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S,O-ligand-promoted palladium-catalyzed C–H olefination of arenes with allylic substrates

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ABSTRACT

An efficient catalytic system for the C-H olefination of arenes with different allylic substrates is reported. The catalytic system is based on $Pd(OAc)_2$ and a readily accessible bidentate S,O-ligand. The methodology shows high activity with a wide range of arenes, including bulky and, electron-rich and -poor arenes. The applicability of this catalyst is demonstrated in the late-stage functionalization of the complex molecule *O*-methylestrone.

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In recent years, metal-catalyzed C–H functionalization reactions have become an attractive strategy to introduce complexity to organic molecules since no pre-functionalization of the starting materials is required.[1] 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 the 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 the use of suitable ligands capable of promoting these transformations.[4] We recently reported a new type of bidentate S,O-ligand, namely 2-*i*-propyl-2-(phenylthio) acetic acid (**L1**), that enables the non-directed Pd-catalyzed C–H olefination[5] of arenes with activated olefins.[6] The methodology is scalable and applicable to the late-stage functionalization of complex molecules. Although our standard reaction conditions ($Pd(OAc)_2$/**L1**; $PhCO_3{}^tBu$; AcOH) provided poor yields and did not accelerate the reaction with non-activated alkenes, the use of AgOAc in DCE was observed to have a beneficial effect in promoting the olefination of benzene with allylbenzene when **L1** was present in the reaction mixture (Scheme 1).[7]

Inspired by this preliminary result, we decided to explore the scope of the new catalytic system in the C–H olefination of arenes with allylic substrates, including allyl acetate and *N*-allylphthalimide. Herein, we report the S,O-ligand promoted palladium(II)-catalyzed C–H olefination of arenes with allylic substrates. The new methodology is suitable for a wide range of arenes and allylic substrates and its applicability is demonstrated in the late-stage functionalization of a complex molecule.

We started our investigation optimizing the reaction conditions by testing several solvents, oxidants and palladium sources (see ESI for further details). However, no improvement was observed in comparison with the original conditions (10 mol% $Pd(OAc)_2$, 10 mol% **L1**, 1.5 equiv. AgOAc, DCE, 80 °C). With the optimized conditions in hand, we then explored the scope of the reaction with respect to the arene and allyl partners (Table 1). The reaction of naphthalene with allylbenzene provided the desired allylated products **2** in high yield (89%) (Entry 1). Similarly, the reaction with *o*-xylene and anisole furnished the allylated products **3** and **4** in good isolated yields, 62% and 68%, respectively (Entries 2 and 3). We also studied the generality of this reaction using other allylic substrates such as allyl acetate and *N*-allylphthalimide. These allyl substrates have been scarcely used in coupling reactions due to the low selectivities regarding the Pd insertion (internal *vs* terminal) and the β elimination (β-H *vs* β-OAc or β-NPhth and styrenyl *vs* allylic).[8] Using our method, the reaction of allyl acetate with benzene, naphthalene or arenes with alkyl substituents, such as *o*-xylene, *m*-xylene and mesitylene, provided the desired allylated products in good isolated yields (53–75%,

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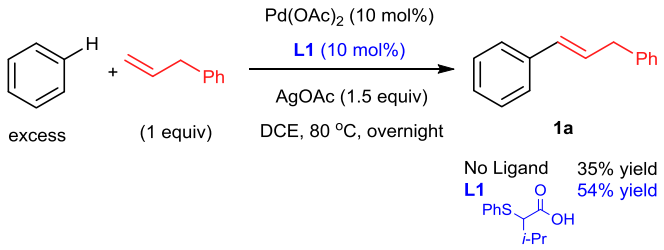
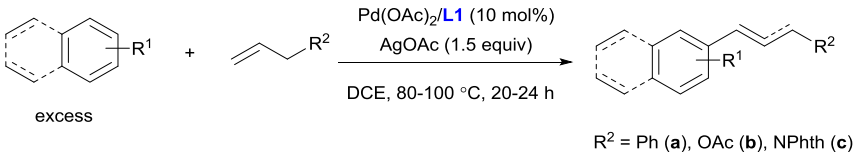


Scheme 1. S,O-Ligand promoted C–H olefination of benzene.

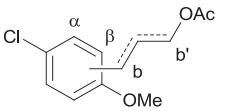
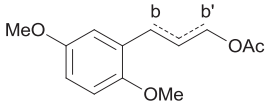
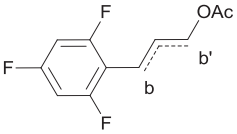
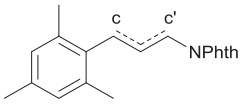
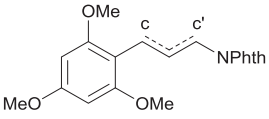
Entries 4–8). Other arenes with different electronic properties, such as anisole, 4-chloroanisole, 4-methoxyanisole and 1,3,5-trifluorobenzene were also evaluated in the reaction with allyl acetate. In all cases, the allylated products were obtained in good isolated yields (40–88%, Entries 9–12). In addition, we tested the reaction of *N*-allylphthalimide with mesitylene and 1,3,5-trimethoxybenzene. In both cases, the allylated products were isolated in good yields (73% and 61%, respectively, Entries 13–14). Importantly, in all cases, the reaction was accelerated in the presence of **L1** and low yields were obtained without the ligand after 20–24 h (Table 1, Entries 1–14). It is worth highlighting the effect of the ligand **L1** in

Table 1
Scope of the **L1**-promoted palladium-catalyzed C – H olefination with allyl substrates.



Entry	Product	Yield (%)[a] with **L1**	Yield (%)[a] [or] [b] without **L1**	α/β or *o*/*m*/*p* (%)[c]	**a/a'** or **b/b'** or **c/c'** (%)[c]	*E*/*Z* (%)[c]
1	**2a/a'**	**89**	50[a]	64/36[d]	42/58[d]	[e]
2	**3a/a'**	**62**	37[a]	38/62[d]	50/50[d]	[e]
3	**4a/a'**	**68**	37[a]	62/4/34[d]	65/35[d]	[f]
4	**5b/b'**	**65**	36[b]	–	92/8	90/10
5	**6b/b'**	**75**	55[b]	60/40[g]	95/5	[f]
6	**7b/b'**	**74**	38[b]	36/64	91/9	[f]
7	**8b/b'**	**53**	36[b]	13/65/22 (*o*/*o*'/*m*)	85/15	[f]
8	**9b/b'**	**67**	12[b]	–	71/29	86/14
9	**10b/b'**	**78**	38[b]	68/0/32[g]	93/7	[f]

Table 1 (*continued*)

Entry	Product	Yield (%)[a] with **L1**	Yield (%)[a] or [b] without **L1**	α/β or *o*/*m*/*p* (%)[c]	**a/a'** or **b/b'** or **c/c'** (%)[c]	*E*/*Z* (%)[c]
10	 **11b/b'**	**82**	30[a]	17/83	91/9	[e]
11	 **12b/b'**	**88**	47[b]	–	94/6[d]	95/5[d]
12	 **13b/b'**	**40**	25[b]	–	62/38	69/31
13	 **14c/c'**	**73**	20[b]	–	71/29	93/7
14	 **15c/c'**	**61**	36[b]	–	98/2	[f]

Reagents and conditions: arene (33 or 66 equiv.), olefin (1.0 equiv.), $Pd(OAc)_2$/S,O-Ligand (10 mol%), AgOAc (1.5 equiv.), DCE, 80–100 °C, 20–24 h.

[a] Isolated yield.

[b] Calculated yield based on ^{1}H-NMR yield using dibromomethane as an internal standard.

[c] Determined by ^{1}H-NMR analysis of the isolated mixture.

[d] Determined by GC analysis.

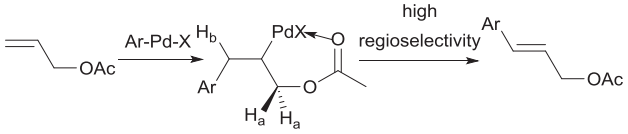
[e] No *Z* isomer detected.

[f] Traces of *Z* isomer detected.

[g] Ratio measured from the **b** isomer.

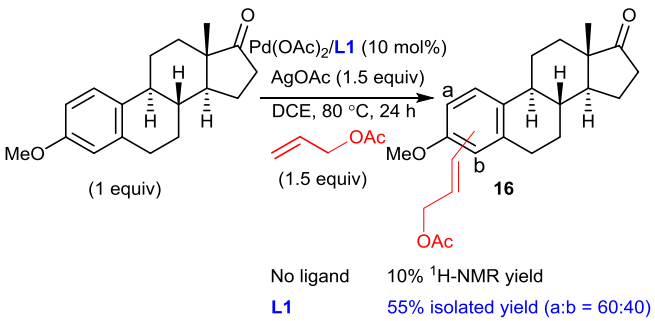
the reactivity with the bulky mesitylene. The reaction of mesitylene with allyl acetate or *N*-allylphthalimide in the absence of **L1** proceeded with conversions lower than 20%. In contrast, the allylated products **9** and **14** were obtained in 67% and 73% isolated yield, respectively, in the presence of **L1** (Entries 8 and 13). In general, the new catalytic system promoted the allylation of a wide variety of arenes including bulky, electron-rich and electron-poor arenes, providing a broader substrate scope than the majority of the reported examples.[7–9] With respect to other arenes, we found that the reaction of different dichlorobenzene derivatives provided the corresponding allylated products in low yields, with and without **L1**. Regarding the site-selectivity of the process, the allylation reaction takes place, preferentially, at the most electron-rich position in the arene (see α/β or *o*/*m*/*p* values in Table 1). Similar behaviour was observed in our previous work using activated olefins.[6]

Concerning the selectivity of β-hydride elimination in the reaction with allylbenzene, a *c.a.* 1:1 mixture of isomers was observed (Entries 1–3).[9] For the olefination reactions with allyl acetate or *N*-allylphthalimide, more complex mixtures of products can be formed.[8] However, in all of the examples evaluated, we observed only the products from internal carbopalladation (Entries 4–14). After the carbopalladation step, β-OAc [or β-(NPhth)] elimination or β-hydride elimination can take place. However, under our reaction conditions, we did not detect the products derived from β-OAc [or β-(NPhth)] elimination. Furthermore, with respect to the β-hydride elimination pathway, although two possible products can be formed, we observed mainly the products from the β-hydride elimination that leads to the double bond in conjugation with the arene. This high regioselectivity has been previously attributed to chelation between the O and the Pd atom.[7,8a,8b] This chelation impedes rotation around the C–C bond and therefore, hinders the *syn* relationship between the Pd and H_a (Scheme 2).



Scheme 2. Source of the high observed regioselectivity.

To this general trend, we found that the reaction with mesitylene and 1,3,5-trifluorobenzene afforded the allylated products **9**, **13** and **14** with moderate regioselectivity (71/29 for mesitylene and 62/38 for 1,3,5-trifluorobenzene; Entries 8, 12 and 13, respectively). In addition, some isomerization of double bond to the *Z* isomer occurred in the reaction of these arenes with allyl acetate (Entries 8 and 12). The low regioselectivity observed can be explained by the steric hindrance of the arene, which hampers rotation around the C–C bond, disfavouring the *syn* relationship between the Pd and H_b.[10]



Scheme 3. Late-stage C–H olefination of Estrone.

To further prove the generality of the new catalytic system, we applied the new developed methodology to the late-stage functionalization of a complex molecule (Scheme 3). The reaction of *O*-methylestrone (1 equiv.) with allyl acetate (1.5 equiv.) and Pd $(OAc)_2$ (10 mol%) provided the desired product in only 10% ^{1}H-NMR yield. To our delight, the same reaction in the presence of **L1**, furnished the olefinated product **16** in 55% isolated yield as a mixture of *ortho*-olefinated isomers (a:b = 60:40).

In summary, the combination of $Pd(OAc)_2$ and the bidentate S, O-ligand **L1**, was found to promote the C—H olefination of arenes with different allyl substrates, providing the desired allylated products in good yields. This transformation tolerates a wide range of arenes, including bulky, electron-rich and electron-poor arenes. The olefination reaction occurs preferentially at the most electron-rich position of the arene. Regarding the regioselectivity of the β-hydride elimination, mixtures of isomers were obtained in the reaction with allyl benzene and mainly one isomer in the reaction with allyl acetate and *N*-allylphthalimide; these results are in line with the general outcome of the Heck reaction. The applicability of the new catalytic system has been demonstrated in the late-stage functionalization of *O*-methylestrone.

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Notes

The authors declare no competing financial interest.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.2017.12.047.

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