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Palladium-Catalyzed Oxirane-Opening Reaction with Arenes via C−H Bond Activation

Zhen Wang,[†,‡] Yoichiro Kuninobu,*[,†,‡] and Motomu Kanai*[,†,‡]

[†]Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
[‡]Kanai Life Science Catalysis Project, ERATO (Japan) Science and Technology Agency (JST), 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Supporting Information

ABSTRACT: We achieved a palladium-catalyzed C−H activation/C−C coupling reaction between arenes with a pyridyl, aminoquinolinyl, imino, or amide directing group, and oxiranes. The reaction proceeded at room temperature without any additives and tolerated a wide variety of functional groups, and the products were obtained in good to excellent yields, even on gram scale. This is the first example of a transition-metal-catalyzed intermolecular direct coupling reaction between a C−H bond of aromatic compounds and a carbon atom of oxiranes via C−H bond activation. By using *N*-methoxybenzamide as a substrate, we obtained 3-substituted isochroman-1-ones in one pot. The coupling reaction proceeded with stereoretention. Kinetic isotope effect experiments suggested that C−H bond activation is the rate-determining step.

In the last few decades, C−H bond transformations have attracted widespread attention as efficient and ideal reactions.[1] Among the transition-metal-catalyzed C−H transformations, there are several reports of C−H alkylation reactions of arenes[2] using alkyltin[3] and alkylboron[4] reagents, alkyl halides,[5] alkenes,[6] and alkanes[7] as alkylation reagents. Another possible alkylation reagent is oxiranes, and synthetically useful substituted-phenethyl alcohols could be synthesized with high atom economy if we would achieve a C−C bond formation reaction via ring-opening of oxiranes with arenes. To our knowledge, however, there is only one report of transition-metal-catalyzed, intermolecular S_N2'-type reactions via C−H activation using vinyl oxiranes as coupling partners (Figure 1a).[8−13] The S_N2-type ring-opening reactions of oxiranes by carbon nucleophiles are difficult due to low reactivity of oxiranes. For example, it is necessary to activate oxiranes by $BF_3{\cdot}OEt_2$ even when highly reactive organolithium reagents are used.[14] Here, we report a palladium-catalyzed C−H activation/S_N2-type oxirane-opening reaction with broad substrate scope (Figure 1b). This is the first example of palladium-catalyzed C−H transformation via ring-opening of strained substrates.[12,13]

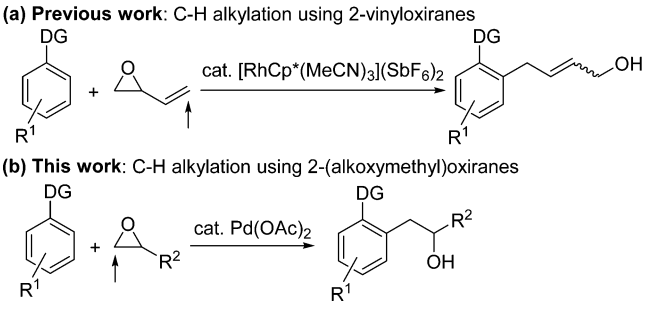

Figure 1. Examples of transition-metal-catalyzed C−C bond formation via C−H activation using oxiranes.

We initially investigated the reaction between 2-phenylpyridine (**1a**) and 2-ethyloxirane. Formation of the desired coupling product, however, was not achieved using various transition-metal salts and complexes under different reaction conditions. We thought that using oxiranes bearing additional heteroatoms, which act as catalyst coordination sites, might solve the weak coordination ability of oxiranes. Therefore, we investigated the reaction using 2-(phenoxymethyl)oxirane (**2a**), because the two oxygen atoms of **2a** should coordinate to a metal center by chelation. As a result, the desired coupling product **3a** was obtained quantitatively (Table 1).[15] This result is especially noteworthy because of the few examples of palladium-catalyzed C−H transformations that proceed at room temperature.[16]

We next explored the scope and limitations of this system under the optimized reaction conditions (Table 1). 2-Phenylpyridines bearing an electron-donating (MeO and Me) or -withdrawing (CO_2Et, Br, and F) group at the 4-position of the benzene ring coupled smoothly with oxirane **2a**, without loss of the functional groups. Although two possible regioisomers might be formed when a substituent exists at the 3-position of an aromatic ring of 2-phenylpyridines **1g** and **1h**, only single isomers **3g** and **3h** formed because the reaction occurred only at the less hindered site. The coupling reaction was not inhibited by steric hindrance from a substituent at the 2-position of **1i** and **1j**. The corresponding products **3k**, **3l**, and **3m**, derived from pyridylnaphthalenes **1k** and **1l**, and benzo[*h*]quinoline **1m**, were produced in high yields. An electron-donating or -withdrawing substituent on the pyridine ring of **1n** and **1o** was also tolerated in this reaction. The yield of alkylated product **3p** was not obviously decreased by steric hindrance from a substituent at the 6-position of the pyridine ring. An isoquinolinyl or quinolinyl group also worked as a directing group, and the corresponding alkylated products **3q**[17] and **3r** were obtained in 87% and 97% yields, respectively.

Next, we investigated coupling reactions between different type of oxiranes and arenes with different directing groups (Table 2).

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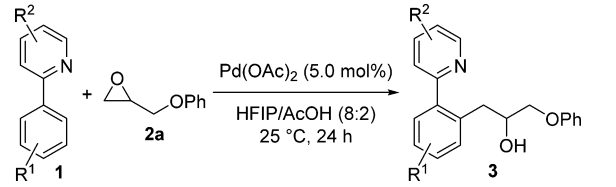
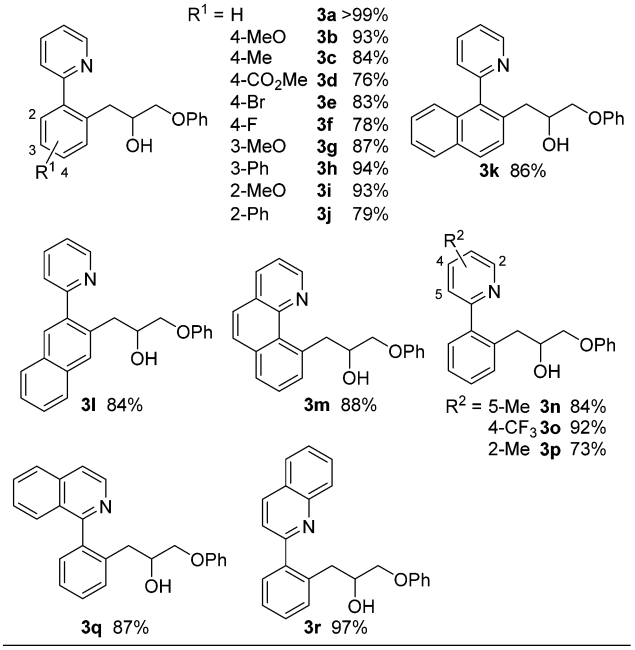
Table 1. Investigation of 2-Phenylpyridine Derivatives[a]

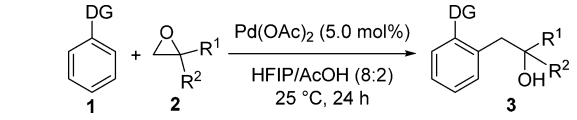


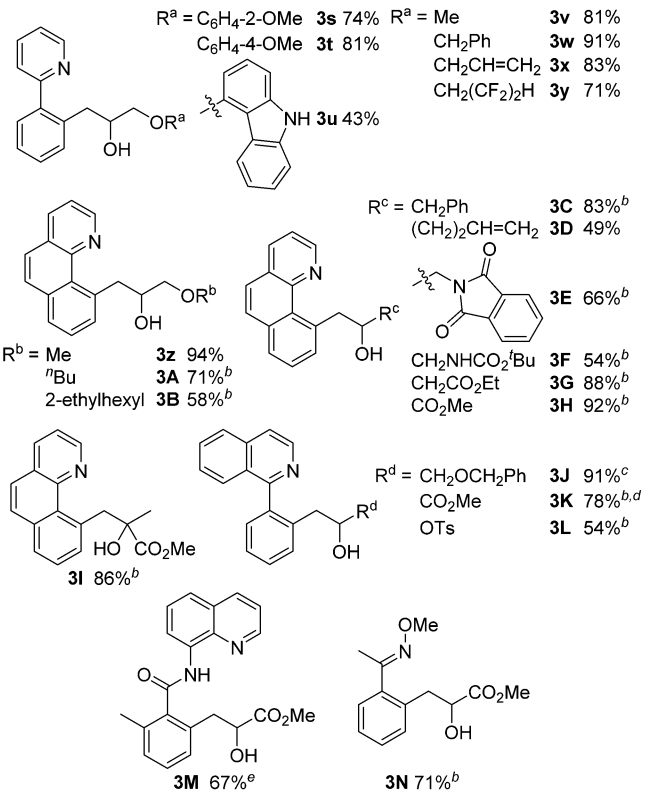


[a]Reaction conditions: **1** (0.200 mmol), **2a** (0.400 mmol), solvent (1.0 mL).

We found that a substituent on the oxygen atom of 2-(phenoxymethyl)oxirane (**2a**) could be changed to several different types of substituents. 2-(Aryloxymethyl)oxiranes produced the corresponding coupling products **3s**–**3u** in 43%–81% yields. In the case of oxirane with a 4-(9*H*-carbazolyl) group, the desired reaction proceeded without NH group protection. The corresponding coupling products **3v**–**3z**, **3A**-**3B**, **3J** were obtained in 58%–94% yields when oxiranes bearing an aliphatic substituent on the oxygen atom were used as substrates. The desired products were not produced, however, when the substituent on the oxygen atom was larger, namely, a trityl group. These results are likely due to inhibition of the coordination of an oxygen atom to a palladium center by steric hindrance. By changing 2-phenylpyridines to other aromatic compounds, such as benzo[*h*]quinoline and 1-phenylisoquinoline, the coupling reaction proceeded in good to excellent yields using a variety of oxiranes other than 2-(alkoxymethyl)oxiranes. The coupling reaction proceeded using an oxirane without an oxygen atom at the *β*-position and provided the coupling product **3C** in 83% yield. The coupling reaction had high functional group tolerance and gave the desired product with the following functional groups, including C═C double bond (**3D**), isoindoline-1,3-dione (**3E**), and carbamate (**3F**) moieties, and ester (**3G**, **3H**, **3I**, **3K**, and **3M**) and tosyl (**3L**) groups. In the case of an oxirane with a double bond, the yield of **3D** was moderate, likely due to decomposition of the palladium catalyst with the formation of a palladium black. A coupling product **3I** was also produced using a 1,1-disubstituted oxirane. By using an aromatic compound with an aminoquinolinyl directing group, the desired product **3M** was obtained in 67% yield. A coupling product **3N** was obtained

Table 2. Investigation of Aromatic Compounds 1 and Oxiranes 2[a]



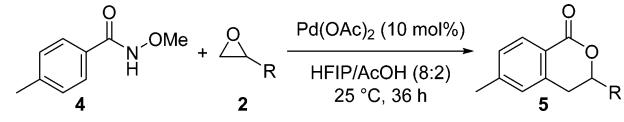


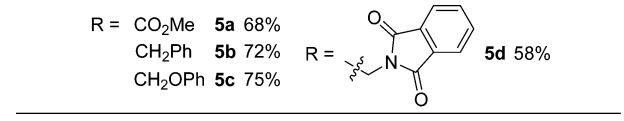
[a]Reaction conditions: **1** (0.200 mmol), **2a** (0.400 mmol), solvent (1.0 mL). [b]$Pd(OAc)_2$ (10 mol %), 36 h. [c]Ratio of rotamers = 3:1 in $CDCl_3$. [d]Ratio of rotamers = 3:1 in $CDCl_3$ or 1:1 in CD_3OD. [e]$Pd(OAc)_2$ (20 mol %).

in 71% yield using acetophenone *O*-methyl oxime as a substrate. The desired reaction did not proceed, however, using 2-vinyloxirane and 1,2-disubstituted oxiranes (methyl 3-methyloxirane-2-carboxylate and dimethyl (2*S*,3*R*)-oxirane-2,3-dicarboxylate) under the same reaction conditions.

3-Substituted isochroman-1-ones are important frameworks in natural products and pharmaceutical compounds.[18] When *N*-methoxybenzamide and oxiranes were used as substrates, coupling reaction and successive cyclization proceeded, and 3-substituted isochroman-1-ones **5a**–**5d** were obtained in 58%–75% yields (Table 3). The desired product **5b** was obtained using

Table 3. Formation of 3-Substituted Isochroman-1-ones 5 from *N*-Methoxybenzamide 4 and Oxiranes 2





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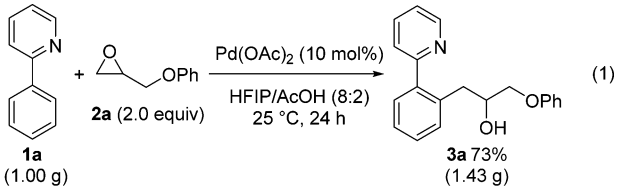
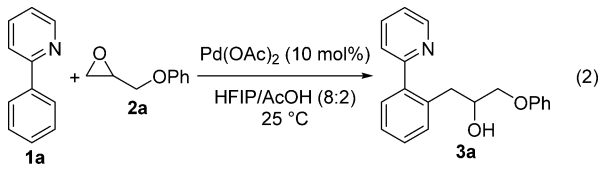
an oxirane without an additional coordinating oxygen atom, but 2-hexyloxirane did not produce a coupling product at all. This result indicated that π-electrons of the phenyl group of the oxirane might coordinate to the palladium catalyst.

The reaction could be performed on gram scale (eq 1). Treatment of 1.00 g of **1a** with 2.0 equiv of oxirane **2a** gave 1.42 g of **3a** in 73% yield.

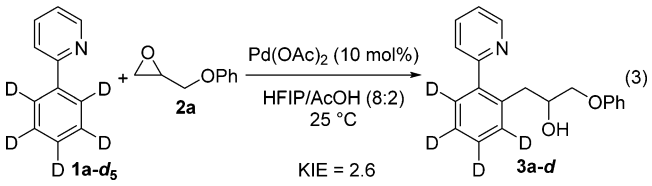


(1)

To determine the rate-determining step of the present reaction, we performed a deuterium-labeling experiment. Treatment of 2-phenylpyridine (**1a**) or deuterated 2-phenylpyridine (**1a**-d_5) with oxirane **2a** revealed a kinetic isotope effect value of 2.6. This result suggested that C−H bond activation is the rate-determining step (eqs 2 and 3; for details see Supporting Information).

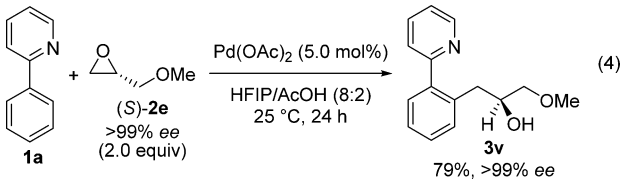


(2)

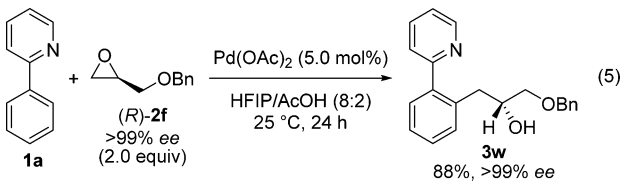


(3)

When an enantiomerically pure oxirane (*S*)-**2e** or (*R*)-**2f** was used, the coupling reactions proceeded with stereoretention and the corresponding products **3v** and **3w** were obtained in more than 99% ee (eqs 4 and 5). These findings suggested that



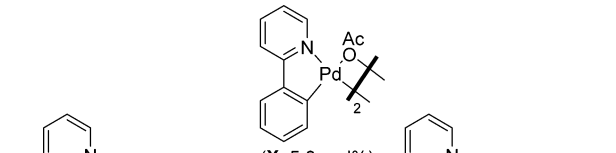
(4)



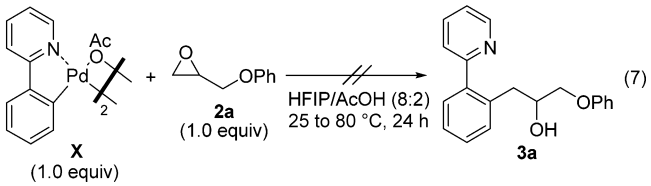
(5)

oxiranes **2** were not racemized by ring-opening and reconstruction of the oxirane rings under the reaction conditions.

In previous reports, dinuclear palladium complex **X** (eqs 6 and 7) was demonstrated to be an active intermediate for Pd-catalyzed C−H bond transformations of 2-phenylpyridines.[19] Therefore, we investigated the following two reactions: (1) a reaction between 2-phenylpyridine (**1a**) and oxirane (**2a**) in the presence of a catalytic amount of **X** (eq 6); and (2) a reaction between a stoichiometric amount of palladium complex **X** and



(6)



(7)

oxirane **2a** (eq 7). The desired coupling reaction, however, did not proceed at all even at an elevated temperature (80 °C). Based on these results, we concluded that dinuclear palladium(II) complex **X** was not a catalytic species in our reaction. The result implies that palladium(IV) species generated via oxidation by substrate oxiranes might be an active catalyst for this reaction (See Supporting Information).[19,20] Further detailed studies are required to clarify this intriguing point.

In summary, we achieved a palladium-catalyzed coupling reaction between an *ortho*-C(sp^2) atom of arenes and a C(sp^3) atom of oxiranes. This is the first example of a transition-metal-catalyzed, intermolecular direct coupling reaction between a C−H bond of arenes and a carbon atom of oxirane rings via C−H bond activation. The reaction exhibited a wide substrate scope and proceeded at room temperature in good to excellent yields without any additives, even in gram scale. By using *N*-methoxybenzamide as a substrate, we obtained 3-substituted isochroman-1-ones in one-pot. Kinetic isotope effect experiments suggested that C−H bond activation is a rate-determining step of the coupling reaction. These findings provide useful insights into synthetic organic chemistry, especially, C−H bond transformations. Further mechanistic studies are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization, and additional data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02435.

■ AUTHOR INFORMATION

Corresponding Authors

*kuninobu@mol.f.u-tokyo.ac.jp
*kanai@mol.f.u-tokyo.ac.jp

Notes

The authors declare no competing financial interest.

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(15) For the detail of optimization of reaction conditions, see Table S1.

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