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Synthesis of oxazoles through Pd-catalyzed cycloisomerization–allylation of *N*-propargylamides with allyl carbonates

Akio Saito *, Koichi Iimura, Yuji Hanzawa *

Laboratory of Organic Reaction Chemistry, Showa Pharmaceutical University, 3-3165 Higashi-Tamagawagakuen, Machida, Tokyo 194-8543, Japan

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ABSTRACT

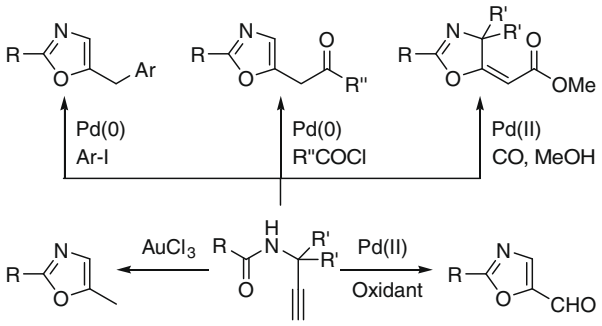
In the presence of $Pd_2(dba)_3$-Cy_3P catalyst, IPr·HCl salt [IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene], and Cs_2CO_3, *N*-propargylamides react with allyl carbonates to give 2,5-disubstituted oxazoles having homoallyl groups through the tandem cycloisomerization–allylation.

Transition metal-catalyzed cyclizations of alkynes containing heteroatom nucleophiles are developing into one of the most efficient strategies for the heterocyclic synthesis.[1] In particular, the Pd-catalyzed procedure provides us with a tandem approach to the synthesis of functionalized heterocycles through the regio- and stereoselective addition of a heteroatom to the triple bond and the subsequent cross-coupling with organic halides and so on.[2] Although the incorporation of aryl, vinyl,[3] and acyl[4] groups into heterocycles by such a methodology has been well studied, the tandem procedures including an allylation process have been less reported.[5]

Oxazoles are important heterocyclic compounds due to widespread application not only to biologically active compounds[6,7] but also to synthetic intermediates.[6] Thus, a novel and an efficient procedure for the construction of oxazole nucleus has remained an attractive goal,[8] and some metal-catalyzed protocols from *N*-propargylamides have been reported (Scheme 1).[9–12] For example, a tandem cycloisomerization–coupling reaction of propargylamides with aryl iodides in the presence of Pd(0) catalyst is an effective access to 2,5-disubstituted oxazoles having arylmethyl groups at 5-position.[9a] The Pd(0)-catalyzed cycloisomerization–coupling reaction with acyl chlorides[9b] and Pd(II)-catalyzed oxidative carbonylation in the presence of CO and MeOH[9c] lead to the incorporation of acyl groups into the side chain. The preparation of 5-oxazolecarbaldehydes by the oxidative Pd-catalyzed process[10] and the formation of 5-methyl-oxazoles via the simple cycloisomerization catalyzed by $AuCl_3$[11] has been known. We herein describe the new and useful incorporation procedure of unsaturated side chain into the oxazoles from propargylamides and allyl carbonates catalyzed by palladium complex.

Our initial effort was focussed on the evaluation of palladium catalytic systems for the reaction of *N*-propargylamide **1a** with allyl ethyl carbonate (1.2 equiv), and the results are shown in Table 1. At the outset, it turned out that monodentate ligands were important for the formation of **2a** (entries 1, 3–5), and the bidentate phosphine ligands such as BINAP, dppe, dppp, dppb, and dppf did not give **2a** (entry 2). Thus, in the presence of $Pd_2(dba)_3$, Cy_3P, and K_2CO_3 in refluxing MeCN, **1a** was consumed within 20 h giving rise to the oxazole **2a** in 17% yield along with **3a** in 60% yield (entry 5). The use of Cs_2CO_3 instead of K_2CO_3 increased the yield of **2a** to 24% with suppressing the formation of **3a** (entry 6).[13] The additive of imidazolium salt[14] IPr·HCl was effective in the reaction of **1a** in the presence of $Pd_2(dba)_3$ and Cs_2CO_3 in MeCN (entry 9), and the combined usage of IPr·HCl with Cy_3P improved the yield of **2a** up to 46% (entry 10).[15] Furthermore, by the dilution of the reaction solution and increasing the amount of allyl ethyl carbonate (3 equiv), **2a** was obtained in 70% yield (entry 12).[16] It should be mentioned that the other solvents such as THF, DME, dioxane, and DMF were inferior.

We next investigated the scope of propargylamides **1** and **5** in the reaction with allyl ethyl carbonate by the present catalytic systems [$Pd_2(dba)_3$, Cy_3P, IPr·HCl, Cs_2CO_3/MeCN] (Table 2). As well as the terminal alkyne **1a**, inner alkynes **1b**, **1d**, and **1e** successfully



Scheme 1. Synthesis of oxazoles from *N*-propargylamides.

* Corresponding authors. Tel.: +81 (0) 42 721 1571; fax: +81 (0) 42 721 1569.
E-mail addresses: akio-sai@ac.shoyaku.ac.jp (A. Saito), hanzaway@ac.shoyaku.ac.jp (Y. Hanzawa).

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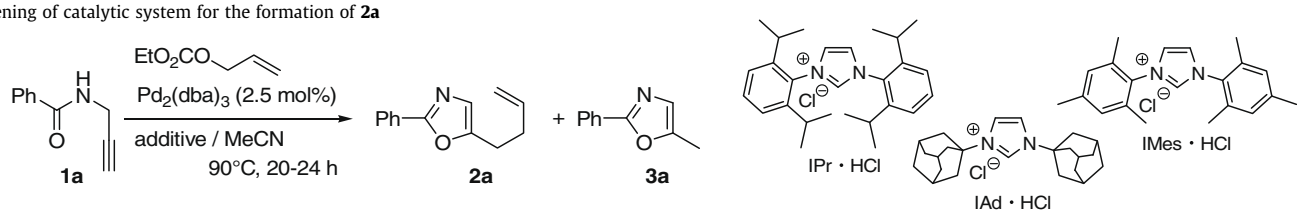
Table 1
Screening of catalytic system for the formation of **2a**

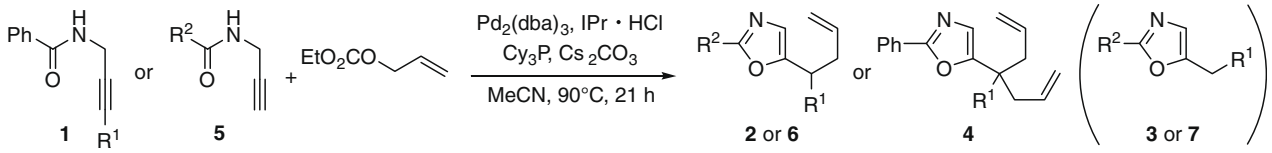


Entry	Ligand (mol %)	Base (equiv)	Allyl carbonate (equiv)	MeCN (mL)	**2a**[a] (%)	**3a**[a] (%)	**1a**[a] (%)
1[b]	—	K_2CO_3 (5.0)	1.2	2	9	—	—
2	BINAP (10)	K_2CO_3 (5.0)	1.2	2	—[c]	—	29
3	Ph_3P (20)	K_2CO_3 (5.0)	1.2	2	6	3	17
4	$(2\text{-furyl})_3P$ (20)	K_2CO_3 (5.0)	1.2	2	9	5	26
5	Cy_3P (20)	K_2CO_3 (5.0)	1.2	2	17	60	0
6	Cy_3P (20)	Cs_2CO_3 (3.0)	1.2	2	24	28	15
7	IAd·HCl (6)	Cs_2CO_3 (3.0)	1.2	2	—	—	0
8	IMes·HCl (6)	Cs_2CO_3 (3.0)	1.2	2	—	64	0
9	IPr·HCl (6)	Cs_2CO_3 (3.0)	1.2	2	30	35	11
10	IPr·HCl (6), Cy_3P (10)	Cs_2CO_3 (3.0)	1.2	2	46	28	0
11	IPr·HCl (6), Cy_3P (10)	Cs_2CO_3 (3.0)	1.2	4	64	18	0
12	IPr·HCl (6), Cy_3P (10)	Cs_2CO_3 (3.0)	3.0	6	70	8	0

[a] Yields were determined by ^1H NMR analysis.
[b] 5 mol % $Pd(Ph_3P)_4$ was used instead of $Pd_2(dba)_3$.
[c] *N*-allyl-*N*-(prop-2-ynyl)benzamide: 71%.

reacted with allyl ethyl carbonate to give the corresponding allylated products **2** in good yields (entries 1, 2, 4, and 5). A similar observation has been reported in the Pd-catalyzed reaction of propargylamides with aryl iodides.[9a] It has been proposed that the incorporation of aryl groups into the oxazoles proceeds via the oxypalladation–reductive elimination domino mechanism.[9a] Therefore, the present incorporation of allyl groups would consist of the cyclization of propargylamides through the oxypalladation caused by π-allyl palladium complex, which was generated by palladium(0) and allyl ethyl carbonate, and the subsequent reductive

Table 2
Cycloisomerization–allylation of various propargylamides **1** or **5** with allyl ethyl carbonate[a]



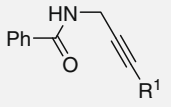
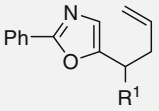
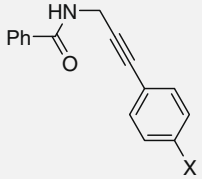
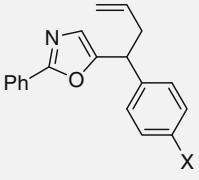
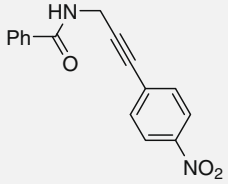
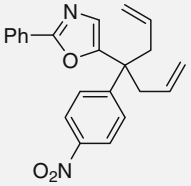
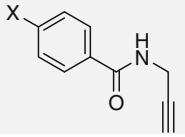
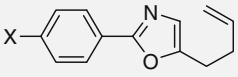
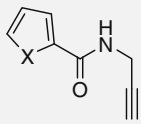
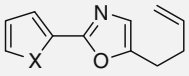
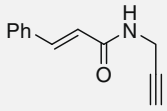
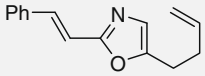
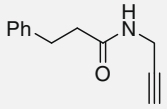
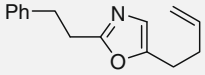
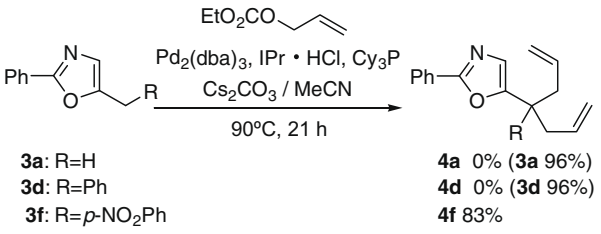
Entry	Substrate		Product		Yield[b] (%)	
1		**1a**: R^1 = H		**2a**: R^1 = H	70	(**3a** 8)
2		**1b**: R^1 = Et		**2b**: R^1 = Et	32	(**3b** 5)
3		**1c**: R^1 = ^{t}Bu		**2c**: R^1 = ^{t}Bu	0	(**1c** 44)
4		**1d**: X = H		**2d**: X = H	62	(**3d** 11)
5		**1e**: X = MeO		**2e**: X = MeO	60	(**3e** 13)
6		**1f**		**4f**	80 (**2f** 0)	
7		**5a**: X = MeO		**6a**: X = MeO	55	(**7a** 26)
8		**5b**: X = Me		**6b**: X = Me	70	(**7b** 12)
9		**5c**: X = Cl		**6c**: X = Cl	70	(**7c** 10)
10		**5d**: X = NO_2		**6d**: X = NO_2	7	(**7d** 31)

Table 2 (*continued*)

Entry	Substrate		Product		Yield[b] (%)	
11		**5e**: X = O		**6e**: X = O	50	(**7e** 10)
12		**5f**: X = S		**6f**: X = S	58	(**7f** trace)
13		**5g**		**6g**	67	(**7g** 29)
14		**5h**		**6h**	22	(**7h** 56)

[a] Conditions for **1**: $Pd_2(dba)_3$: 2.5 mol %, IPr·HCl: 6 mol %, Cy_3P: 10 mol %, Cs_2CO_3: 3 equiv, allyl ethyl carbonate: 3 equiv, MeCN: 6 mL. Conditions for **5**: $Pd_2(dba)_3$: 5 mol %, IPr·HCl: 12 mol %, Cy_3P: 20 mol %, Cs_2CO_3: 6 equiv, allyl ethyl carbonate: 6 equiv, MeCN: 6 mL.
[b] Isolated yield.



Scheme 2. Allylation of oxazole **3**.

elimination. In the case of **1f**, diallylated **4f** was observed in 80% yield due to the high acidity of *p*-nitrobenzylic protons (entry 6). Actually, the treatment of **3f** with allyl ethyl carbonate under the same conditions led to the formation of **4f** (Scheme 2). In contrast to **3f**, methyl derivative **3a** or benzyl derivative **3d** did not bring about the allylated **2a** or **2d** and the diallylated **4a** or **4d**. Thus, the simply cyclized compound **3** would not be considered to take part into the present formation of **2** from **1**.

The reactions of **5a–h** having a different acyl group yielded the desirable oxazole compounds, albeit a slight increase in the amount of Pd-catalyst (entries 7–14).

The present catalytic systems could be applied to the other allyl carbonates in the reaction of **1a** (Scheme 3). Thus, the reaction with cinnamyl ethyl carbonate (R^1 = H, R^2 = Ph) afforded **8** in 89% yield without a detection of the regioisomer and stereoisomer. On using ethyl 1-phenylallyl carbonate (R^1 = Ph, R^2 = H), **8** was also obtained in good yield. Furthermore, ethyl methallyl carbonate brought about the corresponding oxazole **9**.

In conclusion, we demonstrated the facile synthesis of the oxazole compounds possessing the unsaturated side chains through the palladium-catalyzed cycloisomerization–allylation reaction of propargylamide derivatives with allyl carbonates. The present procedure would raise new possibilities for the incorporation of allyl groups into heterocycles. Synthetic applications and detailed mechanistic studies of the present reaction are underway.

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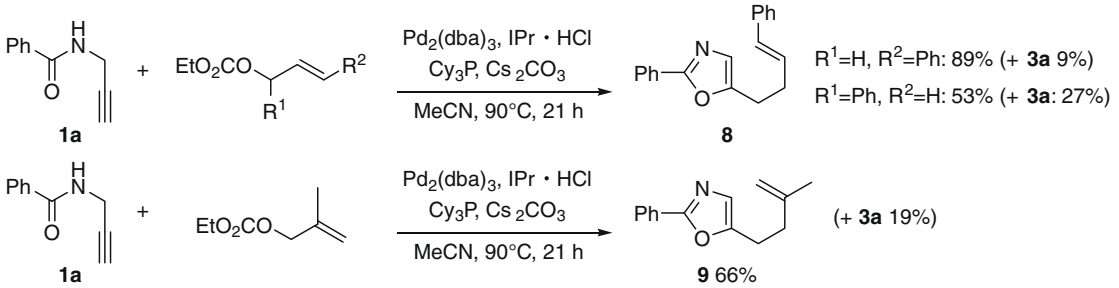

Scheme 3. Cycloisomerization-allylation of **1a** with various allyl carbonate derivatives.

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15. The catalytic system such as (IPr)Pd(Cy_3P), (IPr)Pd(Cy_3P)-Cy_3P, or (IPr)Pd(allyl)Cl-Cy_3P brought about the inferior results to the present catalytic system. See, (a) Preparation of (IPr)Pd(Cy_3P): (a) Fantasia, S.; Nolan, S. P. *Chem. Eur. J.* **2008**, *14*, 6987; Preparation of (IPr)Pd(allyl)Cl: (b) Normand, A. T.; Stasch, A.; Ooi, L.-L.; Cavell, K. J. *Organometallics* **2008**, *27*, 6507.
16. Although the Pd-catalyzed formation of 3-allylated indoles from *o*-alkynyltrifluoroacetanilides and allylation reagents was reported to proceed via *N*-allyl-*o*-alkynyl-trifluoroacetanilide intermediates, *N*-allyl-*N*-(prop-2-ynyl)benzamide was not converted into the oxazole **2a** by the present catalytic system. See, Ref. 5c.