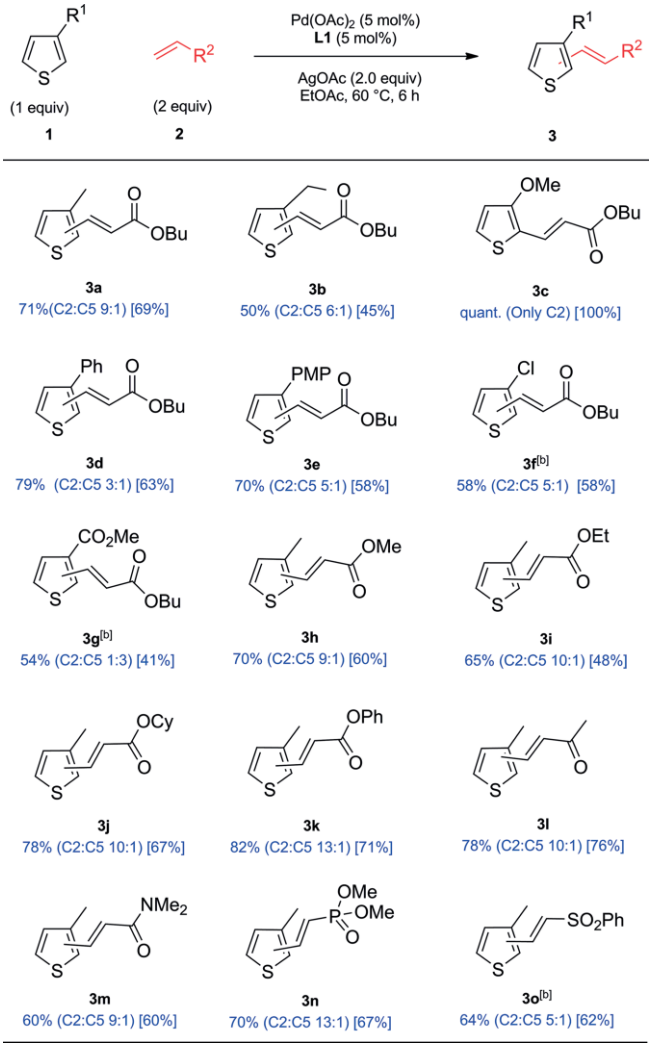




Scheme 2. S,O-Ligand promoted Pd-catalyzed C-2 olefination of thiophenes.

With the optimized conditions in hand, several thiophene derivatives bearing both electron withdrawing- and electron donating groups at the C-3 position were tested (Table 1). The reaction of 3-ethylthiophene provided the desired C-2 olefinated product **3b** in moderate yield and slightly lower selectivity (C2/C5 = 6:1) than the 3-methylthiophene. Perfect C-2 selectivity and quantitative yield was obtained using 3-methoxythiophene. 3-Phenylthiophene reacted to form the olefinated product **3d** in 63 % yield with moderate C-2 selectivity (C2/C5 = 3:1). When the thiophene is substituted with a more electron rich aromatic ring, namely 3-(*p*-methoxyphenyl)thiophene, the olefinated product **3e** was obtained in good yield and with better C-2 selectivity (C2/C5 = 5:1) than using 3-phenylthiophene. When the reaction was performed with 3-chlorothiophene the olefinated product **3f** was obtained in good yield and still in good C-2 selectivity (C2/C5 = 5:1). As expected, when the thiophene is substituted with a strong electron withdrawing group such as methyl ester, the olefination occurred mainly at the C-5 position (C2/C5 = 1:3). After proving the generality of the catalyst to enhance the C-2 selectivity in diverse 3-substituted thiophenes, different activated olefins were tested. The reaction of 3-methylthiophene with methyl, ethyl, cyclohexyl and phenyl acrylates furnished the desired olefinated products **3h**–**3k** in good yields (48–71 %) and high C2-selectivities (C2/C5 > 9:1 in all cases). Other activated olefins such as methyl vinyl ketone, vinyl amide and vinyl phosphonate reacted efficiently to form the olefinated products **3l**–**3n** in good yields and C-2 selectivities (C2/C5 > = 9:1). The reaction with vinyl sulfone gave the olefinated product **3o** in 62 % yield and with moderate C-2 selectivity (C2/C5 = 5:1). In all these reactions, except for the 3-methoxythiophene, the formation of diolefinated thiophenes at the C-2 and C-5 positions were detected (10–22 %) (see Supporting Information for further details). In addition, we performed all these reactions in the absence of the S,O-ligand (see Supporting information for the results) and we ascertained that the presence of the S,O-ligand is key in the reaction to obtain high yields and high levels of C-2 selectivity.

Table 1. C–H Olefination of 3-substituted thiophenes.[a]



[a] Yields and selectivities were determined by ^{1}H-NMR analysis of the crude mixture using CH_2Br_2 as internal standard. Isolated yield is given in square brackets. [b] The reaction was stirred at 100 °C.

We further studied the new catalytic system in the C–H olefination of other thiophene derivatives bearing substituents with different electronic properties at the C-2 position (Table 2). First, thiophene was used as a substrate affording the corresponding adduct **4a** in 48 % yield together with a small amount

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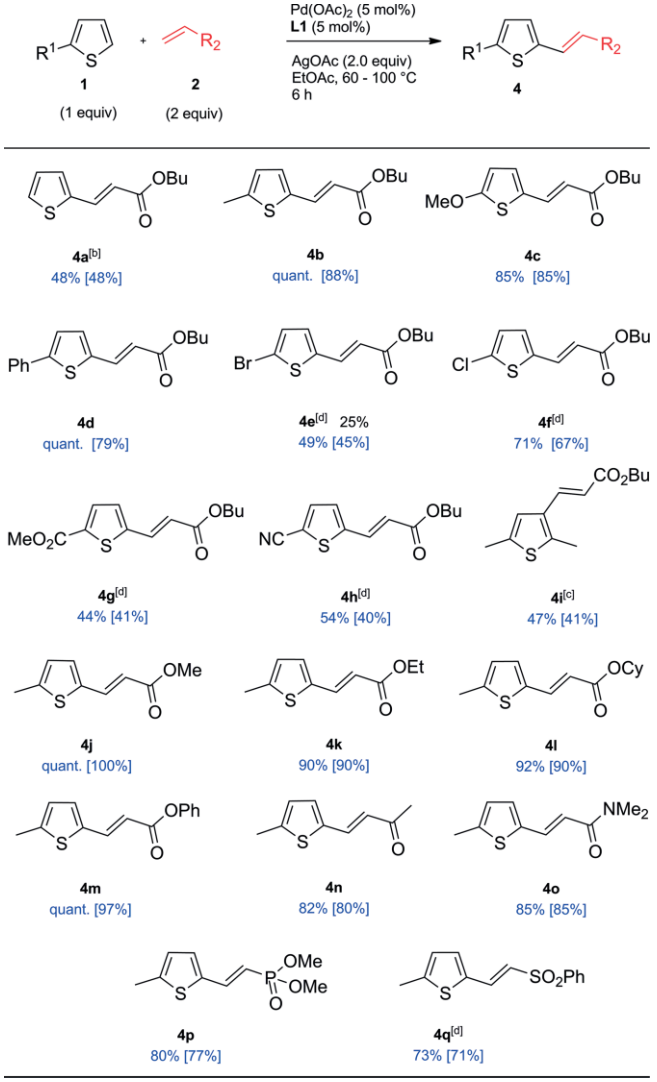
of the diolefinated product **4a'**. The reaction of 2-methyl-, 2-methoxy- and 2-phenylthiophene with butyl acrylate afforded the corresponding 2,5-disubstituted thiophenes **4b**–**4d** in excellent yields (79–88 %). Thiophenes bearing electronwithdrawing groups such as Br-, Cl-, CO_2Me- and CN were also reactive using our Pd/S,O-ligand catalytic system, although higher temperatures were required (**4e**–**4h**). Overall, the reaction showed good functional group compatibility, tolerating thiophenes bearing halogens, esters and cyanide groups. In addition, 2,5-dimethylthiophene reacted at the less activated C-3 position affording the product **4i** in 41 % yield. Finally, we tested different activated olefins in the reaction with 2-methylthiophene. As expected, in all cases the olefinated products **4j**–**4q** was obtained with excellent yields (71 %-quant).

Table 2. C–H Olefination of 2-Substituted Thiophenes.[a]



[a] Yields were determined by ^{1}H-NMR analysis of the crude mixture using CH_2Br_2 as internal standard. Isolated yield is given in square brackets. [b] 13 % NMR yield of the diolefinated product was detected in the crude mixture. [c] 10 % NMR yield of the diolefinated product was detected in the crude mixture. [d] The reaction was stirred at 100 °C.

Conclusions

In summary, we have develop a new catalytic system based on Pd/S,O-ligand, that efficiently promotes the C-2 olefination in a wide range of thiophenes bearing both, electron donating and withdrawing groups. The catalytic system proceeds under mild reaction conditions and shows good functional group tolerance. Importantly, the methodology provides access to 2,3-disubtituted thiophenes, which are difficult to obtain as major products by other C–H functionalization routes. The presence of the S,O-ligand is key in the reaction to obtain high yields and high levels of C-2 selectivity in 3-substituted thiophenes. Further applications and mechanistic studies are currently ongoing in our laboratory.

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Keywords: C–H activation · Thiophene · S,O-ligand · Palladium · Olefination

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