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Pd-Catalyzed Carboetherification of β,γ-Unsaturated Oximes: A Novel Approach to Δ²-Isoxazolines

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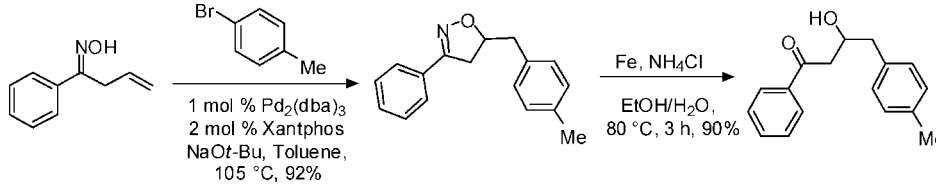
ABSTRACT



A novel route to the synthesis of Δ²-isoxazoline derivatives is described. Reaction of β,γ-unsaturated oximes with aryl bromides via palladium-catalyzed carboetherification affords 3,5-disubstituted Δ²-isoxazolines in good yields. The use of Xantphos as ligand is crucial for the transformation. The carboetherification products can be further converted to β-hydroxy ketones in the presence of Fe powder and NH_4Cl.

Δ²-Isoxazolines are frequently found in a diverse array of compounds, including biologically active agents,[1] chiral ligands,[2] and intermediates in organic synthesis.[3] In particular, because of their easily cleaved N−O bond, Δ²-isoxazolines also serve as precursors for β-hydroxy ketones,[4] β-amino acids,[5] and γ-amino alcohols.[6] Therefore, the construction of a Δ²-isoxazoline ring has received much attention. The conventional method for their synthesis is via cycloaddition of nitrile oxides and alkenes, which generates the O−C5 and C3−C4 bond in one step (1).[7,8] Although

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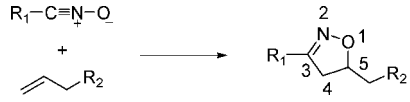
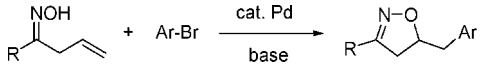
these transformations are widely used, some challenges still remain especially for the issue of the regioselectivity.[8]



(1)

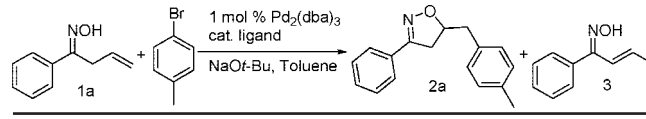
Recently, Pd-catalyzed inter- and intramolecular carboetherification of olefins has been proved to be a very efficient way to produce elaborate and important heterocyclic structures.[9] We felt that the formation of substituted Δ^2-isoxazolines could be achieved by this method with a judicious choice of palladium catalyst (2). However, Mosher et al. reported that β,γ-unsaturated oximes were easily rearranged to α,β-unsaturated oximes when a strong base was employed.[10] Furthermore, the annulations of oximes were dependent on the geometry of the hydroxyimino moiety in the oxime precursors.[11] On the basis of these observations, we envisioned that this transformation may form several undesired byproducts. In this paper, we report a novel, highly chemoselective formation of Δ^2-isoxazolines from β,γ-unsaturated oximes and aryl halides via palladium-catalyzed carboetherification reactions, in which the intramolecular C−O bond and intermolecular C−Ar bond are formed in one step.



(2)

During the course of our studies on palladium-catalyzed cascade reactions of aryl bromides with *N*-homoallylhydroxylamines, we found that use of $Pd_2(dba)_3/PPh_3$ as catalyst could lead to the formation of 5-arylmethylisoxazolidines.[12] Hence, in our preliminary experiments we first examined the reaction of β,γ-unsaturated oxime **1a**[13] with 1.2 equiv of *p*-bromotoluene in the presence of NaO*t*-Bu (1.2 equiv) and catalytic amounts of $Pd_2(dba)_3$ (1 mol %) and PPh_3 (4 mol %). To our disappointment, no detectable Δ^2-isoxazoline **2a** was observed, while only the rearranged α,β-unsaturated oxime **3** was obtained (entry 1, Table 1). This is likely because the rearrangement of the alkene into conjugation may be much faster than the cyclization of β,γ-unsaturated oxime **1a**. We reasoned that a proper phosphine ligand might accelerate the cyclization reaction and thus suppress the rearrangement reaction. We were gratified to find that P(*o*-tol)$_3$ as ligand was effective in the carboetherification process although the yield was relatively low (entry 2, Table 1). To improve the yield, different supporting ligands were examined for the transformation of **1a** with *p*-bromotoluene to **2a** in toluene (Table 1). The use of a DPPF-derived catalyst was unsuccessful under similar reaction conditions (entry 3, Table 1). With the addition of DPE-Phos,[14] the reaction afforded **2a** in a similar low yield (entry 4, Table 1). However, the use of the ligand Xantphos[14] at 90 °C provided Δ^2-isoxazoline **2a** in 80% yield (entry 5, Table 1).

Table 1. Effect of Ligand on the Pd(0)-Catalyzed Carboetherification of β,γ-Unsaturated Oxime **1a** and *p*-Bromotoluene[a]



entry	ligand	isolated yield of **2a** (%)	isolated yield of **3** (%)
1	PPh_3	0	95
2	P(*o*-tol)$_3$	32	60
3	DPPF	<5	92
4	DPE-Phos	28	48
5[b]	Xantphos	80(92)	12(<5)

[a] Reaction conditions: 1.0 equiv substrate **1a**, 1.2 equiv ArBr, 1.2 equiv NaO*t*-Bu, 1 mol % $Pd_2(dba)_3$, 2 mol % bidentate phosphine or 4 mol % monodentate phosphine, toluene (0.1 M), 90 °C. [b] Numbers in parentheses are the yield conducted at 105 °C.

To optimize the present reaction, various palladium complexes, bases, and reaction temperatures were screened for the carboetherification reaction (see Supporting Information). $PdCl_2$/Xantphos was active for the reaction but gave **2a** in only 30% yield, while $Pd(PPh_3)_4$ and $PdCl_2/PPh_3$ were completely inactive. Lowering the reaction temperature resulted in poorer yield due to the rising byproduct **3**, whereas by increasing the reaction temperature to 105 °C, a 92% isolated yield of **2a** was obtained (entry 6, Table 1). NaO*t*-Bu was proved to be clearly superior to other bases, such as Na_2CO_3, K_2CO_3, K_3PO_4, and KO*t*-Bu, which gave **2a** in 0%, 12%, 20%, and 72% yields, respectively.

With the optimized reaction conditions secured, we studied the synthesis of a wide range of substituted Δ^2-isoxazolines **2a**−**p** from β,γ-unsaturated oximes **1a**−**i** and different aryl halides. The results are summarized in Table 2. From the results in the Table, this method is effective for the conversion of a variety of 1-substituted β,γ-unsaturated oximes **1** such as aryl (entries 1−10, Table 2), heteroaryl (entries 11 and 12, Table 2), alkenyl (entries 13 and 14, Table 2), and alkyl (entries 15 and 16, Table 2) to 3,5-disubstituted Δ^2-isoxazoline derivatives. The electronic and steric effects of the aryl substituents on the reaction were also examined. The electron-neutral (entries 1 and 2, Table 2), electron-rich (entries 3, 7 and 8, Table 2), electron-poor (entries 4−6, 9,

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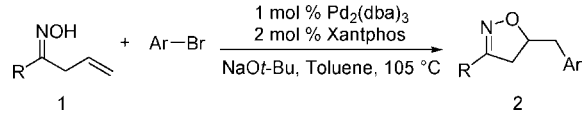
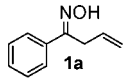
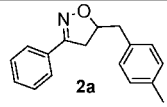
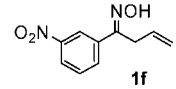
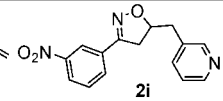
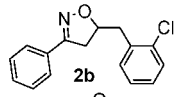
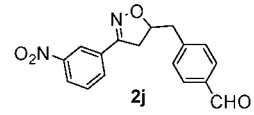
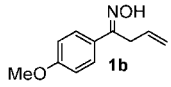
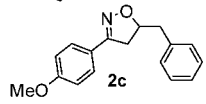
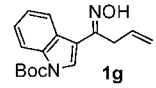
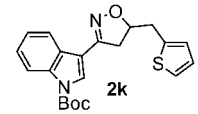
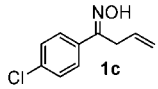
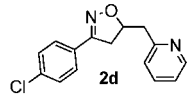
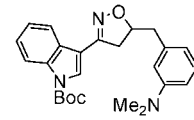
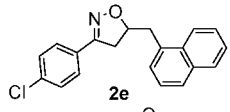
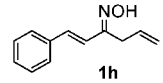
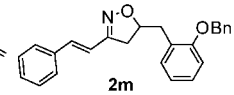
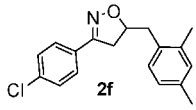
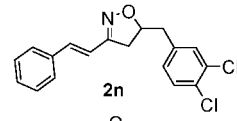
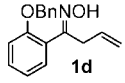
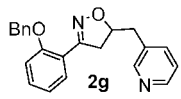
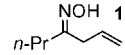
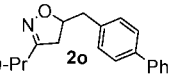
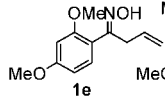
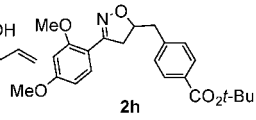
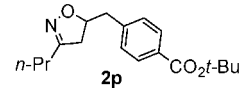
(13) A mixture containing both *Z* and *E* isomers of β, γ-unsaturated oxime **1a** in the hydroxyimino moiety was used.

(14) DPE-Phos = 1,1-bis(diphenylphosphinophenyl)ether, Xantphos = 9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene.

Table 2. Pd-Catalyzed Carboetherification of β,γ-Unsaturated Oximes with Aryl Bromides to Δ^2-Isoxazolines[a]



1 2

	substrate[b]	isoxazoline	yield (%)[c]		substrate[b]	isoxazoline	yield (%)[c]
1	 1a	 2a	92	9	 1f	 2i	65
2		 2b	86	10		 2j	71
3	 1b	 2c	94	11	 1g	 2k	48
4	 1c	 2d	81	12		 2l	62
5		 2e	66	13	 1h	 2m	46
6		 2f	47	14		 2n	78
7	 1d	 2g	89	15	 1i	 2o	82
8	 1e	 2h	73	16		 2p	64

[a] Unless noted, all reactions were carried out using **1** (0.2 mmol), ArBr (0.24 mmol), $Pd_2(dba)_3$ (1 mol %), Xantphos (2 mol %), and NaO*t*-Bu (0.24 mmol) in toluene at 105 °C for 3 h. [b] The geometries of **1a**−**c** were unclear and a mixture of **E**/**Z** isomers in hydroxyimino moiety was used in the cases of **1d**−**i**. [c] Isolated yield.

and 10, Table 2), *o*-substituted (entries 7 and 8, Table 2), and *m*-substituted (entries 9 and 10, Table 2) aryl substituents are well tolerated.

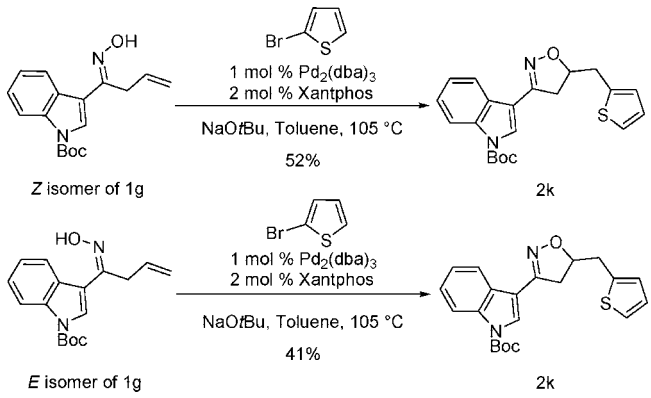
On the other hand, a variety of electron-neutral (entries 1, 3, 5, 6, and 15, Table 2), electron-rich (entries 12 and 13, Table 2) and electron-deficient (entries 2, 8, 10, 14, and 16, Table 2) aryl bromides are effectively transformed under these conditions. Several functional groups are tolerated (entries 2, 8, 10, 14, and 16, Table 2), and heteroaryl bromides also afford the desired products in good yields (entries 4, 7, and 9, Table 2), indicating the generality of the above method. However, for 2-bromothiophene (entry 11, Table 2), the expected Δ^2-isoxazoline **2k** was obtained only in 48% yield, probably due to the decomposition of 2-bromothiophene. Some *o*-substituted aryl bromides resulted in modest yields of the desired products (entries 6 and 13, Table 2).

On the basis of the observation that some transformations can afford high yields though the starting β,γ-unsaturated oximes were the mixture of *E*/*Z* isomers in hydroxyimino moiety, we presumed that the *E* isomer (relative to allyl moiety) can be quickly converted to the *Z* isomer under the reaction conditions. Then cyclization of the *Z* isomer with aryl bromide affords the desired Δ^2-isoxazoline product. Additional evidence of this conversion was obtained by subjecting both the *Z* and *E* isomers of (*N*-Boc-3-indolyl) β,γ-unsaturated oxime **1g** to the reaction conditions with 2-bromothiophene (Scheme 1).[15] The product isoxazoline, **2k**, was obtained in 52% and 41%, yield respectively.

Although the substituted Δ^2-isoxazolines are in themselves useful compounds, we have carried out their conversion to the corresponding β-hydroxy ketones. For example, the Δ^2-isoxazoline **2a** undergoes reductive *N*−*O* bond cleavage and imine hydrolysis in the presence of Fe (5 equiv) and NH_4Cl (5 equiv) in EtOH/H_2O at 80 °C for 3 h, providing β-hydroxy ketone **4** in 90% yield (Scheme 2).

In summary, we have shown a novel protocol for the construction of 3,5-disubstituted Δ^2-isoxazolines through Pd-

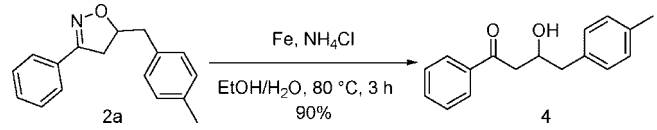
Scheme 1. Reactions of *Z* and *E* Isomers of (*N*-Boc-3-indolyl) β,γ-Unsaturated Oxime **1g** and 2-Bromothiophene[a]



[a] The geometry of *Z* and *E* is relative to the allyl moiety.

catalyzed carboetherification reactions of β,γ-unsaturated oximes, which is complementary to that of nitrile oxide cycloadditions. Both isomers of the oxime substrates have proven to be effective for this transformation. The resulting Δ^2-isoxazolines can be reductively cleaved to β-hydroxy ketones. A study of the application of this method in the stereoselective preparation of 3,4,5-polysubstituted Δ^2-isoxazolines is currently being carried out in our laboratory.

Scheme 2. Synthesis of β-Hydroxy Ketones



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Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The geometries of *Z* and *E* of **1g** were determined by ^{1}H NMR analysis. See Supporting Information for further details.