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Photoinduced Wolff rearrangement/Pd-catalyzed [3+2] cycloaddition sequence: an unexpected route to tetrahydrofurans

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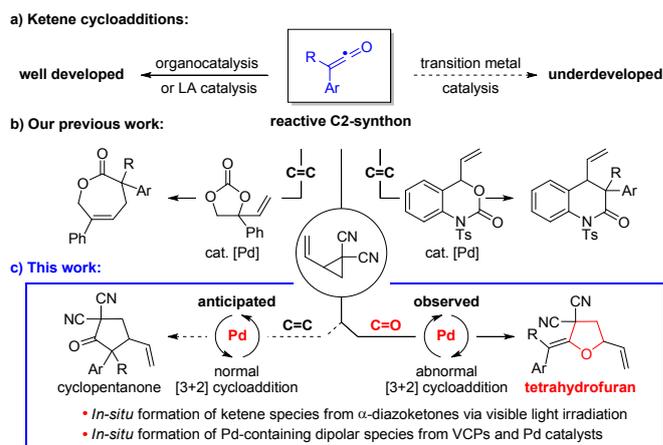
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A novel sequential reaction that combines a visible light-induced Wolff rearrangement of α -diazoketones and a Pd-catalyzed [3+2] cycloaddition of vinyl cyclopropanes with the resulting ketenes is described in this work. Selective *O*-allylic alkylation was observed over *C*-allylic alkylation, which unexpectedly led to a series of highly functionalized tetrahydrofurans with high efficiency (20 examples, 58-99% yields).

Due to the pioneering work of Staudinger (namely, the Staudinger ketene cycloaddition),¹ ketenes have been established as effective C2-synthons for [n+2] cycloadditions.²⁻⁴ Particularly in the past few decades, the application of organocatalysis³ and Lewis acid (LA) catalysis⁴ to this research field (Scheme 1a, left) has resulted in many significant transformations towards structurally diverse heterocycles. Although it is recognized as a powerful strategy in modern organic synthesis,⁵ transition metal (TM) catalysis has received less attention from the synthetic community in the field of ketene cycloadditions and other conversions (Scheme 1a, right). As indicated by many proceeding studies, this is likely due to the TM-promoted decarbonylation of ketenes to form stable M-CO complexes, the cycloaddition of ketenes with M=O and ketene homodimerizations under thermal conditions, which impede the wide application of this catalysis strategy in ketene transformations.⁶ Up to now, there were only isolated examples in this field. In 2007, Tang, Zhou and co-workers developed a Fe-catalyzed asymmetric olefination reaction of ketenes with diazoacetates for synthesizing chiral allenes.⁷ In 2011, the group of

Louie disclosed a Ni-catalyzed cycloaddition of ketenes with diynes, affording 2,4-cyclohexadienones in moderate to good yields.^{6d} Very recently, by means of sequential visible light photoactivation and asymmetric palladium catalysis, we successfully achieved [4+2]^{8a} and [5+2] cycloadditions^{8b} of photogenerated ketenes (from α -diazoketones)^{9,10} with Pd-containing dipoles (*in-situ* generated from vinyl carbonates) (Scheme 1b).^{11,12} Despite these successes, it is still desirable to use transition metal catalysis to exploit the reactivity of ketenes for constructing new and diverse molecular skeletons.



Scheme 1 a) Previous work on catalytic cycloadditions of ketenes. b) Our previous work on Pd-catalyzed dipolar cycloadditions of ketenes with vinyl carbonates. c) This work: unexpected [3+2] cycloaddition of ketenes and VCPs.

Given that ketenes are highly electron-deficient species that can react with carbon anions,^{8c} we wondered whether [3+2] cycloadditions of vinyl cyclopropanes (VCPs)¹³ and α -diazo ketones could occur by means of the strategy that combines visible light photoactivation and palladium catalysis.¹⁴ To our surprise, the anticipated cyclopentanone via the normal [3+2] cycloadditions was not observed (Scheme 1c, left). Instead, an unexpected tetrahydrofurans via an abnormal [3+2] reaction was afforded with good efficiency and selectivity (Scheme 1c, right). Notably, the synthesis of tetrahydrofurans and their derivatives is an important

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task for synthetic chemists due to their popularity in many natural products and pharmaceutical and agrochemical agents.¹⁵ To this end, Lewis acid-catalyzed [3+2] cycloadditions of donor-acceptor cyclopropanes with aldehydes¹⁶ and Rh- or Cu-catalyzed [3+2] cycloadditions of carbonyl ylides with alkenes¹⁷ have been well established. Herein, we describe our experimental results of a novel reaction sequence by combining a photoinduced Wolff rearrangement and a Pd-catalyzed [3+2] cycloaddition, providing functionalized tetrahydrofuran products in good efficiency and selectivity.

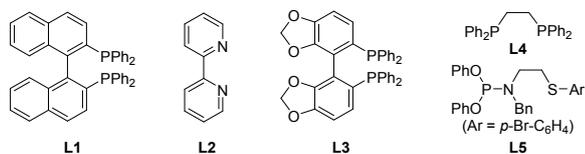
Initially, we performed the sequential photoinduced Wolff rearrangement/Pd-catalyzed [3+2] cycloaddition reaction with α -diazoketone **1a** and VCP **3a** as the model substrates and a mixture of Pd₂(dba)₃•CHCl₃ and racemic BINAP as the catalyst. Irradiation of the reaction mixture with 6 W blue LEDs at room temperature only produce trace amount of product **4aa**. Within 10 minutes, only the rapid decomposition of VCP **3a** and slow conversion of α -diazoketone **1a** were observed (Table 1, entry 1). Then, a revised procedure was chosen in which α -diazoketone **1a** was irradiated first for 4 h in toluene and then, the resulting ketene solution together with VCP **3a** were introduced to the solution of the pre-

Table 1 Optimization of conditions for the sequential reaction^a



entry	ligand	time	solvent	yield (%) ^b
1 ^c	L1	10 min	toluene	trace
2	L1	9 h	toluene	41
3	L2	9 h	toluene	0
4	L3	9 h	toluene	trace
5	L4	9 h	toluene	33
6	L5	9 h	toluene	63
7	L5	9 h	DCM	86
8	L5	9 h	CH ₃ CN	56
9	L5	9 h	PhCl	93
10	L5	4 h	DCE	96
11 ^c	L5	4 h	DCE	trace
12 ^d	-	4 h	DCE	0

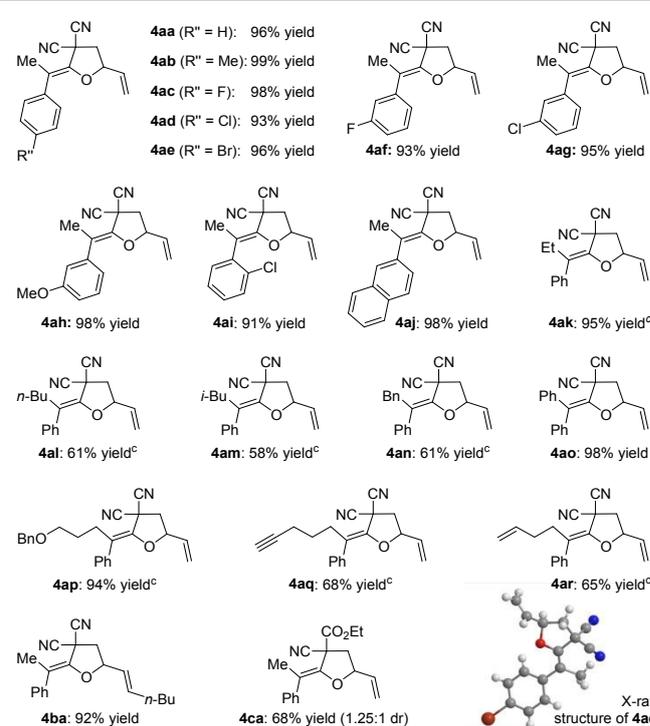
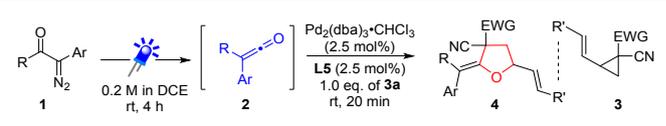
^aConditions: **1a** (0.4 mmol) in 2 mL of solvent was irradiated at rt under 6 W blue LEDs for 4h; then, the resulting solution **2a** together with **3a** (0.2 mmol) were added to the pre-prepared solution of palladium complex (2.5 mol%) and ligand (5 mol%) in 2 mL of solvent and stirred at rt for 20 minutes. ^bIsolated yield. ^cSimultaneously, add **1a** and **3a** to the reaction system. ^dNo ligand. DCM: dichloromethane; PhCl: chlorobenzene; DCE: 1,2-dichloroethane.



prepared palladium catalyst. Delightedly, the reaction did indeed occur and the tetrahydrofuran **4aa** was produced in 41% yield with the new procedure (Table 1, entry 2). Encouraged by this promising result, we evaluated a series of ligands as shown in entries 2-6 of Table 1. As a result, hybrid P,S-ligand **L5** stood out as the optimal ligand for this sequential reaction, affording the desired product in 63% yield (Table 1, entry 6). Routine screening of solvents (Table 1, entries 6-10) indicated that DCE resulted in the best reaction efficiency (Table 1, entry 10: 96% yield). Control experiments further indicated that both the irradiation of α -diazoketone **1a** with 6 W blue LEDs, a stepwise operation and the hybrid P,S ligand **L4** were important for this sequential reaction (Table 1, entry 10 vs entries 11 and 12).

After establishing the optimal conditions, we began to determine the generality of this sequential photoinduced Wolff rearrangement/Pd-catalyzed [3+2] cycloaddition reaction. First, we studied the scope of α -diazoketones **1**. We generally observed excellent reaction efficiency and selectivity. As highlighted in Table 2, aryl-substituted 1-diazopropan-2-ones were successfully used in this sequential transformation, regardless of the electronic feature and substitution pattern

Table 2 The generality of the sequential reactions^{a,b}

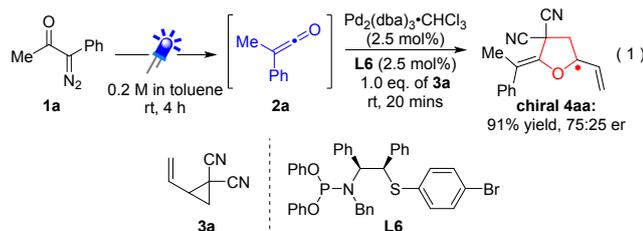


^aUnless noted otherwise, reactions were implemented under the conditions as described in entry 10 of Table 1 at 0.2 mmol scale.

^bIsolated yield. ^cThe Wolff rearrangement was performed at -10 °C for 8 h.

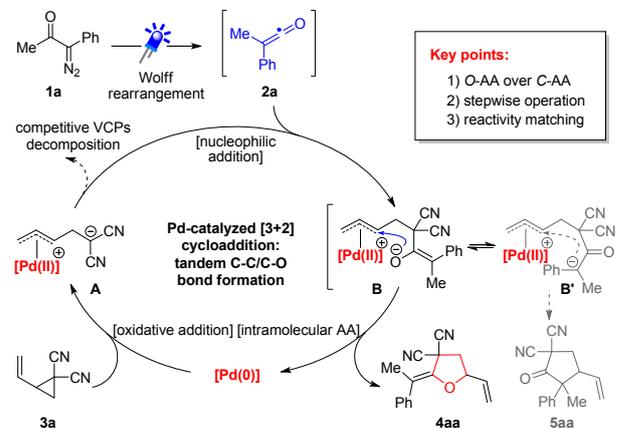
on the benzene ring. A range of tetrahydrofurans were obtained in high reaction yields (Table 2, **4aa-4aj**, 91-99% yields). The structure of product **4ae** was further confirmed through single-crystal X-ray diffraction analysis.¹⁸ In addition, replacement of the methyl group of α -diazoketone **1a** with other linear or branched alkyl group, and benzyl or phenyl groups were also shown to be feasible, producing the corresponding products in moderate to high yields (Table 2, **4ak-4ao**, 58-98% yields). Notably, reactions with α -diazoketones having functional groups such as BnO, alkenyl and alkynyl also proceeded well, likely benefiting from the mild reaction conditions of the *in situ* ketene formation (Table 2, **4ap-4ar**, 65-94% yields). Notably, the success of the photoinduced Wolff rearrangement/Pd-catalyzed [3+2] cycloaddition sequence can be further extended to other VCPs. For example, when (E)-2-(hex-1-en-1-yl)cyclopropane-1,1-dicarbonitrile **3b** or ethyl 1-cyano-2-vinylcyclopropane-1-carboxylate **3c** was subjected to the standard reaction conditions, the desired products **4ba** and **4ca** were delivered in satisfactory yields (Table 2, **4ba**, 92% yield; **4ca**, 68% yield).¹⁹ Monoaryl- and dialkyl-substituted α -diazoketones were also tested in this transformation; however, only the generation of the ketene species and decomposition of VCPs were observed, without the production of tetrahydrofuran products.

After determining the scope of this sequential reaction, we turned our attention to probing an asymmetric variant. As highlighted in Eq. 1, when the hybrid P,S ligand **L5** was replaced with a chiral ligand **L6**, which was developed by our group and exhibited high levels of enantio-control in Pd-catalyzed decarboxylative [4+2] cycloadditions, an obvious enantio-induction and good reaction efficiency were observed for this reaction sequence (chiral **4aa**: 91% yield and 75:25 er). In contrast, many other classic chiral ligands, such as MonoPhos, Trost ligand, and PHOX ligand did not result in the desired product and *R*-BINAP only delivered a racemic product in 33% yield.²⁰



Next, on the basis of previously published results^{9,11} and our experiences in the field of transition metal-catalyzed dipolar cycloadditions,^{8,12} we proposed a possible mechanism to explain the production of tetrahydrofuran **4** from α -diazoketone **1a** and VCP **3a**. As depicted in Scheme 2, the photoinduced Wolff rearrangement of α -diazoketone **1a** first occurs under the irradiation of blue light, producing reactive ketene species **2a** which can exist in solution at room temperature for some time. Then, the reaction between VCP **3a** and the Pd(0) catalyst generates a Pd-containing 1,3-dipolar intermediate **A**. The nucleophilic addition of the carbanion partner of **A** to ketene **2a** generates a new zwitterionic intermediate **B** and its enol tautomer **B'**. Finally,

intramolecular allylic alkylation (AA) of the *O*-nucleophile, produces the unexpected tetrahydrofuran compound **4aa** (**B** \rightarrow **4aa**), replacing the anticipated cyclopentanone **5aa** via the AA process of the *C*-nucleophile (**B'** \rightarrow **5aa**). According to our experimental observations, the stepwise procedure is a good choice to ensure that enough ketene molecules are present to react with intermediate **A**, thus reducing the decomposition of VCP **3a** in the presence of palladium catalysts.



Scheme 2 Proposed mechanism.

In summary, we have developed a novel photoinduced, sequential Wolff rearrangement/Pd-catalyzed [3+2] cycloaddition reaction of α -diazoketones and VCPs. The unexpected selectivity of *O*-allylic alkylation over *C*-allylic alkylation in the ring-closing step results in the formation of highly functionalized tetrahydrofurans with high efficiency. The stepwise procedure and the choice of a hybrid P,S ligand were two key components of this success, which provides a direct and alternative route to generate significant tetrahydrofuran products under mild reaction conditions.

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- 18 CCDC 1855629 contain the supplementary crystallographic data of product 4ae and it can be downloaded for free (<https://www.ccdc.cam.ac.uk>).
- 19 Please see Scheme S1 in the Supporting Information for the unsuccessful VCPs.
- 20 Please see the details in the Supporting Information.

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