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Tandem C−C/C−N Formation via Palladium-Catalyzed C−H Activation/Styrenation and Sequential Annulation of *O*-Methylketoxime with Styrenes

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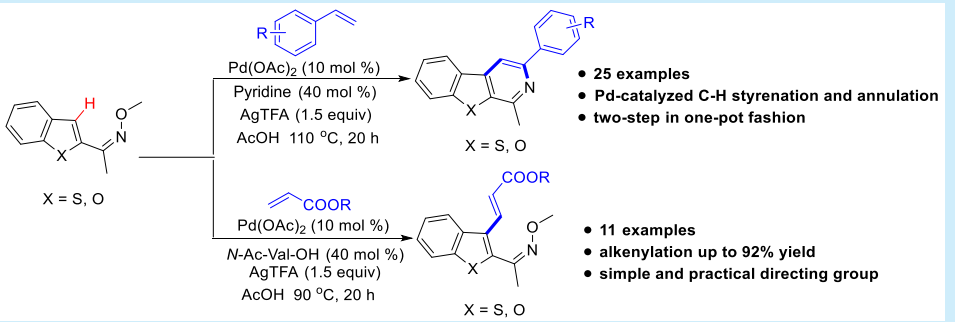
Supporting Information

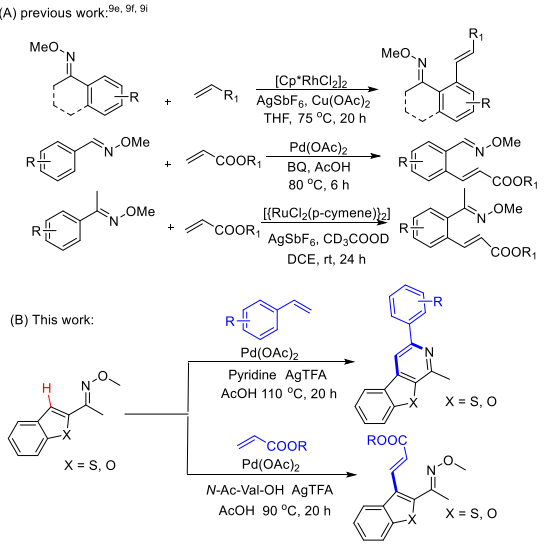


ABSTRACT: A novel route for tandem C−C/C−N formation via palladium-catalyzed C−H activation/styrenation and annulation of *O*-methylketoxime with styrenes to synthesize benzothienopyridines and benzofuropyridines has been developed. Furthermore, the intermolecular alkenylation of the ketoxime with acrylates produces 3-alkenyl *O*-methylketoximes in good to excellent yields. The method features mild reaction conditions and good functional group tolerance, providing a direct approach for the preparation of fused heterocycles.

Over the past decades, the directing group protocol of transition-metal-catalyzed C−H bond functionalization has become a powerful method for C−C and C−X bond formation reactions.[1] The value of this strategy achieves high regio- and stereoselectivity in terms of atom- and step-economic nature. As one of the most widely used protocols, the oxidative functionalizations of alkenes have attracted more attention in recent years.[2] *Ortho* alkenylation with the assistance of various directing groups such as carboxyl,[3] amide,[4] ester,[5] pyridine,[6] and others[7] has been extensively reported.

Oxime ethers possess an excellent directing ability for C−H bond activation.[8] Previous works have demonstrated palladium-catalyzed oxime-ether-directed *ortho* C(sp^2)−H functionalization,[9] such as arylation,[9a,c] acylation,[9b] acyloxylation,[9d,h] alkoxylation,[9h] and hydroxylation.[9g] Aside from the above functionalized reactions, the alkenylation assisted by oxime ether has not been well explored. In 2011, Ellman and co-workers[9e] reported the oxidative coupling of oxime ethers with unactivated alkenes using a cationic Rh (III) catalyst. Sun's group[9f] demonstrated the *ortho* olefination of arylaldehyde oximes with activated olefins through a Pd(II) catalyst. More recently, Jeganmohan's group[9i] described the ruthenium-catalyzed oxidant-free *ortho* alkenylation of aromatic amides, ketoximes, and anilides with alkenes (Scheme 1). Despite

Scheme 1. *O*-Methyloxime-Directed Oxidative Heck Reaction



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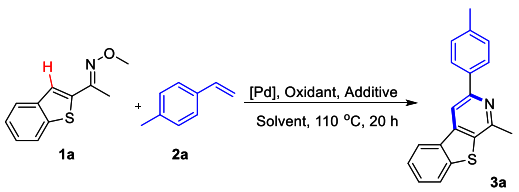
tremendous progress, these reactions were limited in the intermolecular alkenylation. Therefore, the functionalization of oxime ethers, which can not only act as the directing group but also be transformed into value-added molecules with olefins,[10−12] would be of great significance.

Herein, we report the palladium-catalyzed benzothieno- and benzofuro-*O*-methyloxime-directed dual functionalization with substituted styrenes, generating benzothienopyridines and benzofuropyridines. In addition, the intermolecular alkenylation with acrylates produces 3-alkenyl products in good to excellent yields. Benzothieno- and benzofuropyridines are important fused heterocyclic compounds, playing an indispensable role in diverse pharmaceuticals, natural products, druglike scaffolds, and organic materials.[13] Therefore, it is highly desirable to develop a strategy using oxime ethers as the directing group for the synthesis of benzothieno- and benzofuropyridines through a tandem approach.[14]

As an initial experiment, we performed the reaction of the model substrate **1a** and 4-methylstyrene **2a** in the presence of $Pd(OAc)_2$ (10 mol %) as the catalyst, AgTFA (1.5 equiv) as the oxidant, and *N*-Ac-Val-OH as the additive in AcOH at 110 °C (Table1). Surprisingly, the alkenylation−cyclization product **3a** was isolated in 35% yield, and no alkenylation product was observed (Table 1, entry 1). Inspired by the results, we screened different solvents and found that AcOH was a suitable solvent (entries 1−4, Table 1), which is possibly due to the fact that acidic medium was favorable for the reaction.[9f] Among the oxidants tested, AgTFA was ideal (entries 5−8, Table 1). Meanwhile, we also used other Pd catalysts, including $Pd(TFA)_2$, $Pd(PPh_3)_2Cl_2$, $Pd(CH_3CN)_2Cl_2$, and $PdCl_2$, revealing that $Pd(OAc)_2$ was the best choice (entries 9−12, Table 1). Although amino acid was reported to be able to promote C−H activations,[15,16] it was not applicable to our reaction system (entries 13−16, Table1). In contrast, the simple organic base[12a,b] could improve the yield, and pyridine was the best base for the reaction conversion (entries 17−20, Table1). Considering the influence of the reaction temperature, we observed that the yield was slightly decreased to 43% under 90 °C (entry 17). When the amount of pyridine was increased from 40% to 50%, the yield was not improved at all (entry 21). In addition, the yield was slightly decreased under N_2 protection.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	oxidant	additive	yield[b] (%)
1	$Pd(OAc)_2$	AgTFA	Ac-Val-OH	35
2	$Pd(OAc)_2$	AgTFA	Ac-Val-OH	25[c]
3	$Pd(OAc)_2$	AgTFA	Ac-Val-OH	10[d]
4	$Pd(OAc)_2$	AgTFA	Ac-Val-OH	0[e]
5	$Pd(OAc)_2$	AgOAc	Ac-Val-OH	23
6	$Pd(OAc)_2$	Ag_2CO_3	Ac-Val-OH	15
7	$Pd(OAc)_2$	Ag_3PO_4	Ac-Val-OH	9
8	$Pd(OAc)_2$	Ag_2O	Ac-Val-OH	3
9	$Pd(TFA)_2$	AgTFA	Ac-Val-OH	31
10	$Pd(PPh_3)_2Cl_2$	AgTFA	Ac-Val-OH	29
11	$Pd(CH_3CN)_2Cl_2$	AgTFA	Ac-Val-OH	26
12	$PdCl_2$	AgTFA	Ac-Val-OH	21
13	$Pd(OAc)_2$	AgTFA	Glycine	35
14	$Pd(OAc)_2$	AgTFA	Ac-Gly-OH	32
15	$Pd(OAc)_2$	AgTFA	PivOH	22
16	$Pd(OAc)_2$	AgTFA		<10
17	$Pd(OAc)_2$	AgTFA	pyridine	53 (43[f])
18	$Pd(OAc)_2$	AgTFA	NaOAc	44
19	$Pd(OAc)_2$	AgTFA	*t*-BuOK	42
20	$Pd(OAc)_2$	AgTFA	Et_3N	22
21	**$Pd(OAc)_2$**	**AgTFA**	**pyridine**	**69**[g] (68,[h], 68[i])

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), catalyst (10 mol %), oxidant (1.5 equiv), additive (20 mol %), AcOH (2 mL), 110 °C, 20 h. [b]Isolated yield of **3a**. [c]DCE (2 mL). [d]DMSO (2 mL). [e]Dioxane (2 mL). [f]90 °C. [g]Pyridine (40 mol %). [h]Pyridine (50 mol %). [i]N_2

With the established conditions in hand, the scope of substituted styrenes was then explored, and the representative products are shown in Table 2. A variety of substituted styrenes were subjected to the protocol ,favorably delivering the desired products (**3a−s**). Of note, a remarkably broad variety of styrenes with different groups including OCH_3, Me, *i*-Pr, F, Cl, Br, CF_3, NO_2, and naphthyl were transformed. The styrene containing the more electron-withdrawing nitro group at the *para* position was less reactive, which is possibly due to the lower catalytic overturn (**3h**). Notably, electron-withdrawing groups of styrenes provided better yields than those bearing electron-donating groups (**3i**, **3j**, **3l**, **3m−o**). Besides, 1-vinylnaphthalene and 2-vinylnaphthalene were eligible substrates affording the moderate yields (**3q**, **3r**). In addition, trisubstituted partners could be also applied to the transformation to deliver the desired product in moderate yields (**3s**). Meanwhile, benzofuropyridines were also obtained under this reaction system. The reactions of the electron-deficient styrenes with (*E*)-1-(benzofuran-2-yl) ethan-1-one *O*-methyl oxime led to the benzofuropyridine products (**3t−w**). Unfortunately, we did not obtain benzofuropyridines with electron-donating styrenes. In addition, the 1-(1*H*-indol-2-yl)ethan-1-one *O*-methyl oxime was not reacted with styrene (**3x**). The protectd 1-(1*H*-indol-2-yl)ethan-1-one gave a moderate yield of 40% (**3y**). 3-Acetylbenzthiophene *O*-methyl oxime could afford a better yield of 49% (**3z**). Other unactivated alkenes such as *n*-heptene and cyclohexene were not suitable for the reaction (**3A, 3B**).

Then the scope of acrylates as the coupling partners with **1a** was explored, and the 3-alkenylbenzothieno-*O*-methyloximes instead of cycloaddition products were produced. Therein, a series of acrylates was subjected to the protocol to give the corresponding products in 61−84% yields (**5a−f**) when we changed the additive from pyridine to the amino acid and reduced the temperature to 90 °C. Meanwhile, it was found that when (*E*)-1-(benzofuran-2-yl) ethan-1-one *O*-methyl oxime was used as the reactant, the yield was significantly improved up to 92%. However, only a trace amount of product was delivered while using butyl acrylate, due to steric hindrance (see the SI).

In addition, the intermolecular competition experiments[4b,d,f−h] were carried out to probe the electronic effect. When the mixture of electronically biased styrene **2d** and **2b** (1:1) was treated with **1a**, the yield of **3d** was about 8.3 times more than that of **3b** under the standard reaction conditions (Scheme 2), showing electron-deficient alkenes to be preferentially functionalized, which can be attributed to an

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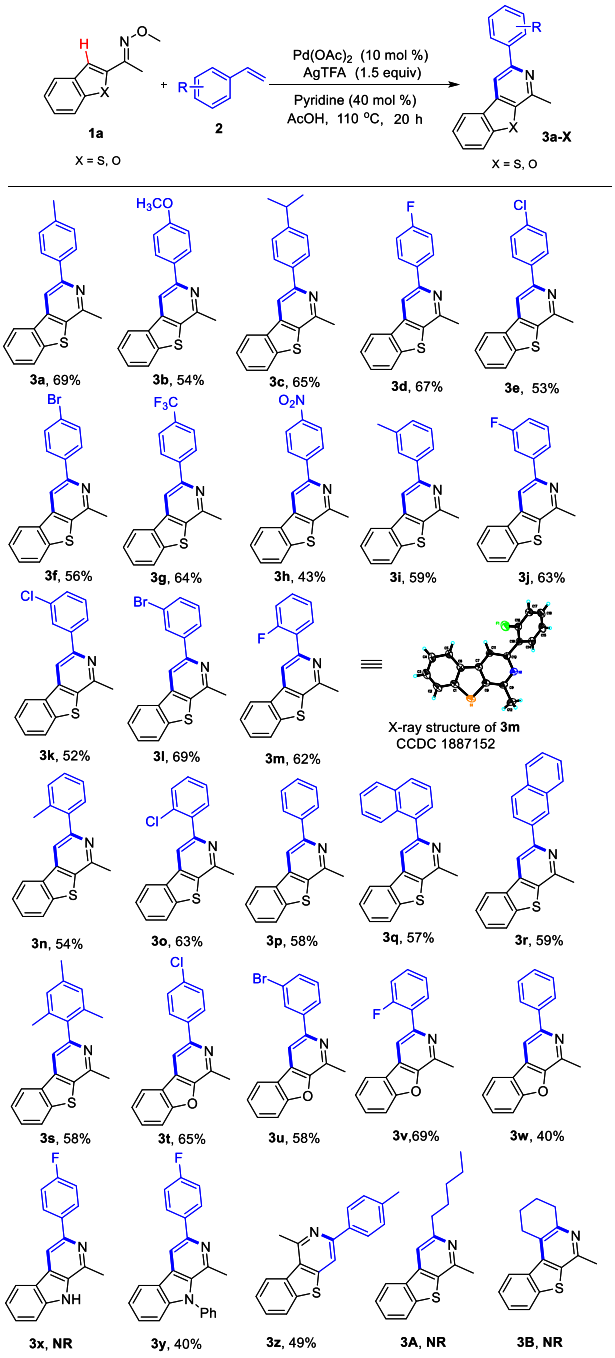
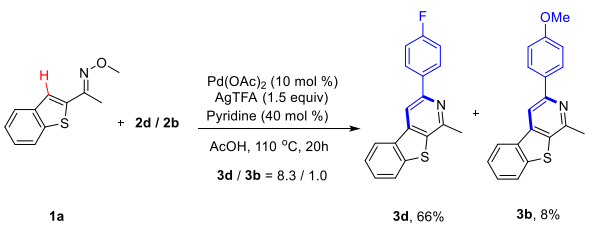
Table 2. Substrate Scope of the Styrenes[a,b]



[a]Reaction conditions: **1a** (0.3 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (10 mol %), AgTFA (1.5 equiv), pyridine (40 mol %), AcOH (2 mL), 110 °C, 20 h. [b]Isolated yield of **3**.

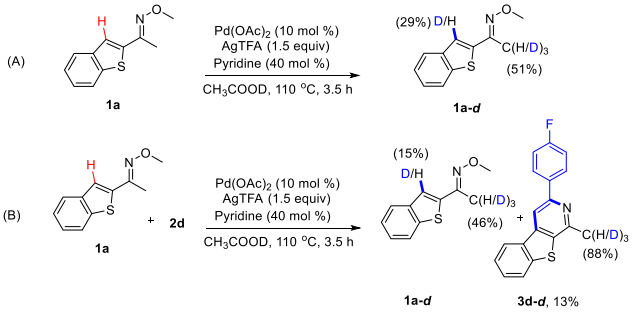
Scheme 2. Competition Experiment



electron-donating group substituted on the stryenes being less active toward formation of the cyclopalladated intermediate.[9f] In addition, the reaction on gram scale has also been completed in good yield (see the SI).

To obtain further mechanistic insight, we performed some control experiments with isotopically labeled solvents. First, when 2-acetylbenzothieno oximes (**1a**) was exposed to the standard conditions in AcOD, deuterium incorporation was observed at the 3-position and the methyl of 2-acetylbenzothieno analogue **1a** (Scheme 3A). In contrast, when the same

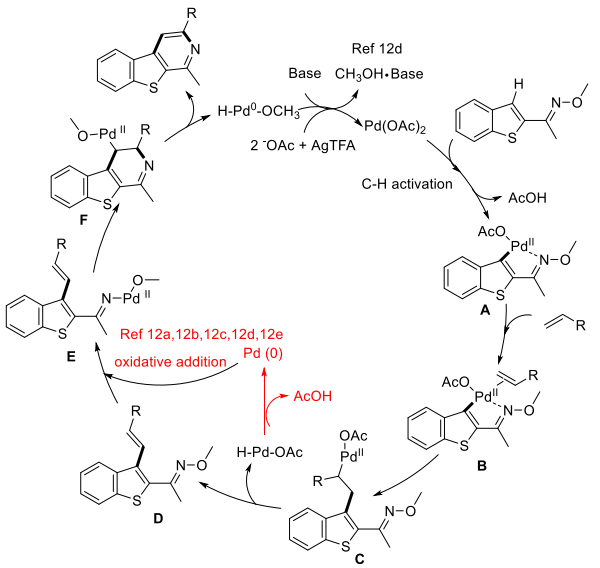
Scheme 3. Deuterium Incorporation Studies



reaction was performed with the styrene **2d**, nearly 90% of the deuterium incorporation at the methyl of **3d** signals a deprotonation step. No other changes of deuterium incorporation at the methyl group as well as the reduction to 15% at the 3-position in unreacted **1a** are observed (Scheme 3B). These results suggest that the first step of the reaction is a reversible C−H activation at the 3-position of **1a**,[10g,h] and the deprotonation at the methyl of **3d** is favorable after the first irreversible step of the reaction.

Based on the mechanistic experiments described above and relevant literature reports,[9f,12] a plausible mechanism for this reaction is depicted in Scheme 4. First, the coordination of the nitrogen atom in compound **1a** with Pd (II) species triggers reversible cyclopalladation to form a five-membered cyclopalladated (II) intermediate **A** through a concerted metalation−deprotonation pathway[9f,18] or an agostic intermediate,[17]

Scheme 4. Proposed Mechanism



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which undergoes an interchange with alkene to generate intermediate **B**. Accordingly, the product **D** is obtained by successive 1,2-migratory insertion, β-hydroelimination, reductive elimination, and liberation of AcOH and Pd (0) species. The N−O bond of the *O*-methylketoxime was cleaved by oxidative addition to the palladium (0) complex, and an alkenylpalladium species (II) was generated as an intermediate E.[12a−e] Oximes directly attacked the olefinic moiety activated by coordination to Pd(II) complexes,[12a,b,d] and then the C−N bond formation/N−O bond cleavage event provided complex F followed by β-hydride elimination[12a,b,d] to furnish the product.

In summary, we have developed a novel method for tandem C−C/C−N formation via palladium-catalyzed C−H activation/styrenation and cyclization of ketoxime with styrenes to synthesize benzothienopyridines and benzofuropyridines, and the intermolecular alkenylation of the ketoxime with acrylates forms 3-alkenyl *O*-methylketoximes in good to excellent yields. This method is anticipated to construct structurally diversified benzothienopyridines and benzofuropyridines for the screening of potential pharmaceuticals in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00702.

Experimental procedures and spectral data (PDF)

Accession Codes

CCDC 1887152 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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