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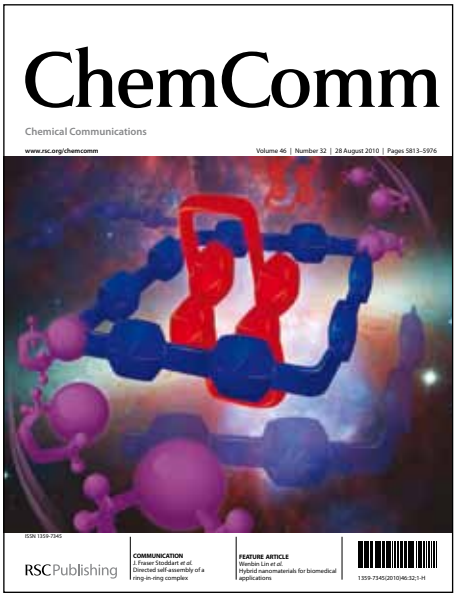

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2-Pyridylmethyl ether: a readily removable and efficient directing group for amino acid ligand accelerated *ortho*-C–H olefination of phenols

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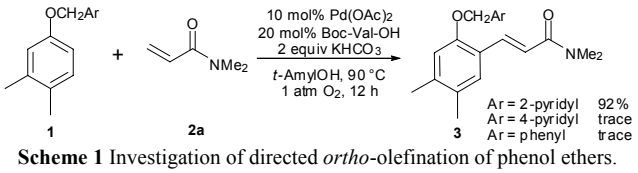
2-Pyridylmethyl ether-directed *ortho*-C–H olefination of phenols via a seven-membered cyclopalladated intermediate has been disclosed to construct a variety of *ortho*-alkenyl phenols and *ortho*-alkyl phenols.

Direct oxidative cross-coupling between arenes and olefins through the cleavage of two C–H bonds would be one of the most ideal strategies to achieve olefination of arenes.[1] Recently, a large variety of direct olefinations of aromatic C–H bonds have been reported.[2] Among these transformations, the direct *ortho*-C–H olefination of phenols is an important area of research. To control the regioselectivity of olefination of phenols, directing groups are usually introduced for the efficient activation of *ortho*-C–H bond. In spite of significant progress, the successful directing groups are under-represented so far.[3] Moreover, the substrate scope mainly includes electron-deficient alkenes and styrene-type olefins, and non-activated linear olefins have been proven to be notorious substrates. It is highly desirable to develop a new readily removable directing group for the practical and highly efficient *ortho*-C–H olefination of phenols.

2-Pyridyl is a common directing group due to its good coordination ability and compatibility with various transition metals.[4] 2-Arylpyridines and benzoquinolines have been frequently employed as the subject of the chelation-assited C–H bond functionalization, in which the process of C–H bond activation proceeds via five-membered cyclometalation.[4,5] Although such an orientating strategy is very successful, the directing group is recalcitrant and irremovable, which constrains further potential synthetic elaboration. Recently, several 2-pyridyl-based directing groups such as 2-pyridoxyl,[6] 2-pyridyl sulfoxide,[7] 2-pyridyldiisopropylsilyl[8] and 2-pyridylmethyl[9] have been developed to perform C–H bond activation through a presumed six-membered cyclometalation transition state, but usually require extra cumbersome steps to be installed and detached, and even are irremovable. The more than six-membered cyclometalated intermediate has commonly been considered more unstable than the five- and six-membered rings.[10] As a consequence, the examples of chelation-directed C–H functionalization reactions through a seven-membered cyclometalated process are fairly rare. Recently, Yu et al. and Carretero et al. reported the Pd-catalyzed C–H olefinations of 3-phenylpropionic acids and anilines via a seven-membered cyclopalladated pathway, respectively.[2h,11] Inspired by these pioneering works, we envisioned that 2-pyridylmethyl might serve as a removable and highly valuable directing and protecting group of phenols to achieve the palladium(II)-catalyzed direct *ortho*-C–H olefination through the formation of a seven-membered cyclopalladated intermediate.

In the initial experiments, 2-(pyridin-2-ylmethoxy)toluene (**1a**) was used as a model substrate for evaluating the feasibility of the hypothesis. The coupling of **1a** with *N*,*N*-dimethylacrylamide (**2a**) was investigated using the ligand developed by Yu et al.,[2h] and the *ortho*-alkenylated product (**3a**) was obtained in 17% yield (Table S1, entry 1). It was gratifying that **3a** was obtained in excellent yield (90%) in the absence of benzoquinone (BQ), and none of *para*- or *meta*-alkenylated products were observed (Table S1, entry 2). The other amino acid-derived ligands such as Ac-Val-OH, Ac-Leu-OH and Ac-Ile-OH were able to work in this transformation, but led to a slight decrease of yield (Table S1, entries 3-5). In controlled experiments, trace of cross-coupling product was observed in the absence of ligand (Table S1, entry 6). Apparently, amino acid ligands are competent in accelerating the Pd(II)-catalyzed C–H activation with 2-pyridylmethyl as a directing group. Of the oxidants screened, other oxidants such as AgOAc, $Cu(OAc)_2$, $PhI(OAc)_2$, $K_2S_2O_8$ and air were inferior to molecular oxygen (Table S1, entries 7, and 10-15).

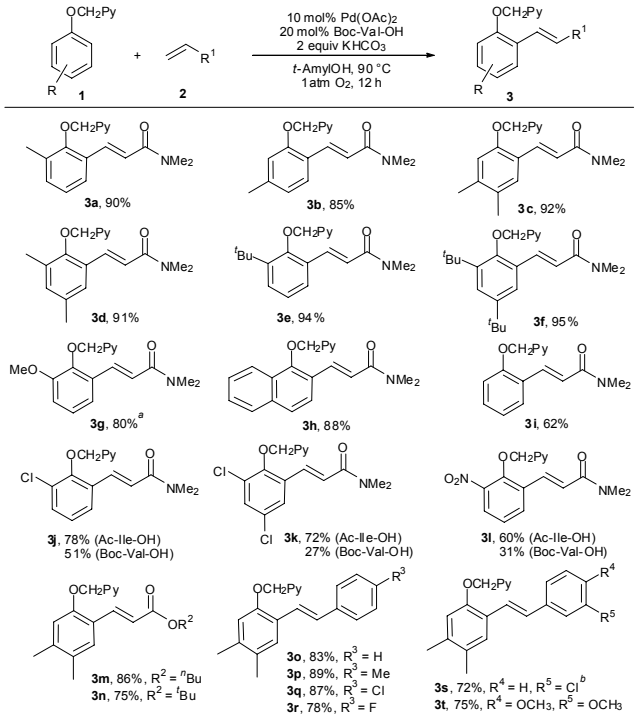


Scheme 1 Investigation of directed *ortho*-olefination of phenol ethers.

Next, the directing role of the 2-pyridylmethyl group was further examined. As shown in Scheme 1, the coupling of 1,2-dimethyl-4-(pyridin-2-ylmethoxy)benzene **1c** with **2a** could afford the *ortho*-alkenylated product in 92% yield under the optimized conditions. While the 2-pyridylmethyl group was replaced by the 4-pyridylmethyl or benzyl group, the corresponding coupling products were detected hardly. Therefore, the 2-pyridylmethyl group played an important directing role in the *ortho*-C–H olefination of phenol ether. We assumed that the 2-pyridylmethyl group might chelate palladium(II), and then lead to the formation of a seven-

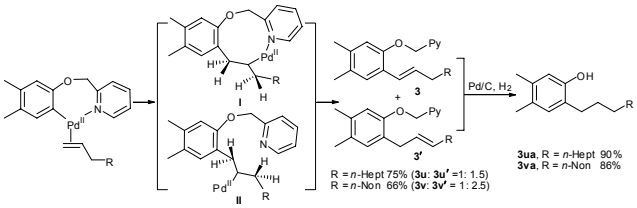
membered cyclopalladated intermediate.

Using **2a** as the olefin coupling partner, the scope of phenol ether substrates was investigated as summarized in Scheme 2. As expected, various methyl, *tert*-butyl and *othor*-methoxy substituted phenol ethers and 1-naphthol ethers could be olefinated to give the *ortho*-alkenyl phenol ethers in good to excellent yields (Scheme 2, **3a**-**3h**). The unsubstituted phenol ether can also be transformed to the *ortho*-monoalkenylated product in good yield (Scheme 2, **3i**). The chloride and nitro groups were tolerated under the optimized conditions, but gave rise to low yields. When Boc-Val-OH was replaced by Ac-Ile-OH considered as an optimal ligand for electron-poor arenes,[2h,2i] the *ortho*-alkenyl phenol ethers were obtained in good yields (Scheme 2, **3j**-**3l**).



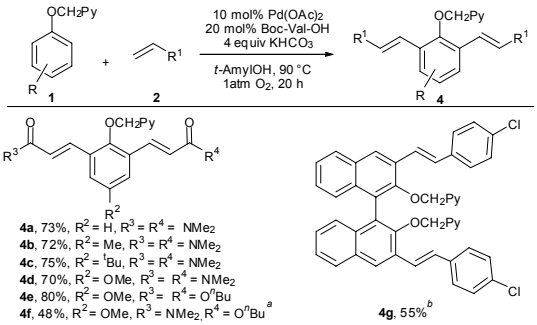
Scheme 2 Pd(II)-catalyzed direct C–H *ortho*-olefination of phenol ethers. Reactions were carried out using **1** (0.5 mmol) and **2** (0.75 mmol). Isolated yield. [a] 24 h. [b] 3-Chlorostyrene (4.0 equiv). Py = 2-pyridyl.

Subsequently, the scope of olefins was examined (Scheme 2, **3m**-**3t**). Both *n*-butyl and *t*-butyl acrylates readily reacted with **1c** to generate the *ortho*-alkenylated products in good yields (Scheme 2, **3m**-**3n**). Gratifyingly, a range of styrene derivatives, which are usually considered as lowly reactive substrates, could smoothly undergo the olefination, affording the desired products in good to excellent yields (Scheme 2, **3o**-**3t**).



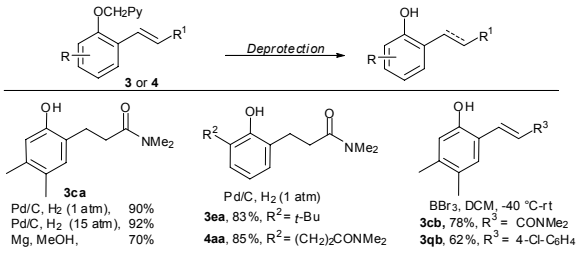
Scheme 3 Cross-coupling reaction of phenol ether with linear alkenes.

It was worth noting that the more challenging non-activated *n*-decene and *n*-dodecene could couple efficiently with **1c** to provide the corresponding alkenylated products in 75% and 66% yields, respectively (Scheme 3). Although a mixture of double bond isomerization products (**3** and **3′**) was given in both cases, a single *ortho*-alkyl substituted phenol could be obtained after the carbon–carbon double bond was hydrogenated with simultaneous removal of the protective group. We speculated that the mixture of the double bond isomerization products was generated as a consequence of different *β*-hydride elimination pathways of the cyclized intermediate **I** or the uncyclized intermediate **II** (Scheme 3).



Scheme 4 Pd(II)-catalyzed diolefination. Reactions were carried out using **1** (0.5 mmol) and **2** (2.5 mmol). Isolated yield. [a] *N,N*-Dimethylacrylamide (1.0 equiv) was initially added for 10 h, and then *n*-butyl acrylate (1.5 equiv) was added for another 10 h. [b] (±)-1,1'-BINOL.

Divinylphenol derivatives are a class of important structural motif in organic chemistry and materials science, and their synthesis has recently aroused great interest of scientists.[12] Therefore, we further expanded the scope of our methodology to diolefination of phenols. It was gratifying to find that a variety of phenol ether substrates reacted smoothly with *N,N*-dimethylacrylamide or *n*-butyl acrylate (5.0 equiv) to yield the dialkenylated products in good yields (Scheme 4, **4a**-**4e**). The unsymmetrical dialkenylated product was also successfully obtained in an acceptable yield through a Pd-catalyzed semi-one-pot procedure (Scheme 4, **4f**). Furthermore, BINOL ethers could couple with 4-chlorostyrene in 55% yield of 3,3′-bisolefinated product **4g**.

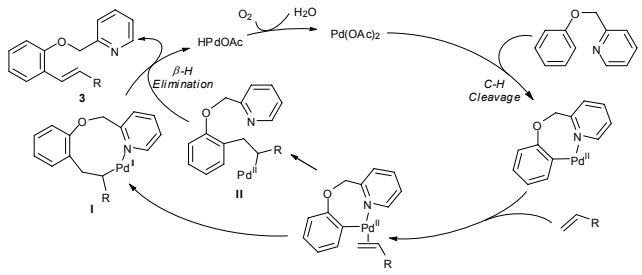


Scheme 5 Removal of the directing group.

To demonstrate the synthetic potential of this methodology, we sought to explore the possibility of removal of the directing group through using different methods. In view of the similarity between 2-pyridiylmethyl and benzyl, the catalytic hydrogenation was taken. Not surprisingly, the 2-pyridiylmethyl group of **3c** was removed successfully together with the hydrogenation of the alkenyl double bond, producing the *ortho*-alkyl phenol **3ca** in 90% (1atm) and 92% (15 atm) yields, respectively (Scheme 5). Magnesium could also reductively deblock 2-pyridiylmethyl of **3c** in methanol, and

similarly the carbon–carbon double bond was reduced (Scheme 5, **3ca**). The 2-pyridiylmethyl moiety of **3c** and **3q** could be detached easily by BBr_3 in CH_2Cl_2, and more importantly, the alkenyl was remained, giving the corresponding *ortho*-alkenyl phenols in good yields (Scheme 5, **3cb** and **3qb**).

A plausible mechanism of this transformation was illustrated in Scheme 6. The presumed seven-membered cyclopalladated intermediate was formed through the chelation-assisted *ortho*-C–H cleavage. Subsequently, the intermediate coordinated with an olefin and then formed the cyclized intermediate **I** or the uncyclized intermediate **II** via the insertion of alkene, followed by *β*-hydride elimination to give the desired product **3** together with the species HPdOAc. HPdOAc was transformed to Pd(0) through reductive elimination, which was possibly stabilized by the amino acid ligand, and was then oxidized to Pd(II) by molecular oxygen to finish the catalytic cycle.



Scheme 6 Plausible mechanism for directed *ortho*-C–H olefination.

In summary, we have demonstrated that 2-pyridiylmethyl ether can serve as an efficient directing group for amino acid ligand accelerated *ortho*-C–H olefination of phenols via a seven-membered cyclopalladated intermediate. A wide range of phenols and alkenes could be employed in this transformation, affording the *ortho*-alkenyl products with high regioselectivity in good to excellent yields. Especially, non-activated linear alkenes can serve as amenable coupling partners. This methodology can also be applied to the diolefination of phenols, providing symmetrical and unsymmetrical divinylphenol derivatives. Furthermore, the 2-pyridylmethyl group can be easily removed through several different methods, giving the *ortho*-alkenyl phenols or *ortho*-alkyl phenols. We expect that the 2-pyridylmethyl ether directing strategy would be a potential pathway to a variety of selective *ortho*-C–H functionalization of phenols.

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Notes and references

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