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S,O-Ligand-Promoted Palladium-Catalyzed C–H Functionalization Reactions of Non-Directed Arenes

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Supporting Information Placeholder

ABSTRACT: Pd(II)-catalyzed C–H functionalization of non-directed arenes has been realized using inexpensive and easy accessible type of bidentate S,O-ligand. The catalytic system shows high efficiency in the C–H olefination reaction of electron rich and electron poor arenes. This methodology is operationally simple, scalable and can be used in late-stage functionalization of complex molecules. The broad applicability of this catalyst has been showcased in other transformations such as Pd(II)-catalyzed C–H acetoxylation and allylation reactions.

Over the past decade, metal-catalyzed C–H functionalization has emerged as a powerful methodology for the synthesis of valuable chemicals and materials.¹ This approach brings the opportunity to introduce complexity in organic molecules in a most efficient manner since no prefunctionalization of the starting materials is required. Many elegant and efficient methodologies have been described for the direct functionalization of C–H bonds, but the vast majority of these examples require the presence of a directing group to enhance the reactivity and selectivity of the process.² Reports of direct C–H functionalization of simple arenes, without a directing group, are still scarce.³ An attractive alternative to the use of directing groups is by developing suitable ligands that may lead to the discovery of new catalytic systems capable of promoting these transformations. However, to date, the arsenal of ligands that enable metal-catalyzed C–H functionalization reactions is very limited.⁴ The research in our group aims at the development of novel ligands/catalytic systems capable of promoting selective C–H functionalization reactions to broaden the applicability of this strategy in organic synthesis. In this field, groundbreaking developments by the groups of Yu,⁵ Sanford,⁶ Stahl⁷ and Glorius⁸ have identified pyridine-based ligands as very versatile and efficient ligands for non-directed Pd-catalyzed C–H functionalization reactions. In the particular case of the Pd-catalyzed C–H olefination (Fujiwara-Moritani reaction) of simple arenes,⁹ Yu's initial report shows good results with electron poor arenes using a bulky pyridine ligand.⁵ Subsequent investigations on the topic from Sanford's group describe the beneficial effect of 3,5-dichloropyridine ligand as a promotor of the Fujiwara-Moritani reaction for electron rich and electron poor arenes.¹⁰

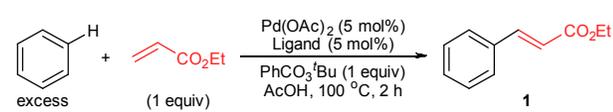
Recently, our group reported an increase in reactivity and site selectivity in the C–H acetoxylation of simple arenes in the presence of picolinic acid ligands.¹¹ We postulate that the carboxylic

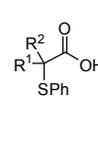
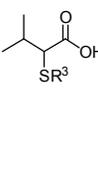
acid functionality of the picolinic acid ligand promotes the C–H bond cleavage *via* a concerted metalation-deprotonation (CMD) mechanism.¹² In addition, the chelating ability of the ligand enhances the stability of the catalyst. However, the irreversible formation of an inactive palladium complex bearing two picolinic acid molecules is a major drawback for this system. We envisioned that a bidentate ligand with weaker coordination ability to Pd(OAc)₂ than the bidentate picolinic acid ligand would lead to a more efficient catalyst. Thus, we decided to investigate the performance of bidentate thioethercarboxylates, which are easily accessible and have hemilabile behavior in palladium chemistry.¹³ To the best of our knowledge, this type of ligands has never been used in metal-catalysis. Here, we report the discovery of a new class of S,O-ligands, that enable non-directed Pd-catalyzed C–H functionalization reactions of arenes. These S,O-ligands show higher activity and stronger influence on the site selectivity than the well-established pyridine based ligands in the C–H olefination of simple arenes. The new methodology is also successful in preparative scale and in late-stage functionalization of complex molecules, a step that could not be taken with previously described catalytic systems. Moreover, the new Pd/S,O-ligand catalyst is also active in the C–H acetoxylation and allylation of benzene.

Thioethercarboxylic acid ligands can be easily made in gram scale in two steps starting from commercially available carboxylic acids.^{14,15} We started our investigations by studying the performance of these thioethercarboxylic acid ligands in the Pd(II)-catalyzed C–H olefination reaction employing benzene and ethyl acrylate as model substrates under standard reaction conditions (Table 1). The reaction in the absence of ligand provided, after 2 h, the alkenylated product **1** in only 16% yield. In contrast, the presence of 2-ethy-2-(phenylthio)acetic acid (**L1**) resulted in an increase in yield up to 64%. Other thioethercarboxylic acid ligands with different side chain of the thioetheracetic acid were studied. Similar yields were obtained with ligands bearing aliphatic chains in α -position (**L2-L3**), including the gem-dimethyl (**L4**) and cyclopropane (**L5**) ligands. The phenylthioetheracetic acid (**L6**), 2-phenyl-2-(phenylthio)acetic acid (**L7**) and the 2-(phenylthio)benzoic acid (**L8**) furnished the olefinated product **1** in lower yields (20-40%) than **L1-L5**. We next explored the reactivity of the catalytic system regarding the substituents attached to the sulfur atom. In particular, electron rich, electron poor, bulky aromatic (**L9-L14**) and aliphatic substituents (**L15-L16**) were investigated. Unfortunately, all these ligands provided similar or slightly lower yields than those obtained with **L1-L5**, with the

exception of the bulky ligand **L10**, with a triphenylmethyl group, which did not furnish any product. The reaction with the tetrahydro-2-thiophenecarboxylic acid (**L17**) and the 2-thiophenecarboxylic acid (**L18**) provided the desired product in 61% and 26% yield, respectively. From these initial studies, we concluded that, in general, thioethercarboxylic acid ligands bearing aliphatic substituents in α -position and with a neutral aromatic ring attached to the sulfur atom constitute the most active catalyst for the Pd-catalyzed C–H olefination of benzene.

Table 1. Ligand optimization of dehydrogenative Heck reaction.



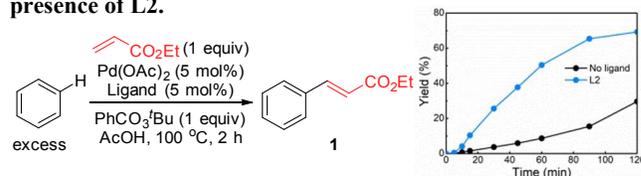
Entry	Ligand	Yield (%) ^a
1	No ligand	16
2		R ¹ Et, R ² H (L1) 64
3		R ¹ <i>i</i> -Pr, R ² H (L2) 63
4		R ¹ <i>t</i> -Bu, R ² H (L3) 64
5		R ¹ Me, R ² Me (L4) 71
6		R ¹ -CH ₂ CH ₂ -, R ² H (L5) 61
7		R ¹ H, R ² H (L6) 40
8		R ¹ Ph, R ² H (L7) 20
9		(L8) 16
10		R ³ Mes (L9) 62
11		R ³ Tr (L10) NR
12		R ³ <i>p</i> -OMe-C ₆ H ₄ (L11) 53
13		R ³ 2,4,6-(OMe) ₃ -C ₆ H ₂ (L12) 40
14		R ³ C ₆ F ₅ (L13) 39
15		R ³ <i>p</i> -CF ₃ -C ₆ H ₄ (L14) 46
16		R ³ CH ₂ C ₆ H ₅ (L15) 37
17	R ³ <i>i</i> -Pr (L16) 44	
18		(L17) 61
19		(L18) 26
20		(L19) 16
21		(L20) 20
22		(L21) 27
23		(L22) 37

^aYields were determined by ¹H NMR analysis of the crude mixture, using CH₂Br₂ as internal standard.

The kinetic profile in Scheme 1 clearly indicates that 2-*i*-propyl-2-(phenylthio)acetic acid (**L2**) increased the reaction rate dramatically. Having established the positive effect of the S,O-ligand in the dehydrogenative Heck reaction, different experiments were conducted to ascertain the role of each functionality in the ligand (Table 1). First, we performed the reaction with the corresponding sulfoxide (**L19**) and sulfone (**L20**) to confirm that these species are not responsible for the observed catalytic activity. Indeed, the reaction in the presence of either of these ligands proceeded with similar outcome as the reaction carried out without any ligand. The use of thioanisole (**L21**) or methyl 2,2-dimethyl-2-(phenylthio)acetate (**L22**) as ligands furnished the olefinated product **1** in 27% and 37% yield, respectively. These

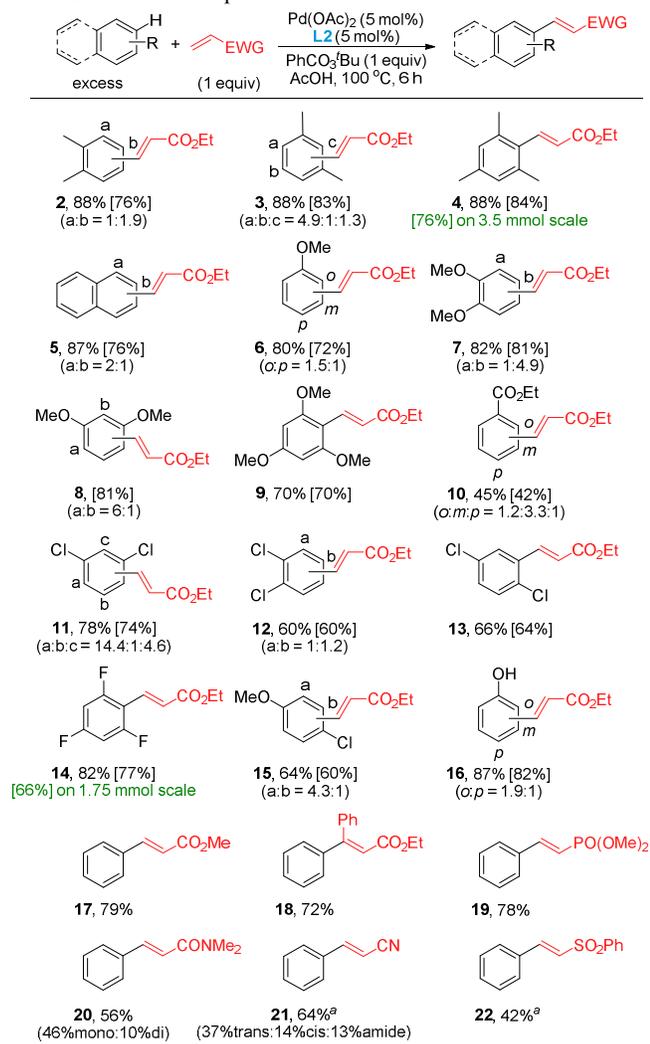
results confirmed that the presence of both functionalities, the thioether and the carboxylic acid, are crucial for the acceleration of the reaction. Different conditions for the oxidative Heck reaction were examined in the presence of **L2** (see Supporting Information, Table S2-S5), but no improvement was observed compared to the standard conditions.

Scheme 1. Kinetic profile of the dehydrogenative Heck coupling of benzene and ethyl acrylate without ligand and in the presence of L2.



With the optimized conditions in hand, we set out to explore the substrate scope of this transformation with different substituted arenes (Table 2).¹⁶ All the reactions were carried out in a pressure tube using 5 mol% of catalyst and stirring at 100 °C for 6 h. At this time, the formation of Pd black was observed in most cases. The reaction of arenes with alkyl substituents such as *ortho*- and *meta*-xylene and mesitylene provided the alkenylated products **2**, **3** and **4** with excellent yields (76%, 83% and 84%, respectively). Regarding the selectivity, the *ortho*-xylene provided a 1:1.9 ratio of the α (a) and β (b) isomers, respectively and the *meta*-xylene provided a mixture of isomers (a:b:c = 4.9:1:1.4 ratio) in favor of the less sterically *ortho* olefinated product. In a similar manner, 76% yield was obtained in the reaction using naphthalene as starting material with a ratio 2:1 in favor to the α -olefinated product **5**. We also tested the reaction of arenes bearing strong electron donating groups. Excellent yields were obtained employing anisole, 1,2- and 1,3-dimethoxybenzene and 1,3,5-trimethoxybenzene as starting materials (70-82%). Anisole provided a 1.5:1 ratio of the *ortho* and *para* isomers, respectively and only traces of the *meta* isomer were detected. 1,2-Dimethoxybenzene yielded a 1:4.9 ratio of the corresponding α (a) and β (b) isomers. Similarly, the C–H olefination of 1,3-dimethoxybenzene occurred mainly at the least sterically hindered C–H bond at the *ortho* position of the methoxy group (6:1 ratio). The C–H olefination of electron poor arenes was also explored. The reaction with ethyl benzoate provided the desired olefinated products **10** in 42 % yield as a mixture of isomers in favor of the *meta* olefinated product (*o*:*m*:*p* = 1.2:3.3:1). When 1,2- 1,3- and 1,4-dichlorobenzene were employed as starting materials the desired products were obtained as mixture of regioisomers in good yields (60-74%). The reaction with 1,3,5-trifluorobenzene furnished the desired product **14** in 77% yield. When 4-chloroanisole was subjected to standard reaction conditions, the olefinated product **15** was obtained in 60% yield in 4.3:1 ratio in favor of the *ortho* product respect to the methoxy substituent. Moreover, the direct C–H olefination of unprotected phenol provided the *ortho*- and *para*-olefinated product **16** in excellent yield (82%) and in a ratio of 1.9 to 1, respectively. Taking into consideration that only few reports deal with the direct functionalization of phenols, both the yield obtained and the preference for the *ortho* olefination are remarkable.¹⁷ In all cases, we observed much higher yields using **L2** in comparison with those in which the ligand was absent (see Supporting Information, Table S6). Finally, the C–H olefination in preparative scale using mesitylene and 1,3,5-trifluorobenzene as starting materials afforded the corresponding olefinated products **4** and **14** with good yields without any significant erosion from the original values.

Table 2. Substrate scope.



Yields were determined by ¹H NMR analysis of the crude mixture using CH₂Br₂ as internal standard. Isolated yield was given in square bracket. ^aThe reaction was stirred overnight.

Regarding the site selectivity of the reaction, our results indicate that it is mainly dictated by the substrate and controlled by electronic factors, with preferential functionalization at the most electronic-rich position in the arene. However, when we compare the site selectivity of the reaction with and without **L2**, it is evident the influence of **L2** on the site selectivity (see Supporting Information, Table S6). In Table 3, we show some substrates where different trend in site selectivity in the presence of **L2** was observed in comparison with the reaction without ligand. The reaction of naphthalene in the absence of ligand provided a 1 to 1 ratio of isomers versus the 2 to 1 ratio obtained in the presence of **L2** in favor to the *α*-olefinated product. The reactions of anisole or phenol without ligand provided a mixture of *ortho*- and *para*-products with a clear preference for the former. In contrast, in the presence of **L2**, the *ortho*-olefinated products were preferred. On the other hand, similar trend in the site selectivity of the reaction of naphthalene and anisole was observed without ligand and with 3,5-dichloropyridine, which was the best ligand reported by Sanford for the C–H olefination of simple arenes.¹⁰ The reaction of phenol using 3,5-dichloropyridine provided a mixture of *ortho*- and *para*-products in 50% NMR yield with a small preference for the *ortho*-product (1.4o:1p). These results indicate that the S,O-ligand has stronger influence on the site selectivity of the C–H olefination reaction than the pyridine-based ligand.

Table 3. Comparison of the site selectivity.

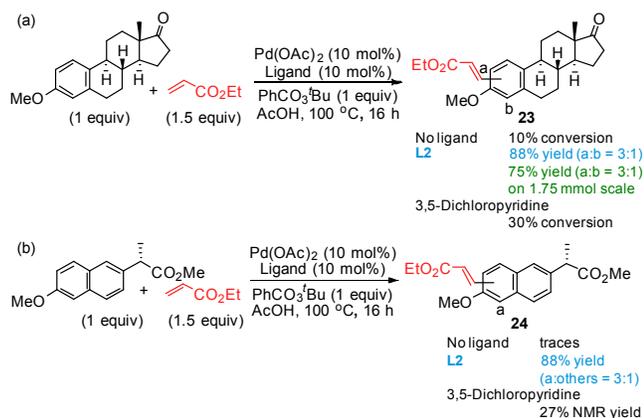
Ligand	a : b	o : m : p	o : p
No ligand	1 : 1	1 : 0 : 1.7	1 : 1.3
L2	2 : 1	1.5 : 0 : 1	1.9 : 1
3,5-Dichloropyridine	1.1 : 1 ^a	4.1 : 1 : 7.4 ^a	1.4 : 1

The site selectivity was determined by ¹H NMR analysis of the isolated olefinated product. ^aSite selectivity reported previously in ref. 10.

Next, we explored the olefin scope. The reaction with methyl acrylate and ethyl cinnamate furnished the olefinated products **17** and **18**, respectively, in high yields. Other electrophilic alkenes such as vinyl phosphonates, vinyl amides, vinyl nitriles and vinyl sulfonates reacted efficiently with benzene, leading to the olefinated products **19–22** in good yields (42–78%). Unfortunately, we did not observe any improvement in the yield using non-activated alkenes such as styrene when using **L2** in comparison with the reaction without ligand.

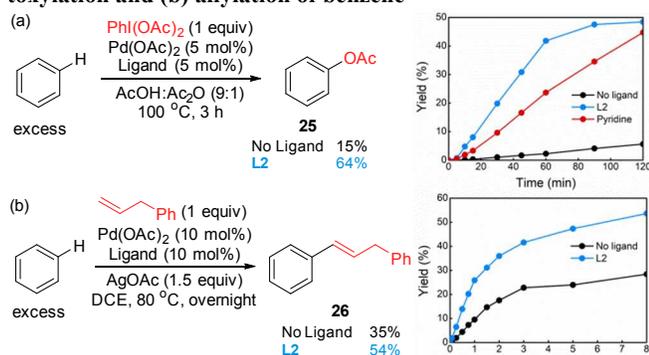
Having revealed the high reactivity of the new catalytic system in simple arenes, we assessed the suitability of this methodology for late-stage functionalization of complex molecules (Scheme 2). To the best of our knowledge, the intermolecular Fujiwara-Moritani reaction of arenes without directing groups, has not been applied in late-stage functionalization. The reaction of *O*-methylestrone (1 equiv) with ethyl acrylate (1.5 equiv) and 10 mol% of Pd(OAc)₂ provided the desired product **23** in only 10% conversion. In contrast, when the reaction was carried out in the presence of **L2**, the olefinated product **23** was obtained in 88% yield as a mixture of *ortho*-olefinated isomers respect to the methoxy substituents (a:b = 3:1). Moreover, we compared our catalytic system with the one previously reported by Sanford for the C–H olefination of simple arenes using 3,5-dichloropyridine as ligand.¹⁰ Under the same reaction conditions, only 30% conversion was obtained. Similarly, when the reaction of the naproxen derivative was carried out in absence of ligand, only traces of olefinated product **24** were detected by ¹H NMR. The same reaction in the presence of **L2** furnished a mixture of products with a combined isolated yield of 88%, being the main isomer the *ortho*-olefinated product respect to the methoxy substituent (a:other isomers = 3:1). Again, for comparison, we performed the reaction of the naproxen derivative using 3,5-dichloropyridine as ligand. Under the standard conditions, we obtained a mixture of olefinated products in 27% NMR yield. To further prove the applicability of the new catalytic system, the C–H olefination in preparative scale of *O*-methylestrone (1.75 mmol) was performed. To our delight, comparable yield than to the original value was found.

Scheme 2. Late-stage C–H olefination of (a) estrone and (b) naproxen derivatives



In search for a general and efficient catalytic system capable of promoting a large number of C–H functionalization reactions, we decided to test **L2** in C–H acetoxylation and allylation reactions (Scheme 3). The C–H acetoxylation reaction was performed using benzene as substrate and $\text{PhI}(\text{OAc})_2$ as oxidant. Under the standard reaction conditions, the presence of **L2** significantly increased the reaction rate of the process. A 64% yield was reached compared to the 15% obtained in the absence of the ligand (Scheme 3a). We monitored the reaction over time with **L2** and without ligand. Also, the reaction in the presence of pyridine was carried out for comparison.^{6a} The kinetic profile of these reactions indicates that the presence of **L2** dramatically accelerated the reaction. Moreover, the S,O-ligand showed higher activity than the pyridine ligand. In addition, the C–H allylation reaction using benzene and allylbenzene as substrates was also conducted with and without **L2**.¹⁸ Again, we observed an acceleration of the reaction rate in the presence of the S,O-ligand **L2** and the corresponding allylated product was obtained in 54% yield (Scheme 3b). In this case, no acceleration using pyridine as ligand was observed.

Scheme 3. S,O-Ligand promoted Pd-catalyzed (a) C–H acetoxylation and (b) allylation of benzene



The precise role of the S,O-ligand in the C–H olefination, acetoxylation and allylation reactions remains under investigation.¹⁹ However, considering that the C–H activation of the inert C–H bond of the arene is common in all these transformation, it seems reasonable to propose that the S,O-ligand is assisting the C–H bond cleavage.

In summary, we have found a new catalytic system based on $\text{Pd}(\text{OAc})_2$ and easily accessible S,O-ligands that enables non-directed C–H functionalization reactions of arenes. The catalyst promotes the C–H olefination reaction of both, electron rich and

electron poor arenes in high yields. Remarkably, the Pd/S,O-ligand system shows higher activity and influence in the site selectivity than the well establish Pd/pyridine-based catalytic system. The catalytic power of the new methodology is convincingly demonstrated in late-stage functionalization of complex molecules. Furthermore, the new catalyst is also active in the C–H acetoxylation and allylation reaction of benzene. We expect this new class of ligands to find broad application in C–H functionalization reactions.

ASSOCIATED CONTENT

Supporting Information

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

Experimental procedures and compounds characterization (PDF)

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Notes

The authors declare no competing financial interests.

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- (15) The preferred ligand **L2** is prepared in one step from commercial available 2-bromo-3-methylbutanoic acid in 73% isolated yield. See Supporting Information.
- (16) We also tested the reaction of other arenes in the presence of **L4** (NMR yields): naphthalene 89% (2.2a:1b); mesitylene 93% and 1,3,5-trifluorobenzene 62%. The yields obtained are similar or lower than the ones provided using **L2** as ligand.
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- (19) In our preliminary investigations on the mechanism of this transformation, we have isolated and fully characterized by X-ray analysis the palladium complex bearing two molecules of **L4** attached (CCDC 1567101 contains the supplementary crystallographic data for Pd[OCOC(SPh)Me₂]₂). The model reaction using this complex as catalyst furnished the olefinated product **1** in a similar yield (22% NMR yield) to that obtained with Pd(OAc)₂ (Table 1, entry 1), suggesting that this complex is not involved in our catalytic system.

SYNOPSIS TOC

