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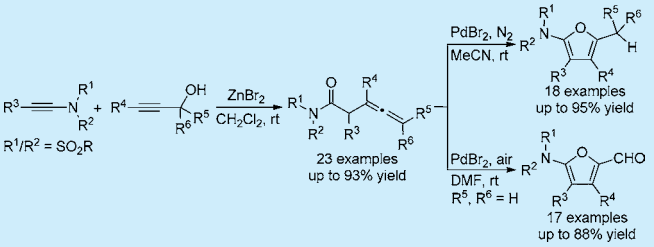
Palladium-Catalyzed Cycloisomerization and Aerobic Oxidative Cycloisomerization of Homoallenyl Amides: A Facile and Divergent Approach to 2-Aminofurans

Cungui Cheng, Shuiyou Liu, and Gangguo Zhu*

Department of Chemistry, Zhejiang Normal University, 688 Yingbin Road, Jinhua 321004, China

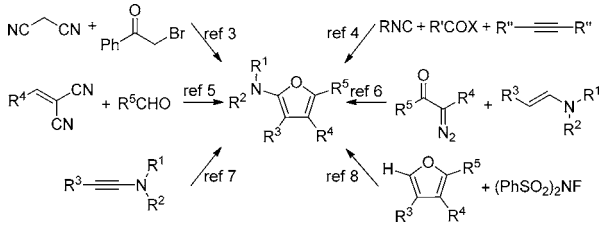
Supporting Information

ABSTRACT: A Pd-catalyzed divergent cyclization, including cycloisomerization and aerobic oxidative cycloisomerization of homoallenyl amides, is described. Varieties of functionalized 2-amino-5-alkylfurans and 2-amino-5-formylfurans can be selectively synthesized in good to excellent yields. Preliminary mechanistic studies show that peroxide may be a key intermediate for this Pd-catalyzed radical aerobic oxidative cycloisomerization of homoallenyl amides. The mild reaction conditions, high atom economy, and utilization of air as the oxygen source make this protocol very environmentally benign and practical to the synthetic community.



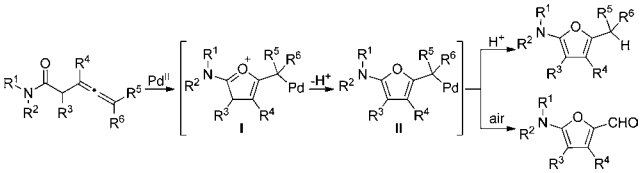
Furans constitute an important structural motif found in a wide range of natural products, pharmaceuticals, and agrochemicals.[1] As a consequence, myriad methods have been devoted to the construction of these scaffolds; however, there are only limited protocols for assembling 2-aminofurans, an important class of synthetic intermediates in organic synthesis.[2] The traditional methods include the reaction of α-bromoacetophenones with malononitrile;[3] three-component coupling of isocyanides, electron-poor alkynes, and carbonyl compounds;[4] Stetter-γ-keto nitrile cyclization between acylidenemalononitriles and aromatic aldehydes;[5] Cu-catalyzed [3 + 2] cycloaddition of carbenoids with enamines;[6] Au- or Rh-catalyzed transformation of ynamides;[7] and Cu-catalyzed direct amidation of furans (Scheme 1).[8] Despite the impressive progress made in this area, the exploration of new methods for the preparation of 2-aminofurans from readily available starting materials is still highly desirable.

Scheme 1. Representative Approaches to 2-Aminofurans



On the other hand, the transition-metal-catalyzed cyclization of allenyl compounds, developed by Marshall,[9] Hashmi,[10] Ma,[11] Gevorgyan,[12] Che,[13] Alcaide,[14] Wang,[15] and others,[16] has become a straightforward and particularly effective entry to polysubstituted furans. It should be noted that the previous reports are mainly restricted to allenyl compounds,[9−14] while the catalytic transformation of homoallenyl derivatives affording furan moieties has attracted less attention.[15,16] Pursuing our recent interest in the functionalization of ynamides,[17] we describe here an operationally simple Pd-catalyzed divergent cyclization including cycloisomerization and aerobic oxidative cycloisomerization of homoallenyl amides, which are assembled by a Zn-promoted Saucy−Marbet rearrangement of *N*-sulfonyl ynamides. The reaction selectively produces 2-amino-5-alkylfurans or 2-amino-5-formylfurans under very mild reaction conditions (Scheme 2).

Scheme 2. Summary of This Work



At the outset, we focused on the preparation of homoallenyl amides. Although Hsung and co-workers have developed an efficient method for the synthesis of homoallenyl amides via a *para*-nitrobenzenesulfonic acid catalyzed Saucy−Marbet rearrangement of oxazolidinone- or lactam-substituted ynamides,[18] the analogue transformation of *N*-sulfonyl ynamides has not been achieved yet. After some trials (for details, see Table S1, in the Supporting Information), we found that the reaction conditions comprised *N*-sulfonyl ynamides (0.25 mmol), propargyl alcohols (0.375 mmol), $ZnBr_2$ (0.3 mmol), and dry CH_2Cl_2 (1 mL) at room temperature under a N_2 atmosphere for

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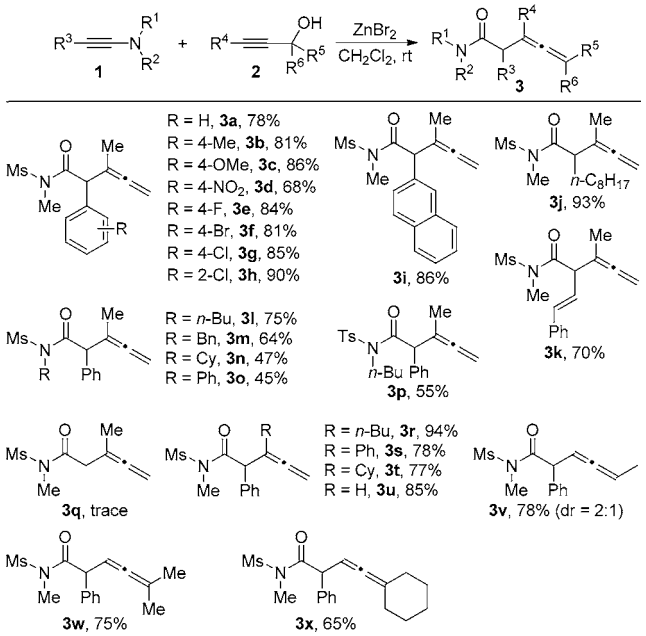
12 h proved to be effective for the generation of homoallenyl amides, providing **3a** in 78% yield.

As shown in Scheme 3, a wide range of functional groups including electron-donating and -withdrawing substituents on the aryl ring of **1** were well tolerated, allowing facile access to homoallenyl amides (**3a**–**3h**). In addition to aryl ynamides, alkyl and alkenyl counterparts offered the desired products in high yields (**3j** and **3k**). In contrast, terminal ynamide **1q** failed to undergo the reaction due to the hydrolysis of starting material. The reaction of *N*-Cy and *N*-Ph substrates gave the corresponding amides in relatively lower yields, probably because of the increased steric hindrance (**3n** and **3o**). On the other hand, we observed a broad scope with regard to propargyl alcohols. For instance, the coupling of **1a** with hept-2-yn-1-ol (**2b**) occurred efficiently to give **3r** in 94% yield. 3-Phenylprop-2-yn-1-ol (**2c**), 3-cyclohexylprop-2-yn-1-ol (**2d**), and prop-2-yn-1-ol (**2e**) furnished the expected products in comparable yields, demonstrating that this protocol is not sensitive to the steric environment of the R^4 group of **2** (**3s**–**3u**). But-3-yn-2-ol (**2f**), a secondary propargyl alcohol, was also a competent substrate for the amide formation (**3v**). As for tertiary propargyl alcohols, 2-methylbut-3-yn-2-ol (**2g**) and 1-ethynylcyclohexanol (**2h**), for example, participated well in this rearrangement to deliver **3w** and **3x** in satisfactory yields.

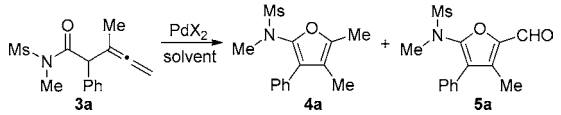
Scheme 3. Synthesis of Homoallenyl Amides[a,b]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.375 mmol), $ZnBr_2$ (0.3 mmol), CH_2Cl_2 (1 mL), under N_2, rt, 12 h. [b]Isolated yield. rt = room temperature.

Next, we turned our attention to the construction of 2-aminofurans. We envisioned that oxypalladation of **3** followed by deprotonation would produce a furfurylpalladium intermediate **II**, and subsequent protonation of the C–Pd bond of **II** might ultimately provide 2-amino-5-alkylfurans in an atom-economic manner (Scheme 2). To this end, **3a** was treated with 5 mol % of $PdCl_2$ in MeCN under an air atmosphere at room temperature for 3 h. As a result, the cycloisomerization product **4a** was isolated in 67% yield (Table 1, entry 1). Switching from $PdCl_2$ to $PdBr_2$ led to a 72% yield of **4a**, and interestingly, a 2% yield of **5a** was obtained as well (Table 1, entry 3). Running the reaction under a N_2 atmosphere inhibited the production of **5a** and exclusively formed **4a** in 78% yield (Table 1, entry 4). In contrast, the utilization of DMF instead of MeCN gave **5a** in 80% yield (Table 1, entry 14). As expected, replacing air with N_2 completely shut down this Pd-catalyzed aerobic oxidative cycloisomerization reaction (Table 1, entry 15).[19] The structure of 2-aminofurans **4a** and **5a** was corroborated by the X-ray crystal analysis.[20]

Table 1. Screening of the Reaction Conditions for Divergent Cyclization of 3a[a]



entry	PdX_2	solvent	yield of **4a** (%)[b]	yield of **5a** (%)[b]
1	$PdCl_2$	MeCN	67	0
2	$Pd(OAc)_2$	MeCN	0	5
3	$PdBr_2$	MeCN	72	2
4[c]	$PdBr_2$	MeCN	78	0
5	$PdBr_2$	HOAc	0	4
6[d]	$PdBr_2$	THF	3	3
7[d]	$PdBr_2$	dioxane	7	36
8[d]	$PdBr_2$	toluene	2	18
9[d]	$PdBr_2$	CH_2Cl_2	6	32
10[d]	$PdBr_2$	EtOH	0	8
11[d]	$PdBr_2$	DMSO	4	75
12[d]	$PdBr_2$	NMP	0	63
13[d]	$PdBr_2$	DMA	0	70
14[d]	$PdBr_2$	DMF	0	80 (81)[d,e]
15[c,d]	$PdBr_2$	DMF	0	0

[a]Reaction conditions: **3** (0.25 mmol), PdX_2 (5 mol %), solvent (2 mL), under air, rt, 3 h. [b]Isolated yield. [c]Under N_2. [d]12 h. [e]Under O_2.

Subsequently, we examined the scope and limitations of this Pd-catalyzed divergent cyclization reaction (Scheme 4). Under the optimized reaction conditions A, a variety of 2-amino-5-alkylfurans could be synthesized in good to excellent yields via the Pd-catalyzed cycloisomerization process, regardless of the electronic nature of the substituents on starting materials **3**. Halogen atoms such as F, Br, and Cl were very compatible, which can be utilized for further transformation (**4e**–**4h**). The *N*-*n*-Bu, *N*-Bn, and *N*-Cy substrates underwent the cycloisomerization smoothly to form **4i**–**4k** in high yields. Besides tetrasubstituted furans, trisubstituted furan **4n** was also assembled in a good yield. Furthermore, the reaction of 2-alkyl- and 2-alkenyl-3,4-dienamides **3j** and **3k** took place efficiently, producing **4o** and **4p** in 82% and 73% yield, respectively. The Pd-catalyzed cycloisomerization of **3v** proceeded as well to give **4t** in 64% yield. No reaction occurred when **3w** and **3x** were employed as the substrates, probably due to the increased steric environment.

Under the optimum reaction conditions B, a number of 2-amino-5-formylfurans could be synthesized successfully. Functional groups such as OMe, NO_2, F, Cl, and Br presented good compatibility (**5c**–**5h**). For example, **5f** was generated from **3f** in 80% yield. Likewise, the reaction was applicable to **3j** and **3k**, delivering **5o** and **5p** in respective yields of 70% and 63%. The Pd-catalyzed aerobic oxidative cycloisomerization of **3v**, **3w**, or **3x** failed to proceed, indicating that substitution at the C5 site of **3** had a detrimental effect on this transformation.

To gain some insights into the mechanism of this Pd-catalyzed divergent cyclization process, **3a**-D (81% *D*) was subjected to the

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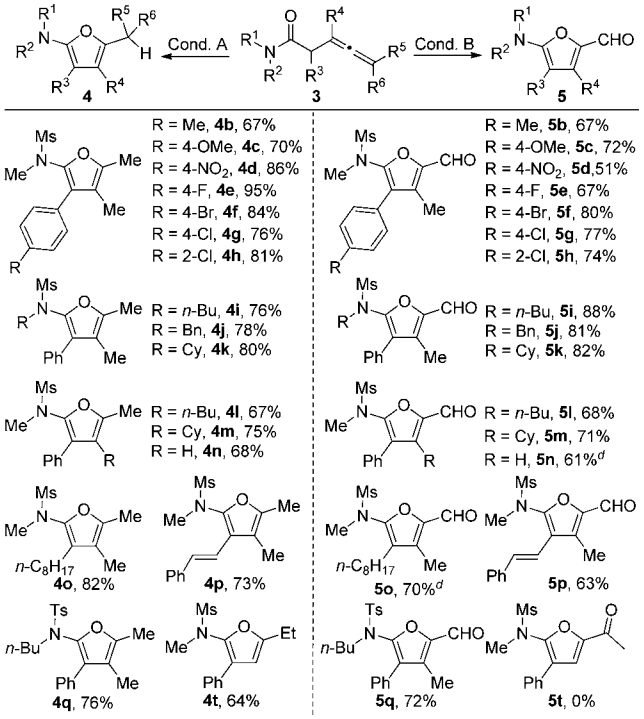
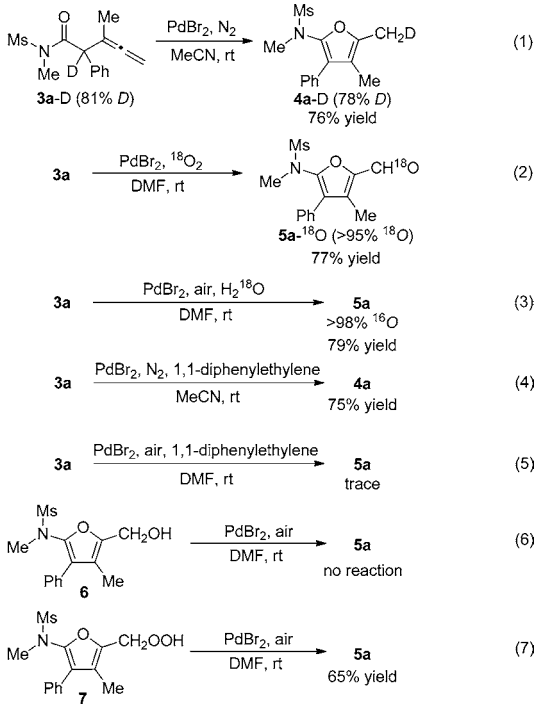
Scheme 4. Scope of Pd-Catalyzed Divergent Cyclization of Homoallenyl Amides[a,b,c]



[a]Reaction conditions A: **3** (0.25 mmol), $PdBr_2$ (5 mol %), MeCN (2 mL), under N_2, rt, 3 h. [b]Reaction conditions B: **3** (0.25 mmol), $PdBr_2$ (5 mol %), DMF (2 mL), under air, rt, 12 h. [c]Isolated yield. [d]Run at 50 °C.

standard reaction conditions A. Consequently, **4a**-D was isolated in 76% yield with 78% deuterium incorporation (eq 1). We



conducted the ^{18}O isotope labeling experiments. The reaction took place smoothly under an $^{18}O_2$ atmosphere, producing **5a**-^{18}O in 77% yield (eq 2). The ESI-MS spectrum displayed an m/z signal at 296.0845, which matched well with the $[M + H + 2]^+$ ion of **5a**. Moreover, the ^{18}O incorporation was not observed when the reaction was conducted by adding 5 equiv of $H_2{}^{18}O$ to the reaction conditions B (eq 3). These results demonstrated that O_2 took part in this transformation and that the oxygen atom in aldehydes originated from the molecular oxygen. In the presence of 2 equiv of 1,1-diphenylethylene, the Pd-catalyzed cycloisomerization of **3a** occurred uneventfully, affording **4a** in 75% yield (eq 4), while only a trace amount of **5a** was formed with the addition of 1,1-diphenylethylene (eq 5), indicating that a radical mechanism might be involved in the Pd-catalyzed aerobic oxidative cycloisomerization reaction. Further, furfuryl alcohol **6**, generated by reducing **5a** with $NaBH_4$, was unreactive under the reaction conditions B (eq 6), whereas peroxide **7** was smoothly converted into **5a** under the identical conditions (eq 7). These results pointed out that peroxide may be a reactive intermediate for this Pd-catalyzed aerobic oxidative cycloisomerization of **3**. Indeed, the formation of peroxide intermediate **7** was also confirmed by monitoring the transformation of **3a** with NMR analysis (for more details, see Table S2, in the Supporting Information) under the reaction conditions B (Figure 1).

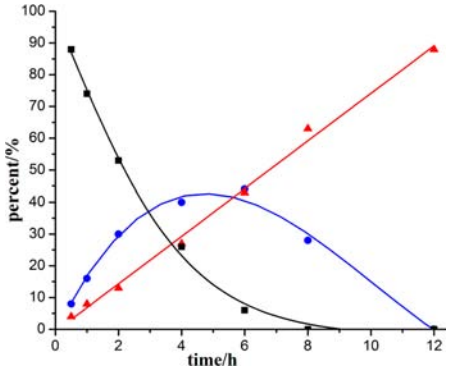


Figure 1. Kinetic profiles of Pd-catalyzed aerobic oxidative cycloisomerization of **3a** under the reaction conditions B, monitored by NMR with $MeNO_2$ as the internal standard. ■ = **3a**, ● = **7**, and ▲ = **5a**.

In summary, we have developed a simple, efficient, and divergent transformation, including the Pd-catalyzed cycloisomerization and aerobic oxidative cycloisomerization, of homoallenyl amides, furnishing 2-amino-5-alkylfurans and 2-amino-5-formylfurans in good to excellent yields. Preliminary mechanistic studies indicate that peroxides may be the key intermediates for this Pd-catalyzed radical aerobic oxidative cycloisomerization of homoallenyl amides. The mild reaction conditions, high atom economy, and utilization of air as the oxygen source make this protocol very environmentally friendly and practical to the synthetic community. Further investigations on the reaction mechanism as well as synthetic application of this protocol are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data for all new compounds **3**−**7**, and crystallographic data for **4a** and **5a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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AUTHOR INFORMATION

Corresponding Author

*E-mail: gangguo@zjnu.cn.

Notes

The authors declare no competing financial interest.

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(20) CCDC 1047914 (**4a**) and 1047915 (**5a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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