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Letter

Optimization of the External Directing Group Depending on the Substrates for the Regioselective C−H Alkenylation of Phenyl Ethers

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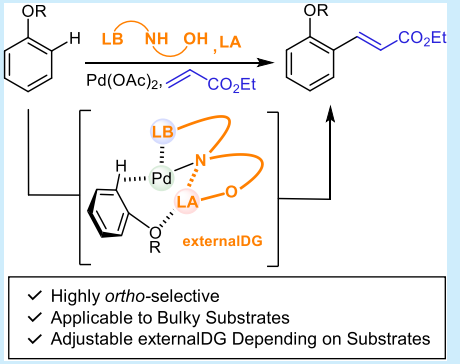
ABSTRACT: Using an external directing group (externalDG), we have succeeded in *ortho*-selective C−H alkenylation of various DG-free phenyl ethers, including bulky silyl ethers. Also, we demonstrated a strategy to develop regioselective C−H activation by optimizing externalDG depending on the substrate. The means for optimizing externalDG include the selection of the precursor, the addition of a Lewis acid, and changing the ratio of the precursor/Pd, to control the reactivity and regioselectivity.



Direct C−H functionalization is an extremely useful tool for late-stage functionalization.[1] The key to perform it is to selectively react the specific C−H bond among numerous bonds with similar properties, which is still a problem to be overcome. Among direct C−H functionalization, a great number of reactions using transition metal catalysts have been reported, and in such a reaction, a directing group (DG) that coordinates to the catalyst is necessary in the substrate to acquire regioselectivity.[2] Each of these C−H activations strictly requires a specific structure as DG, therefore making it extremely difficult to apply in general use. If C−H activations could be carried out using an auxiliary molecule that functions as DG through noncovalent bonds with the substrate, that is an external directing group (externalDG), it is expected to greatly promote the use of such reactions in general and practical synthesis.[3]

An externalDG should equip both a coordination site to the metal catalyst and a recognition site for the substrate, that is, a bifunctional molecule, which fixes a metal catalyst to the desired position on the substrate. By adjustment of both sites, flexible C−H activations can be achieved. In organic chemistry, bifunctional molecules have been developed as asymmetric catalysts[4] and are now a common concept in broad chemistry. A representative example of their application as externalDG to regioselective C−H activation is the Ir-catalyzed aromatic borylation, in which the catalyst coordination site is a bipyridyl group,[5] and concomitantly, various substrate recognition sites have been reported, some of which utilize Lewis acidic property (Scheme 1A).[5b] For another example, aromatic C−H alkenylation has been reported by Yu et al. and Maiti et al. using unique template molecules for nitrogen-containing heterocyclic derivatives (Scheme 1B),[6] and in a similar reaction for carbonyl-containing substrates, other template molecules have been reported.[7] externalDG, having phosphine oxide as the catalyst coordination site and Al linked to phosphine oxide as the substrate recognition site, was reported with Ni or Co catalyst by Ye et al. and Yoshikai et al. (Scheme 1C),[8] and such externalDG was also used for the functionalization of the formyl C−H bond in aldehydes and amides.[9] Similar alkenylation reactions toward anisole and aniline derivatives have been reported using the S,O ligand rather than DG, but the reason for the regioselectivity is unclear.[10] Particularly, Ackermann et al. have reported great regioselectivities with the same ligand in electrocatalyzed manner; however, in this reaction, the specific regioisomer is selectively oxidized to byproducts, which causes the increased regioselectivity.[10e]

This time, we have succeeded in the *ortho*-selective C−H alkenylation of various phenyl ethers using original externalDGs consisting of precursors and additional Lewis acidic metal. We were able to optimize externalDGs depending on substrates by adjusting the catalyst coordination site, substrate recognition site, and molecular framework of precursors. As a precursor of the externalDG, we used an aminoalcohol derivative that equips another Lewis basic moiety, and both the amino group and Lewis basic moiety form catalyst

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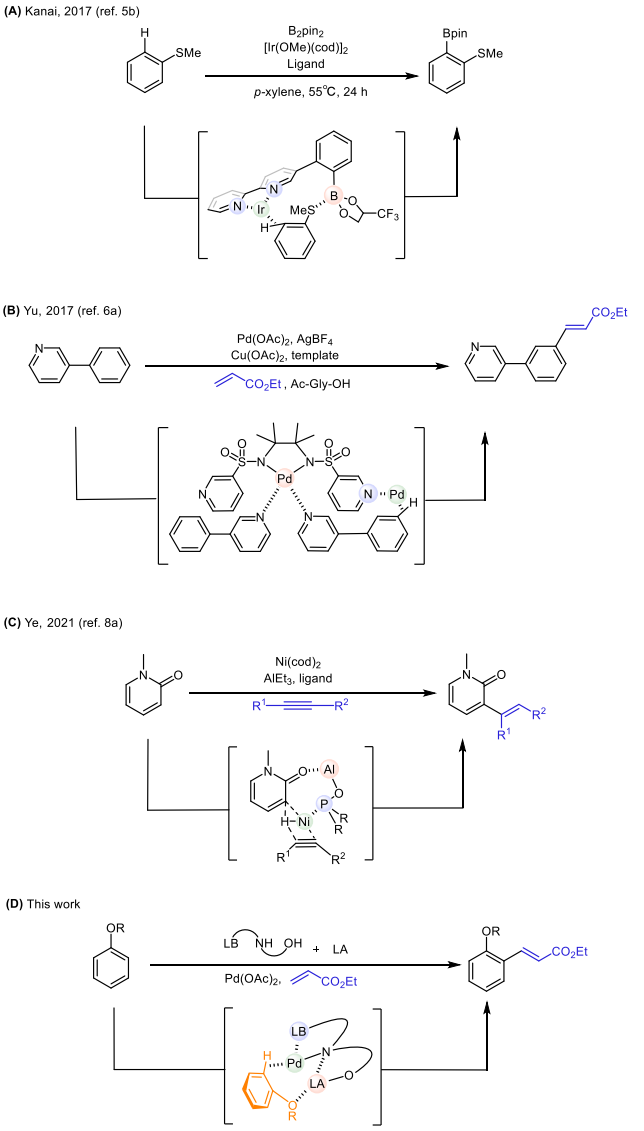
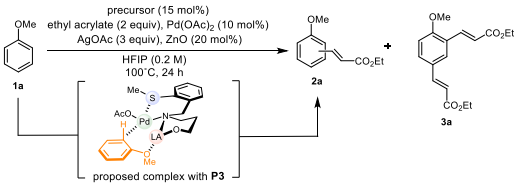
Scheme 1. Research Background and Our Design



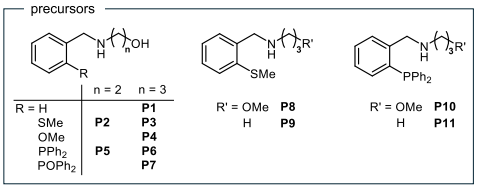
coordination sites. Furthermore, the amino and hydroxyl groups coordinate to an additional Lewis acidic metal, which serves as a substrate recognition site that captures the heteroatom of the functional group in the substrate (Scheme 1D). In these precursors, we can adjust both Lewis acidic and basic moieties, and by changing the number of methylene carbons in aminoalcohol, we are able to tweak the framework and make externalDG construct a compact and rigid spiro ring structure. In the precedent works in Scheme 1 and others, the molecular designs of externalDGs seem to be fixed or less adjustable; however, our externalDG has several adjusting points to accomplish regioselective C−H activations. We think that our approach focusing on the optimization of externalDG demonstrated one strategy toward regioselective C−H activation for DG-free substrates.

We synthesized externalDG precursors by introducing a Lewis basic moiety through the reductive amination of various aldehydes with 2-aminoethanol or 3-aminopropan-1-ol (Scheme S1A). Then, these precursors were used in the Pd-catalyzed alkenylation reaction with anisole as a substrate,[10,11] and among them, **P2**−**P7** were described in Table 1 (Table S1). In this reaction, we assumed that the complex shown in

Table 1. Evaluation of externalDG Precursors[a]



entry	precursor	ZnO	Yield of **2a** (**3a**)	*o*:*m*:*p*	*o*/*m*+*p*
1	-	-	59% (5%)	11.1:1.0:17.8	0.59
2	**P1**	-	42% (3%)	8.6:1.0:10.3	0.76
3	**P2**	-	27% (1%)	2.5:trace:1.0	2.54
4	**P3**	-	50% (3%)	2.6:trace:1.0	2.56
5	**P4**	-	39% (<11%)	10.4:1.0:12.3	0.78
6	**P5**	-	3% (0%)	>20:1.0:4.9	3.79
7	**P6**	-	3% (0%)	4.0:trace:1.0	4.02
8	**P6**	+	12% (trace)	20:1:4.1	4.07
9	**P7**	-	31% (4%)	7.9:1.0:10.0	0.70
10	**P8**	-	62% (10%)	2.8:trace:1.0	2.75
11	**P8**	+	27% (31%)	3.9:trace:1.0	3.93
12	**P9**	-	<37% (3%)	2.9:trace:1.0	2.74
13	**P10**	-	13% (1%)	>20:1.0:4.8	4.86
14	**P11**	-	17% (1%)	>20:1.0:4.0	5.18
15	**P11**	+	35% (3%)	6.3:trace:1.0	5.45



[a]Regioselectivity was determined by ^{1}H NMR analysis of the isolated olefinated product (similar to the other tables).

parentheses would be formed, affording an *ortho*-substituted product. As a control, the reaction was carried out without a precursor, and *para* selectivity appeared along with a small amount of the disubstituted compound **3a**. Similar results were obtained with commercially available *N*-benzyl-2-aminoethanol (**P1**), which lacks another Lewis basic moiety (entries 1 and 2). On the other hand, the sulfide-containing precursors (**P2** and **P3**) brought *ortho* selectivity with moderate yields, despite the absence of any additional Lewis acidic metal (entries 3 and 4). In these cases, it was expected that oxidizing agent AgOAc also acted as a Lewis acid. Using ether **P4** as a control for the sulfides, *ortho* selectivity disappeared (entry 5). Then, much better *ortho* selectivity were observed with precursors having phosphine (**P5** and **P6**), although the yields were significantly reduced (entries 6 and 7). We further tried to confirm the effect of an additional Lewis acidic metal, and after numerous investigations (Table S2), we found that ZnO was efficient for the progress of the reaction to give a relatively higher yield (entry 8). With phosphine oxide **P7** as a control for phosphines, the yield was improved but the *ortho* selectivity was lost (entry 9). From the above results, it was suggested that the appropriate Lewis basic moiety could successfully coordinate to the catalyst Pd, and if Lewis basicity was insufficient to coordinate to Pd, the background reaction not mediated by externalDG should proceed with released Pd, resulting in reduced *ortho* selectivity. The number of methylene carbons in aminoalcohol did not give a large difference to the results (entries 3 and 4 and entries 6 and 7). In all of these reactions, upon the addition of the precursor, the substrate remained, and a significant decrease in reactivity was observed. We assumed that the hydroxyl group of precursors could make a bond with catalyst Pd to form an inactive state (*vide infra*). Therefore, we prepared the precursors whose hydroxyl groups were replaced with a methoxy group (**P8** and

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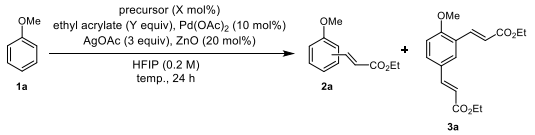
P10) or removed (**P9** and **P11**) (Scheme S1C), and we tried the same reaction. With regard to the sulfide-containing precursors, **P8** afforded a better yield without compromising regioselectivity, and additional ZnO brought much higher reactivity to increase **3a**, which affected the apparent regioselectivity and made the correct value difficult to determine. On the other hand, **P9** reduced reactivity (entries 10−12). With regard to phosphine-containing precursors **P10** and **P11**, relatively higher reactivity was observed with improved regioselectivity, and additional ZnO to **P11** afforded product **2a** in 35% yield and the highest regioselectivity (5.45) (entries 13−15). Based on these results, we further investigated optimal reaction conditions with **P8** and **P11**.

Using **P8**, the lower reaction temperature brought the reduced reactivity and improved regioselectivity, and the prolonged reaction time afforded the better yield with amounts of **3a** (Table 2, entries 1 and 2). Adding ZnO to these

Table 2. Optimization of Reaction Conditions



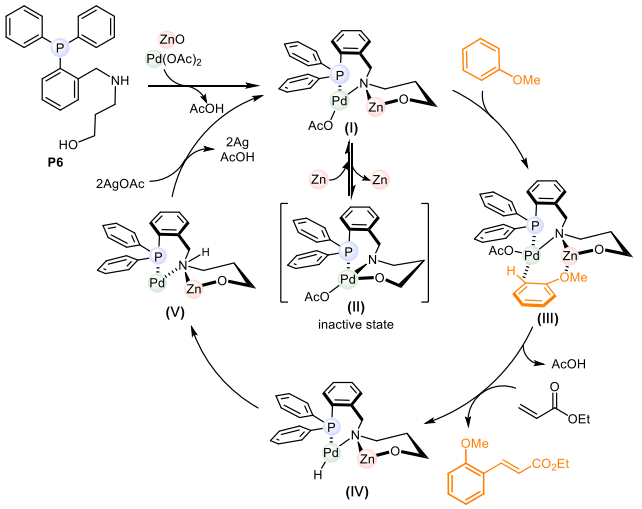
entry	precursor	X (mol%)	Y (equiv)	ZnO	temp. (°C)	yield of **2a** (**3a**)	*o*/*m*+*p*[b]
1	**P8**	15	2	-	80	31% (trace)	3.31
2[a]	**P8**	15	2	-	80	68% (29%)	3.26
3	**P8**	15	2	+	80	50% (3%)	2.93
4[a]	**P8**	15	2	+	80	39% (40%)	4.17
5	**P8**	11	2	-	100	50% (13%)	2.63
6	**P8**	30	2	-	100	74% (11%)	2.66
7	**P11**	15	4	+	100	58% (11%)	5.89
8	**P11**	15	4	+	120	52% (6%)	5.74
9[a]	**P11**	15	4	+	100	53% (13%)	3.21
10	**P11**	11	2	-	100	20% (1.2%)	6.35
11	**P11**	11	2	+	100	45% (5%)	1.35
12	**P11**	30	2	-	100	<4% (0%)	-

[a]The reaction was performed for 48 h. [b]Trace amounts of the *meta*-substituted compound were obtained.

conditions did not give better results (entries 3 and 4). When the amount of the precursor to the catalyst was changed, in the case of 11 mol %, the yield decreased slightly, but with 30 mol %, the yield increased to 74% along with 11% of **3a** (entries 5 and 6). Using **P11**, increasing the amount of ethyl acrylate afforded the desired product in 55% yield, while maintaining a high regioselectivity (entry 7). However, a higher temperature or prolonged reaction time did not result in any further improvement (entries 8 and 9). Changing the amount of the precursor to 11 mol % improved the regioselectivity with almost no change in the yield (entry 10), and the addition of ZnO to it improved the yield but considerably decreased the regioselectivity (entry 11). In contrast, 30 mol % of the precursor significantly decreased the yield (entry 12).

The construction of externalDG and the proposed mechanism of *ortho*-selective C−H alkenylation are described in Scheme 2 using Table 1, entry 8. The precursor **P6** and ZnO construct the externalDG, which form **I** with $Pd(OAc)_2$, and then the oxygen atom of a substrate anisole coordinates to the Lewis acidic moiety Zn of **I** to form **III**, thereby with alkenylation occurring at the *ortho* position. In the case of making a bond between the hydroxyl group of **P6** and Pd, an inactive state (**II**) is formed, resulting in a decreased reactivity. The structures of externalDGs remain speculative but are

Scheme 2. Proposed Construction of externalDG and the Catalytic Cycle (Table 1, Entry 8)



partially supported by ^{1}H NMR and mass spectrometric analyses (Figure S1). Based on the above experiments, we considered the following: The additional Lewis acidic metal contributes to the recruitment of a substrate, leading to an improvement in reactivity (Table 1, entries 7 and 8); however, too high reactivity leads to the formation of disubstituted compound **3a** (Table 1, entries 10 and 11). The hydroxyl or methoxy group of the precursor serves to immobilize the Lewis acidic metal, whereas in a precursor without an oxygen functional group (e.g., **P11**), the amino group can serve a similar function, whose proposed complex is described in Scheme S2A (Table 1, entry 15). With regard to the ratio of the precursor to catalyst Pd (Table 2, entries 6 and 12), a complex of 1:1 or 2:1 could be formed (Scheme S3), and subtle changes in the structure of externalDG were found to have sensitive effects on the yield and regioselectivity (Scheme S2B and C).

With the optimized conditions in hand as in Table 2, entries 6 and 7, other phenyl ethers were investigated next (Table 3). As a control, toluene (**1b**) reacted under condition A, to give alkenylated product **2b** without *ortho* selectivity. Using **1c**−**1f**, condition A brought the results similar to those obtained for anisole **1a** with high *ortho* selectivity even for the large alkyl ethers. In this case, **1c** showed higher reactivity than **1a**, and 2 equiv of ethyl acrylate gave a slightly higher regioselectivity. Using bulky substrate **1g**, unlike **1a** and other alkyl ethers, condition A did not provide the expected results; therefore, condition B was tried, which gave a higher yield. Then, based on Table 1, entry 4, **P3** was tried with ZnO, and interestingly and gratifyingly, it afforded higher regioselectivity (condition C). With a more bulky substrate **1h**, the same tendency as for **1g** appeared, but the yield and regioselectivity were relatively low due to its further bulkiness. With regard to **1g** and **1h**, these results are remarkable considering that the reactions without externalDG gave rather low yields of *ortho*-substituted products (Table S5, entries 5 and 11). The reason why precursor **P8** gave lower regioselectivity than that with **P3** should be the steric hindrance between the silyl group and methyl group in **P8** (Scheme S2D). For the disubstituted substrates, methyl anisols **1i**−**1k** were investigated, and using **P8** or **P11**, **1i** gave an almost *γ*-alkenylated product, which was similar to the control experiment (Table S6). The reason for

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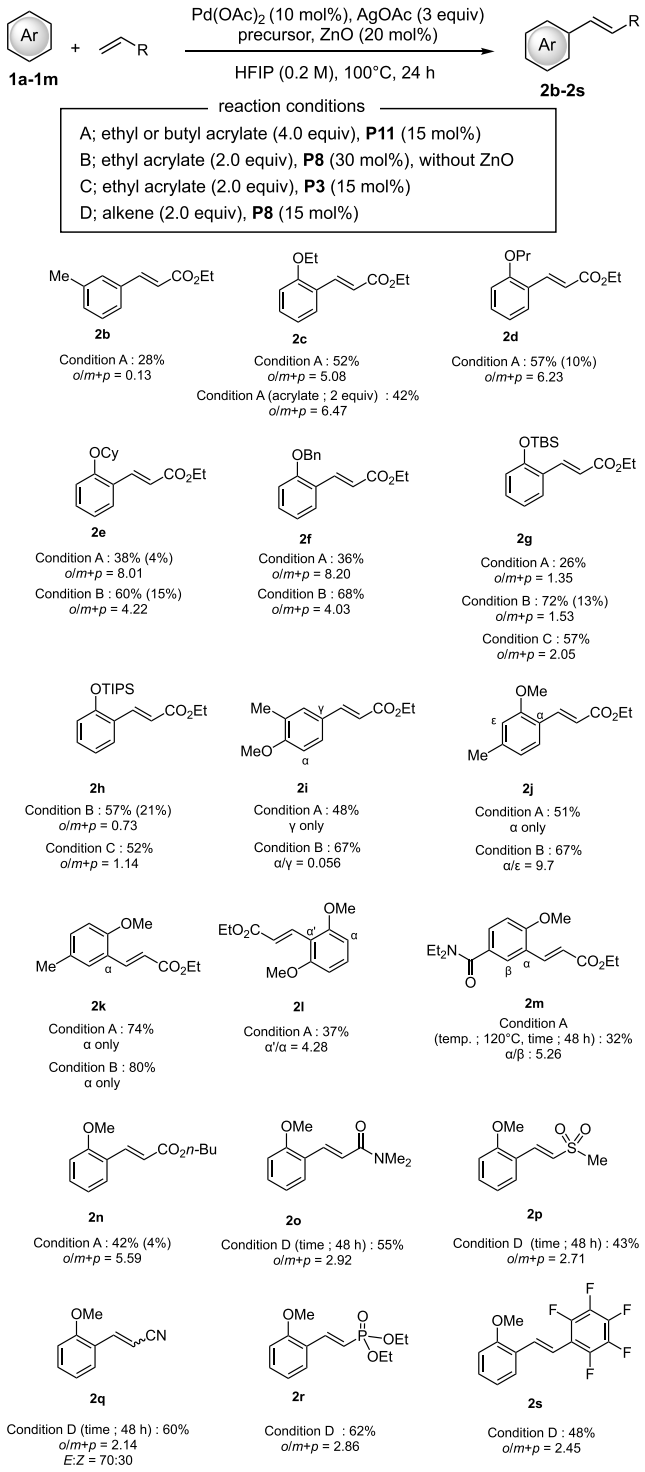
Table 3. Reactions for Other Phenyl Ethers and Alkenes[a]



[a]The yield of the disubstituted compounds was filled in parentheses.

this remains unclear. However, with **1j**, high α-selectivities and yields were obtained, and also with **1k**, much higher α-selectivities and yields were afforded. It is noteworthy that externalDGs led to much higher reactivity compared to the control experiments without externalDGs (Table S6). 1,3-Dimethoxybenzene **1l** afforded an outstanding result, in which α′-alkenylated compound **2l**, that is, 1,2,3-trisubstituted benzene, was selectively obtained, and that did not appear in the precedent works.[10a,d,e] In compound **1m**, which has an amide group at the *para* position, the reaction proceeded with favorable regioselectivity, and this result is noteworthy considering that amides generally act as directing groups. Instead of ethyl acrylate, butyl acrylate was used with **1a**, to give a similar result (**2n**), despite a relatively lower yield. We also investigated alkenes containing functional groups other than an ester and obtained good results using condition D (**2o**−**2s**). As above, optimization of extenalDG and reaction conditions for each substrates afforded better results.

In summary, we have achieved high *ortho* selectivity using the original aminoalcohol-based externalDGs in the C−H alkenylation reactions of various phenyl ethers. Some of these results exceed previous studies and further exhibited previously unreported *ortho* selectivity.[10] The important point is that the optimization of externalDG depending on substrates enables regioselective functionalization, in which the selection of the precursor, the addition of a Lewis acid, and the change of the ratio of precursor/Pd can control the reactivity and regioselectivity. Moreover, we demonstrated one strategy to develop regioselective C−H activation for various substrates that do not have a specific DG. Further investigation for the detailed structure of externalDG and its complex with substrates and the extension of this method to other reactions are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c04448.

Experimental details, analytical data obtained by mass spectrometry, and full characterization of new compounds, including NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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