Palladium-Catalyzed Oxidation and Cyclization of Carbon–Carbon Triple Bonds in Fluorous Media Using Molecular Oxygen

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Received 16 November 2010

Dedicated to Professor Xiyan Lu and Professor Lixin Dai

Abstract: An intriguing, facile, and efficient oxidation and cyclization of alkynes catalyzed by $Pd(OAc)_2$ in a fluorous biphasic system of *N*,*N*-dimethylacetamide (DMA) and perfluorodecalin directly with molecular oxygen is described, which opens an efficient access to tetrasubstituted furans. Under the optimized conditions, intermolecular reaction between diverse alkynes provides the corresponding mixture of regioisomers with appreciable selectivity. Intramolecular oxidation and cyclization of alkynes are also successfully demonstrated. The reaction proceeds efficiently under mild conditions with atmospheric oxygen as the sole oxidant.

Key words: perfluorodecalin, molecular oxygen, alkynes, palladium-catalyzed, oxidation

Functionalized furans play important roles in organic chemistry not only due to their presence as key structural units in many natural products and important pharmaceuticals,[1] but they can also serve as important intermediates for many organic transformations.[2] Therefore, the syntheses of polysubstituted furans continue to attract the interest of many synthetic chemists.[3]

Classical methods for the preparation of substituted furans have been based on direct functionalization of existing furans or cyclization of acyclic substrates.[4] Among different protocols for achieving this goal, transition-metal-catalyzed cycloisomerization of unsaturated acyclic precursors to prepare multiple substituted furans has attracted much attention. However, these known synthetic methods have several drawbacks, for example, insufficient yields of the desired compounds, harsh conditions, and/or the absence of an efficient and general procedure for the preparation of the rather advanced starting materials. There is still a need for new improved routes, which should be suitable for constructing molecular materials and avoid the use of stoichiometric reagents.

Palladium-mediated organic transformations continue to be a fascinating area in organic synthesis as well as organometallic chemistry due to their versatility and ability to give unexpected outcomes.[5] In a preliminary communication, we have reported the utility of a catalytic amount $Pd(OAc)_2$, and $Zn(OTf)_2$ efficiently catalyzed the oxidation and cyclization of aromatic alkynes with molecular oxygen as the oxidant to afford tetrasubstituted furans.[6] However, the method has problems including drastic reaction conditions, narrow substrate scope, and low yield. Therefore, development of a mild and practical synthetic method is more attractive.

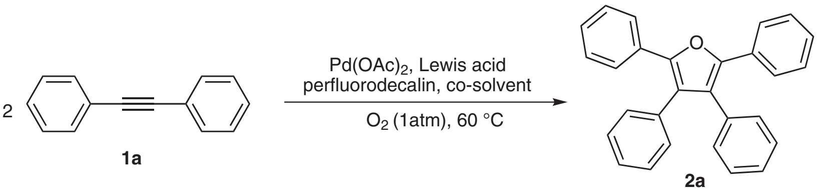
Perfluorinated hydrocarbons, which can fully solubilize a range of gases,[7] were used firstly for synthetic applications by Horvath and Rabai. They showed that perfluorinated hydrocarbons are ideal solvents for organic reactions, in which gases serve as one reactant, particularly suited for oxidation reactions.[8] Indeed, a variety of common organic reactions have achieved in fluorous media.[9]

In this manuscript, we report on using fluorous solvents which can be potentially reused for further reaction runs as medium to synthesize tetrasubstituted furans by $Pd(OAc)_2$-catalyzed oxidation and inter- and intramolecular alkyne–alkyne cyclization with atmospheric oxygen as the sole oxidant under very mild conditions. Reaction of diverse alkynes is also successfully demonstrated. This should significantly expand the range of suitable starting materials for the synthesis of tetrasubstituted furans.

Catalyzed oxidation and cyclization of 1,2-diphenylethyne in perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans* mixture) was selected as a model reaction for studying the effect of co-solvent and Lewis acid. As shown in Table 1, the reaction did not proceed without Lewis acid (Table 1, entry 1). To our delight, we found that the reaction performed with addition of $ZnCl_2$ (Table 1, entry 2). The reaction showed strong co-solvent dependence. Among the co-solvents used, DMF, 1,4-dioxane, and DMA were proved appropriate (Table 1, entries 2–7). A variety of Lewis acids were tried (Table 1, entries 8–10), and the results showed that when $ZnCl_2$ was employed the reaction could afford **2a** in good yields. The lower product yield of 40% was obtained when decreasing the catalyst amount from 10 mol% to 2 mol% (Table 1, entry 11). Moreover, the yield of tetrasubstituted furans decreased dramatically in the absence of perfluorodecalin after 24 hours (Table 1, entry 12). It is noteworthy that the reaction proceeded badly under air atmosphere (Table 1, entry 13). The optimized reaction conditions are as following: **1a** (1.0 mmol), $Pd(OAc)_2$ (10 mol%) with Lewis acid (20 mol%) and co-solvent (0.5 mL), perfluorodecalin($C_{10}F_{18}$, *cis* and *trans* mixture, 0.5 mL) at 60 °C for 24 hours (Table 1, entry 7).

SYNLETT 2011, No. 7, pp 1023–1027
Advanced online publication: 29.03.2011
DOI: 10.1055/s-0030-1259929; Art ID: W34010ST

Table 1 Optimization of Reaction Conditions for the Synthesis of Tetrasubstituted Furans[a]



Entry	Lewis acid	Co-solvent	Yield (%)[b]
1	–	DMA	0
2	$ZnCl_2$	MeCN	3
3	$ZnCl_2$	EtOH	14
4	$ZnCl_2$	DMF	87
5	$ZnCl_2$	1,4-dioxane	81
6	$ZnCl_2$	DMSO	57
7	$ZnCl_2$	DMA	94 (90)
8	$ZnCl_2 \cdot H_2O$	DMA	trace
9	$Zn(OTf)_2$	DMA	5
10	$CuCl_2$	DMA	0
11[c]	$ZnCl_2$	DMA	40
12[d]	$ZnCl_2$	DMA	8
13[e]	$ZnCl_2$	DMA	trace

[a] Reaction conditions: 1,2-Diphenylacetylene (1.0 mmol), $Pd(OAc)_2$ (10 mol%), Lewis acid (20 mol%), co-solvent (0.5 mL), and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans* mixture, 0.5 mL), 60 °C, O_2 (1 atm), 24 h.

[b] Determined by GC. Number in parentheses was isolated yield.

[c] $Pd(OAc)_2$ (2 mol%).

[d] DMA (1.0 mL), perfluorodecalin (0 mL).

[e] Air (1 atm).

With the optimized reaction conditions in hand (Table 1, entry 7), we began to explore the scope and limitations of this method. As shown in Table 2, this transformation was highly efficient for a broad scope of substrates, wherein various functional groups, including halide, methoxy, alkyl, and trifluoromethyl could be tolerated, and product **2g** was structurally characterized by X-ray diffraction measurement (Figure 1). Suitable alkyne substrates were easily prepared by Sonogashira reaction, and the oxidation cyclization reaction proceeded smoothly to give the tetrasubstituted furans **2a**–**k** in good to excellent yields.

It was found that alkynes containing a substituent at the 2-position generally resulted in lower yields than alkynes containing substituent at the 3- or 4-position (Table 2, entries 8–10). This may be attributed to steric effects. Otherwise, 1,2-di-*p*-tolylethyne (**1b**), 1,2-bis(4-butylphenyl)ethyne (**1c**), 1,2-bis(4-methoxyphenyl)ethyne (**1d**), and 1,2-di-*m*-tolylethyne (**1e**) possessing electron-donating groups on the aromatic ring afforded the product **2b**, **2c**, **2d**, and **2e** in 90%, 89%, 80%, and 65% isolated yields, respectively (Table 2, entries 1–4). In comparison, reaction of 1,2-bis(3-chlorophenyl)ethyne (**1f**), 1,2-bis[4-(trifluo-

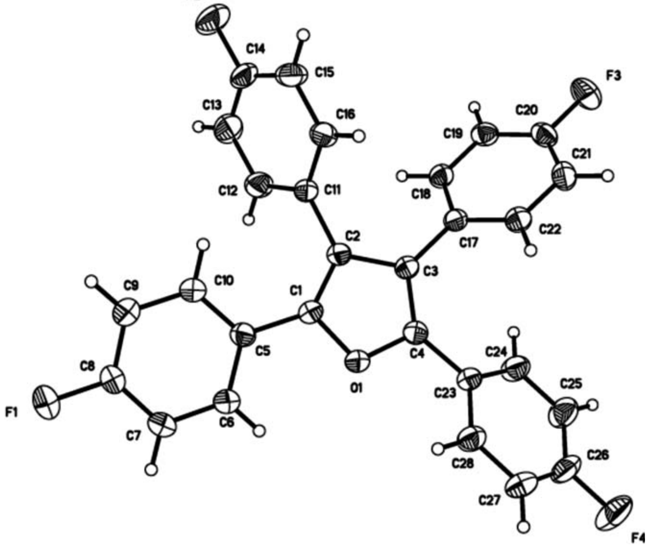
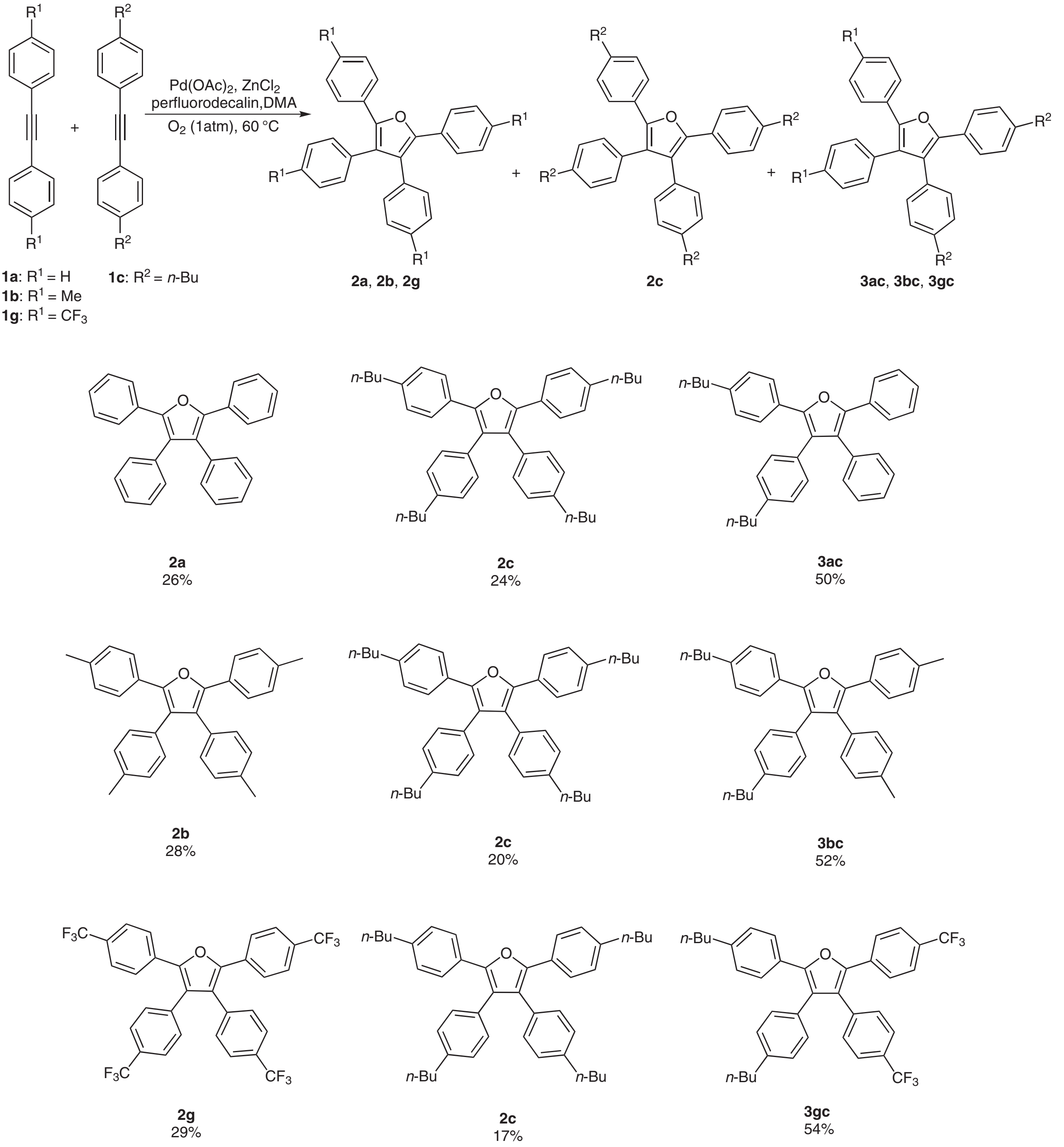


Figure 1 X-ray crystal structure of compound **2g**

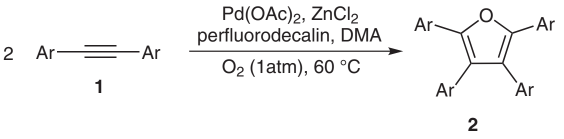
romethyl)phenyl]ethyne (**1g**), and 1,2-bis(4-bromophenyl)ethyne (**1h**) substituted with electron-withdrawing groups took place in higher yield to give products **2f**, **2g**, and **2h** in 74%, 95%, and 86% (Table 2, entries 5–7). Noteworthy, the tetrasubstituted furan formation that tolerates aryl bromides offers potential for further functionalization of furans by, for example, catalytic cross-coupling reactions.

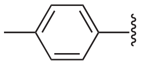
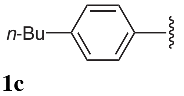
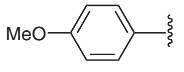
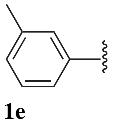
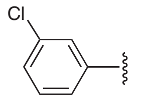
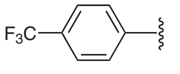
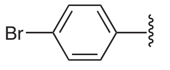
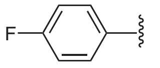
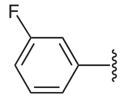
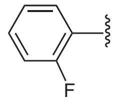
Next, the practical utility of this oxidation and cyclization process between diverse alkynes under typical conditions was evaluated. The reactions of 1,2-diphenylethyne (**1a**), 1,2-bis(4-(trifluoromethyl)phen yl)ethyne (**1g**), or 1,2-di-*p*-tolylethyne (**1b**) with 1,2-bis(4-butylphenyl)ethyne (**1c**) were investigated briefly and resulted in statistical distribution of symmetric tetrasubstituted furans along with the dissymmetric product (Scheme 1).



Scheme 1 Pd(OAc)$_2$/ZnCl$_2$-catalyzed oxidation cyclization of diverse alkynes to afford tetrasubstituted furans. Reactions were carried out using diverse alkynes (0.5 + 0.5 mmol), Pd(OAc)$_2$ (10 mol%), Lewis acid (20 mol%), DMA (0.5 mL), and perfluorodecalin ($C_{10}F_{18}$, *cis* and *trans* mixture, 0.5 mL), 60 °C, O_2 (1 atm), 24 h. Isolated yields are given.

Table 2 Pd(OAc)$_2$/ZnCl$_2$-Catalyzed Oxidation Cyclization of Various Alkynes to Afford Tetrasubstituted Furans[a]

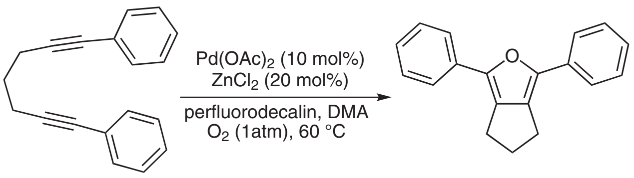


Entry	Ar	Product	Yield (%)[b]
1	 **1b**	**2b**	90
2	 **1c**	**2c**	89
3	 **1d**	**2d**	80
4	 **1e**	**2e**	65
5	 **1f**	**2f**	74
6	 **1g**	**2g**	95
7	 **1h**	**2h**	86
8	 **1i**	**2i**	83
9	 **1j**	**2j**	69
10	 **1k**	**2k**	46

[a] Reactions were carried out using alkyne (1 mmol), Pd(OAc)$_2$ (10 mol%), Lewis acid (20 mol%), DMA (0.5 mL), and perfluorodecalin (C$_{10}$F$_{18}$, *cis* and *trans* mixture, 0.5 mL), 60 °C, O$_2$ (1 atm), 24 h.

[b] Isolated yields.

To further extend the scope of the reaction, we have explored the utility of internal alkynes. Unfortunately, the yields were low under the optimized conditions.



1,7-diphenylhepta-1,6-diyne

2l, 32%

Scheme 2 Pd(OAc)$_2$/ZnCl$_2$-catalyzed oxidation–cyclization of internal alkynes

In summary, we have developed a highly efficient method for palladium-catalyzed oxidation–cyclization reaction of alkynes to synthesize tetrasubstituted furans with an atmospheric oxygen as the sole oxidant in a fluorous biphasic system of *N*,*N*-dimethylacetamide and perfluorodecalin at 60 °C (Scheme 2). The presented results clearly demonstrate that Pd(II) acted as a one-pot catalyst to catalyze the oxidation of alkynes followed by an efficient cyclization reaction, which resulted in a direct conversion of alkynes into tetrasubstituted furans. It is also indicated that not only intermolecular but also intramolecular alkyne–alkyne coupling, oxidation, and cyclization can complete under similar reaction conditions. The utilization of perfluorocarbon should significantly expand the range of suitable starting materials for the oxidation of alkynes. As the reaction tolerates aryl halides, it could potentially provide access to a variety of molecular materials, as well as mixed arylfuran polymers from aromatic diynes. This novel oxidation methodology should find widespread use in organic synthesis. Further synthetic applications and studies of the reaction mechanism are in progress.

Typical Procedure for the Preparation of the Tetrasubstituted Furans

Alkyne (1 mmol), Pd(OAc)$_2$ (10 mol%), and ZnCl$_2$ (20 mol%) were added to an oven-dried Schlenck tube under air. The septum-sealed tube was evacuated and refilled with O$_2$ thrice. DMA (0.5 mL) and perfluorodecalin (0.5 mL) were added via syringe. The reaction mixture was heated in an oil bath at 60 °C for 24 h. After the reaction completed, the product was obtained by silica gel chromatography with light PE–CH$_2$Cl$_2$ as eluent.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

The authors thank the National Natural Science Foundation of China (Grants 20332030, 20572027, 20625205 and 20772034), National Basic Research Program of China (973 Program) (No. 2011CB808600), the Doctoral Fund of the Ministry of Education of China (20090172110014), and Guangdong Natural Science Foundation (No. 10351064101000000) for financial support

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