catalysts

MDPI

Article

Optimization of Palladium-Catalyzed One-Pot Synthesis of Functionalized Furans for High-Yield Production: A Study of Catalytic and Reaction Parameters

Kheira Haiouani [1], Sherif Hegazy [2], Huda Alsaeedi [3], Mikhael Bechelany [4,5] and Ahmed Barhoum [6,*]

1 Department of Chemistry, Faculty of Exact Sciences and Informatics, Djelfa University, Djelfa 17000, Algeria; k.haiouani@univ-djelfa.dz
2 Research Unit of Sustainable Chemistry, University of Oulu, P.O. Box 4300, FI-90014 Oulu, Finland; sherif.hegazy@oulu.fi
3 Department of Chemistry, College of Science, King Saud University, Riyadh 11451, Saudi Arabia; halsaeedi@ksu.edu.sa
4 Institut Européen des Membranes (IEM), UMR 5635, University of Montpellier, ENSCM, CNRS, 34095 Montpellier, France; mikhael.bechelany@umontpellier.fr
5 Functional Materials Group, Gulf University for Science and Technology, Masjid Al Aqsa Street, Mubarak Al-Abdullah 32093, Kuwait
6 NanoStruc Research Group, Chemistry Department, Faculty of Science, Helwan University, Cairo 11795, Egypt
* Correspondence: ahmed.barhoum@science.helwan.edu.eg

Abstract: This study investigates the palladium-catalyzed one-pot synthesis of functionalized furans from 1,3-Dicarbonyl compounds and alkenyl bromides, focusing on various catalysts and reaction parameters. Different catalysts, including $PdCl_2(CH_3CN)_2$, $Pd(OAc)_2$, and $Pd(acac)_2$ as well as solvents, bases, and oxidants, were systematically evaluated. $PdCl_2(CH_3CN)_2$ emerged as the most effective catalyst, achieving a remarkable yield of 94%. Optimal reaction conditions were identified as $PdCl_2(CH_3CN)_2$ in dioxane at 80 °C with K_2CO_3 as the base and $CuCl_2$ as the oxidant. This study also explored various 1,3-diketones including Cyclohexane-1,3-dione, 5,5-Dimethylcyclohexane-1,3-dione, 2*H*-Pyran-3,5(4*H*,6*H*)-dione, Cyclopentane-1,3-dione, Pentane-2,4-dione, Ethyl 3-oxobutanoate, 1,3-Diphenylpropane-1,3-dione, 1,3-Dip-tolylpropane-1,3-dione, 1,3-Bis(4-chlorophenyl)propane-1,3-dione, and 1,3-Bis(4-bromo- phenyl)propane-1,3-dione, alongside different alkenyl bromides such as allyl bromide, (*E*)-1-Bromo-3,4-dimethylpent-2-ene, 1-Bromo-3-methylbut-2-ene, 3-Bromocyclohex-1-ene, and (*E*)-1-Bromohex-2-ene. These variations demonstrated the method's versatility and the significant impact of substituents on reactivity and reaction yield. These findings highlight the importance of optimizing reaction conditions to maximize efficiency and provide insights into improving catalytic processes for enhanced product yields.

Keywords: palladium; catalysis; one-pot reaction; functionalized furans; alkylation–cyclization; 1,3-dicarbonyl compounds

Citation: Haiouani, K.; Hegazy, S.; Alsaeedi, H.; Bechelany, M.; Barhoum, A. Optimization of Palladium-Catalyzed One-Pot Synthesis of Functionalized Furans for High-Yield Production: A Study of Catalytic and Reaction Parameters. *Catalysts* **2024**, *14*, 712. https://doi.org/10.3390/catal14100712

Academic Editor: Antonio Salomone

Received: 5 September 2024
Revised: 8 October 2024
Accepted: 9 October 2024
Published: 11 October 2024

1. Introduction

Synthesis of functionalized furans is of great interest in organic chemistry due to their applications in pharmaceuticals, agrochemicals, and materials science [1–3]. These compounds are key structural elements in many biologically active molecules and are used in plastics, flavorings, fragrances, and pharmaceuticals [4]. Their unique electronic properties and reactivity make furans valuable intermediates in constructing complex molecules [5,6]. Challenges in furan synthesis include managing harsh reaction conditions to achieve selectivity and yield, as well as dealing with functional group sensitivity and reagent costs. Common methods include the Paal–Knorr synthesis [7], where 1,4-dicarbonyl compounds, such as 2-ene-1,4-diones and 2-yne-1,4-diones, are cyclized to furan derivatives under acidic

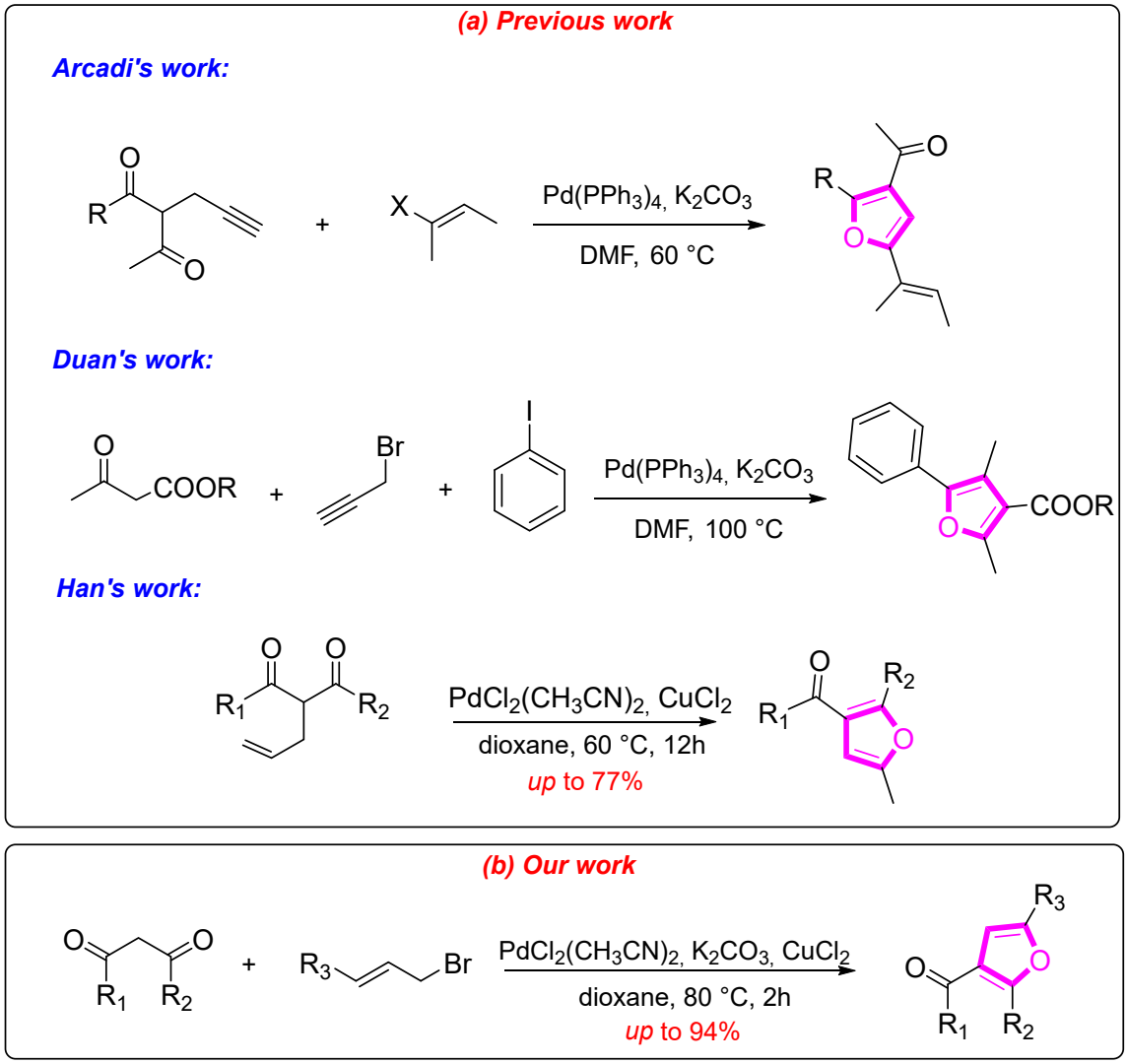
conditions [8]. The Feist–Benary synthesis, involving the reaction between 1,3-dicarbonyl compounds and ethyl bromopyruvate, 3-chloroacetylacetone, or ethyl 2-chloroacetoacetate in the presence of ammonium acetate in aqueous ethanol, is also reported to produce furan derivatives [9]. Another approach is the tandem Diels–Alder cycloaddition/retro-Diels–Alder reaction between oxazoles and acetylenes to yield furans [10]. While potentially efficient, this method is limited by reaction conditions and possible by-product formation.

Several methodologies have been developed for the catalytic synthesis of functionalized furans from 1,3-dicarbonyl compounds, using different catalysts and conditions to achieve the desired furan structures with precise alkyl substitutions [11,12]. Transition-metal catalysis, employing palladium [13], copper [14], and iron [15] catalysts, is a common approach that facilitates carbon–carbon and carbon–heteroatom bond formation. For instance, palladium-catalyzed cross-coupling reactions like Suzuki [16] and Heck reactions [17] are particularly effective for introducing functional groups into the furan core. A notable example is the palladium-catalyzed coupling of 1,3-dicarbonyl compounds with aryl and alkyl halides [18]. This method allows specific alkyl substitutions on the furan ring using alkyl iodides or bromides, leading to complex furan derivatives applicable in pharmaceuticals and agrochemicals [19]. Alternatively, copper-catalyzed Ullmann-type couplings use copper iodide to effectively catalyze the cyclization process, incorporating alkyl groups at various furan ring positions [20]. Organocatalysis, offering a metal-free synthesis route, employs chiral organocatalysts like proline derivatives to achieve enantioselective transformations, yielding furans with high stereocontrol [21]. Photocatalysis has been also reported for synthesis of furans [22] under visible light irradiation [23].

Recent advancements in palladium-catalyzed synthesis of functionalized furans have shown significant progress in reaction conditions, yields, and substrate scope (Scheme 1). Han et al. [24] reported that the treatment of 4-allyl-2,6-dimethyl-3,5-heptanedione with a catalytic amount of $PdCl_2(CH_3CN)_2$ (5 mol %) and a stoichiometric amount of $CuCl_2$ (2.2 equiv) in dioxane at 60 °C for 12 hours formed 3-isobutyryl-2-isopropyl-5-methylfuran in 77% isolated yield. Additionally, several α-alkenyl β-diketones underwent oxidative alkoxylation under these conditions to afford 2,3,5-trisubstituted furans in moderate to good yields. However, the complex preparation of α-alkenyl β-diketones limited its practicality. Zhang et al. [25] introduced a palladium-catalyzed method for synthesizing furans and spirocyclopropanes via C–H activation and alkene insertion. Using palladium acetate ($Pd(OAc)_2$) as the catalyst, copper acetate ($Cu(OAc)_2$) as the oxidant, and trifluoroacetic acid (TFA) as an additive in toluene at 120 °C, they achieved yields of 49% to 87% for furan derivatives, such as 2-benzylfuran, and 60% to 81% for spirocyclopropanes, such as spiro[cyclopropane-1,3′-furan], with good regioselectivity and a broad substrate scope, including various cyclic 1,3-diketones. Arcadi et al. [26] developed an eco-friendly approach to synthesize 2,3,5-trisubstituted furans, such as 2-benzoyl-3-methylfuran, through sequential alkylation and copper(I) iodide (CuI)-catalyzed annulation in toluene at 110–120 °C with 1,8-diazabicyclo [5.4.0] undec-7-ene (DBU) as the base, achieving high yields up to 91%. However, this method encountered limitations in substrate scope and yield when alternative catalysts or solvent-free conditions were employed.

This study introduces a novel approach to the palladium-catalyzed synthesis of functionalized furans via a strategic alkylation–cyclization method. The research addresses a notable gap by focusing on palladium-catalyzed reactions involving alkenyl bromide compounds, a less explored area compared to the extensively studied propargylic compounds. Despite their lower reactivity in palladium catalysis, alkenyl bromides offer significant practical advantages due to their accessibility and ease of handling (Scheme 1). This study explores how various factors influence the efficiency of the one-pot reaction, including the choice of catalyst, solvent, base, and oxidant. Specifically, the study examines different catalysts such as palladium (II) dichloride acetonitrile ($PdCl_2(CH_3CN)_2$), palladium (II) acetate ($Pd(OAc)_2$), and palladium (II) acetylacetonate ($Pd(acac)_2$). It also investigates solvents like 1,4-dioxane and dimethylformamide (DMF), as well as bases including potassium carbonate (K_2CO_3), potassium phosphate (K_3PO_4), cesium carbonate (Cs_2CO_3), and sodium

acetate (NaOAc). Additionally, the impact of oxidants such as copper(II) chloride ($CuCl_2$), 1,4-benzoquinone (BQ), and 2-iodoxybenzoic acid (IBX) is considered. The reactions were conducted at different temperatures and times to determine optimal conditions for synthesizing functionalized furans. By refining these parameters, this study significantly enhances the efficiency of furan synthesis and broadens the range of applicable starting materials, offering new insights and practical applications in synthetic chemistry.



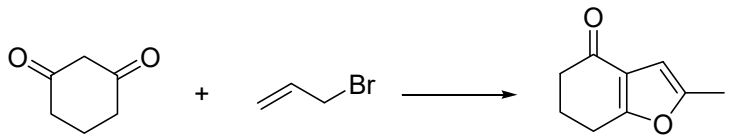
Scheme 1. Comparison between previous work (**a**) and our approach (**b**) in the synthesis of functionalized furans.

2. Results and Discussion

The novelty of this study lies in its evaluation of key parameters influencing the palladium-catalyzed one-pot synthesis of functionalized furans from 1,3-dicarbonyl compounds and alkenyl bromides. This study offers a novel evaluation of critical parameters affecting the palladium-catalyzed one-pot synthesis of functionalized furans from 1,3-dicarbonyl compounds and alkenyl bromides. The results, summarized in Table 1, indicate that $PdCl_2(CH_3CN)_2$ consistently outperforms other palladium sources and transition-metal catalysts, delivering exceptional catalytic efficiency and yield. This is particularly evident when $PdCl_2(CH_3CN)_2$ is used with dioxane as the solvent, K_2CO_3 as the base, and $CuCl_2$ as the oxidant, achieving a peak yield of 94% at 80 °C; other combinations

yielded lower results. The following sections will discuss the entries in Table 1 in detail, highlighting the impact of each parameter on reaction efficiency and product yield.

Table 1. Reaction conditions and yields for the catalyzed reaction of 1,3-cyclohexanedione (**1a**, 1 mmol) with alkenyl bromide (**2a**, 1 mmol), using 0.01 mmol catalyst, 2 mmol base, and 0.05 mmol oxidant in 4 mL solvent.



1a **2a** **3a**

Entry	Catalyst	Solvent	Base	Oxidant	Temp (°C)	Time (h)	Yield (%)
1	$PdCl_2(CH_3CN)_2$	Dioxane	K_2CO_3	$CuCl_2$	80	2	94
2	$Pd(OAc)_2$	Dioxane	K_2CO_3	$CuCl_2$	80	6	80
3	$Pd(acac)_2$	Dioxane	K_2CO_3	$CuCl_2$	80	6	63
4	$PdCl_2(CH_3CN)_2$	Dioxane	K_3PO_4	$CuCl_2$	80	6	25
5	$PdCl_2(CH_3CN)_2$	Dioxane	Cs_2CO_3	$CuCl_2$	80	6	51
6	$PdCl_2(CH_3CN)_2$	Dioxane	KO^tBu	$CuCl_2$	80	6	35
7	$PdCl_2(CH_3CN)_2$	Dioxane	NaOAc	$CuCl_2$	80	6	32
8	$PdCl_2(CH_3CN)_2$	Dioxane	Et_3N	$CuCl_2$	80	6	0
9	$PdCl_2(CH_3CN)_2$	DMF	K_2CO_3	$CuCl_2$	80	12	51
10	$PdCl_2(CH_3CN)_2$	Dioxane	K_2CO_3	BQ	80	6	62
11	$PdCl_2(CH_3CN)_2$	Dioxane	K_2CO_3	IBX	80	6	55

2.1. Effect of Catalyst Type

The choice of catalyst is crucial for optimizing the efficiency of the catalyzed synthesis of functionalized furans [27]. Among palladium catalysts, $PdCl_2(CH_3CN)_2$ (Entry 1) demonstrated significantly higher yields compared to $Pd(OAc)_2$ (Entry 2) and $Pd(acac)_2$ (Entry 3) at 80 °C with longer reaction times of 6 h. $PdCl_2(CH_3CN)_2$ (Entry 1) is the most efficient catalyst for the synthesis of functionalized furans, achieving the highest yield of 94% in just 2 h, compared to $Pd(OAc)_2$ (80% yield in 6 h) and $Pd(acac)_2$ (63% yield in 6 h).

The superior performance of $PdCl_2(CH_3CN)_2$ is attributed to its unique electronic and structural properties. $PdCl_2(CH_3CN)_2$ demonstrates superior catalytic performance due to the unique properties of its acetonitrile ligands. These ligands are weakly coordinating and good π-acceptors, which stabilize the palladium center without obstructing its active sites. This allows the palladium to undergo key catalytic steps like oxidative addition and reductive elimination more efficiently, which are critical for carbon–carbon bond formation in furan synthesis. In contrast, $Pd(OAc)_2$ and $Pd(acac)_2$ contain bidentate acetate and acetylacetonate ligands, which create a more crowded coordination environment around palladium, potentially hindering substrate access and slowing down the reaction. Acetonitrile's weaker electron-donating nature allows palladium to retain a higher electrophilic character, which enhances its reactivity toward substrates, such as alkenyl bromides. This is particularly important for oxidative addition, a crucial step in cross-coupling reactions. $Pd(OAc)_2$ and $Pd(acac)_2$, with their stronger coordinating ligands, can reduce palladium's electrophilicity, making it less reactive and leading to slower ligand exchange. Structurally, acetonitrile is monodentate, binding through a single coordination site, which gives the palladium center more flexibility and better access to substrates. This simpler coordination environment facilitates faster substrate interaction and promotes higher catalytic turnover rates. The more crowded, bidentate ligands in $Pd(OAc)_2$ and $Pd(acac)_2$ can impede substrate access, slowing the catalytic cycle and reducing overall yields. Thus, the combination

of favorable electronic effects, less steric hindrance, and efficient ligand exchange makes $PdCl_2(CH_3CN)_2$ the most effective catalyst in the reaction, resulting in faster reaction rates and higher yields compared to $Pd(OAc)_2$ and $Pd(acac)_2$ [25,28].

2.2. Effect of Solvent Type

The choice of solvent plays a crucial role in the palladium-catalyzed synthesis of functionalized furans [29], as shown by the varied yields across different solvent conditions in Entries 1, 2, 3, 4, and 12. Among these, dioxane stands out as the most effective solvent, achieving a remarkable 94% yield using $PdCl_2(CH_3CN)_2$ as the catalyst with $CuCl_2$ as the oxidant at 80 °C over 2 h (Entry 1). The polar aprotic nature of dioxane with a dielectric constant of 2.21 and a boiling point of 101 °C promotes strong interactions between the catalyst and substrate by reducing hydrogen bonding. This enhances the reaction efficiency and contributes to the high yield observed.

Acetone is a solvent used in this study but shows significantly lower performance, with 0% yield observed in Entries 1, 2, and 3. Despite being a polar aprotic solvent with a high dielectric constant of 20.7 and a low boiling point of 56 °C, acetone failed to facilitate the reaction effectively under the given conditions. Experiments conducted with $PdCl_2(CH_3CN)_2$ in acetone at 25 °C for 2 h resulted in no product formation, indicating that acetone's characteristics do not promote the necessary interactions between the catalyst and reactants. Despite acetone's polarity, its lower boiling point may lead to volatility issues that hinder catalyst activation and substrate transformation.

DMF, another commonly used solvent, achieves a yield of 51% under the same catalytic conditions with $PdCl_2(CH_3CN)_2$ and $CuCl_2$ at 80 °C over 12 h (Entry 9). DMF possesses a high dielectric constant of 36.7 and a boiling point of 153 °C, suggesting its ability to dissolve a wide range of polar substances. However, the lower yield indicates that DMF may not stabilize the reaction intermediates as effectively as dioxane. Despite its favorable dielectric properties, DMF may lead to side reactions or less optimal interactions between the catalyst and reactants.

These findings highlight the critical role of solvent properties and reaction conditions in optimizing catalytic performance. Dioxane emerges as the preferred solvent due to its optimal balance of dielectric constant, boiling point, and ability to enhance catalyst–substrate interactions, leading to the highest yields in this study.

2.3. Effect of Base Type

The choice of base plays a crucial role in the palladium-catalyzed synthesis of functionalized furans [26], as illustrated by the varying yields reported in Entries 4 and 7–11 (Table 1). K_2CO_3 (Entry 1) emerges as the most effective base, achieving a 94% yield with $PdCl_2(CH_3CN)_2$ in dioxane at 80 °C over 2 h using $CuCl_2$ as the oxidant. Its moderate basicity (pKa of 10.33) and buffering capacity enable efficient deprotonation and reaction facilitation.

K_3PO_4 (Entry 4) yields a significantly lower 25% due to its higher basicity (pKa of 12.4) and insolubility, which impede interactions with reactants. Cs_2CO_3 (Entry 5) achieves a moderate yield of 51%, attributed to its moderate basicity (pKa of 10.46) and solubility. However, its larger ionic radius and lower lattice energy lead to slower dissolution and suboptimal reactant interactions. The bulkiness of KOtBu (Entry 6) may result in a reduced yield of 35%, despite its high basicity (pKa of 19.2).

NaOAc (Entry 7), with a pKa of 4.76, yields 32% due to its mild basicity, affecting deprotonation efficiency and slowing reaction rates. Et_3N (Entry 8), a weak base (pKa of 10.75), produces no yield due to its volatility and reduced deprotonation ability, highlighting the importance of base choice in achieving optimal yields.

2.4. Effect of Oxidant Type

The choice of oxidant is critical in the palladium-catalyzed synthesis of functionalized furans [30–33], as it significantly influences yield. This is evident in when comparing the

performance of $CuCl_2$ (Entry 1, Table 1) and other oxidants (Entries 14 and 15, Table 1). $CuCl_2$ consistently delivers the highest yields. For instance, in Entry 1, $CuCl_2$ achieves a 94% yield with $PdCl_2(CH_3CN)_2$, dioxane, K_2CO_3 at 80 °C over 2 h. This success is attributed to its suitable oxidation potential and ability to facilitate oxidative addition. The oxidant's potential (E^0) of +0.159 V enables efficient reoxidation of palladium (0) to palladium(II), thus enhancing catalyst turnover. In contrast, BQ (Benzoquinone), although achieving a yield of 62% in Entry 10, suffers from lower oxidation potential (E^0 = +0.699 V) and may participate in unwanted side reactions, compromising efficiency. Similarly, IBX (2-Iodoxybenzoic acid) in Entry 11 yields 55%, demonstrating limited interaction with the catalyst due to its relatively high potential (E^0 = +0.70 V), which may hinder the regeneration of the active catalytic species. These comparisons emphasize the role of oxidant type and properties in determining reaction outcomes.

2.5. Synthesis of Functionalized Furans from Different 1,3-Diketones and Alkenyl Bromides

Studying the 14 experiments in this synthesis of functionalized furans is important for understanding how different substituents affect the reaction's reactivity and selectivity. Each experiment shows how changing substituents on 1,3-diketones and alkenyl bromides can impact the reaction's efficiency, yield, and the properties of the final furan products. For example, different substituents on the 1,3-diketone can change how these molecules interact with the palladium catalyst and each other, which affects the outcome of the reaction [34,35]. Similarly, variations in the alkenyl bromides, such as changes in chain length or branching, influence the reaction process and the types of products formed. This knowledge is crucial for improving reaction conditions, increasing yields, and creating new methods to make functionalized furans, which are useful in pharmaceuticals, agrochemicals, and materials science. Table 2 shows different experiments using various 1,3-diketones and alkenyl bromides, highlighting a range of yields and product features. For instance, using Cyclohexane-1,3-dione (**1a**) with Allyl bromide (**2a**) gives a high yield of 2-Methyl-6,7-dihydrobenzofuran-4(5*H*)-one (**3a**), showing the effectiveness of this combination. In contrast, other combinations, like 2*H*-Pyran-3,5(4*H*,6*H*)-dione (**1c**) with Allyl bromide (**2b**), produce lower yields, showing that different reactants affect the reaction in various ways. In the synthesis of functionalized furans from 1,3-diketones and alkenyl bromides, unreacted materials and by-products were occasionally observed due to incomplete reactions or side reactions.

Throughout the experiments, unreacted materials were occasionally noted due to incomplete reactions, often caused by steric or ring strain in the reactants, as well as traces of side-chain substituents. Yields varied between 21% and 94%, with steric hindrance in bulkier 1,3-diketones or branched alkenyl bromides contributing to the lower outcomes. Adjusting reaction parameters, such as temperature, reaction time, and catalyst concentration, could help minimize by-products and enhance the overall efficiency and yield of the furan synthesis. Despite these challenges, the reaction exhibited notable selectivity for the desired products, resulting in minimal formation of by-products. This selectivity is attributed to the optimized reaction conditions, including the careful selection of temperature, catalyst, and reaction duration, which were designed to favor the formation of targeted furan derivatives.

Experiment 1 successfully synthesized 2-Methyl-6,7-dihydrobenzofuran-4(5*H*)-one (**3a**) from Cyclohexane-1,3-dione (**1a**) and allyl bromide (**2a**), achieving a high yield of 94%. This experiment demonstrates the effectiveness of the synthetic route, highlighting precise control over reaction conditions to yield the desired product with high purity and yield.

Experiment 2 achieved the synthesis of 2,6,6-Trimethyl-6,7-dihydro- benzofuran-4(5*H*)-one (**3b**) from 5,5-Dimethylcyclohexane-1,3-dione and allyl bromide (**2a**), reaching an 88% yield. Although this yield is slightly lower than the 94% achieved in Experiment 1, it is still significant. The reduction in yield may be due to increased steric hindrance from the additional methyl groups on the cyclohexane ring, which could complicate the cyclization process. The increased bulk of the substituents in 5,5-Dimethylcyclohexane-1,3-dione may

result in reduced cyclization efficiency compared to the less hindered Cyclohexane-1,3-dione used in Experiment 1.

Table 2. Synthesis of functionalized furans using various 1,3-diketones and alkenyl bromides under optimized conditions using 1 mmol of 1,3-diketones, reacted with 1 mmol of alkenyl bromides in the presence of $PdCl_2(CH_3CN)_2$ (0.01 mmol) as a catalyst, using 4 mL of dioxane as the solvent, K_2CO_3 (2 mmol) as the base, and $CuCl_2$ (0.05 mmol) as the oxidant. The mixture was heated to 80 °C for 2 h to facilitate the reaction.

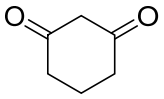
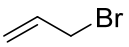
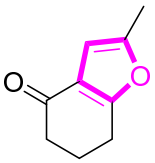
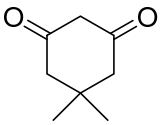
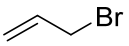
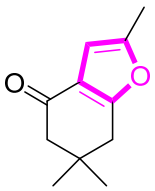
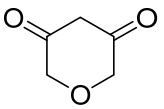
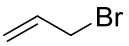
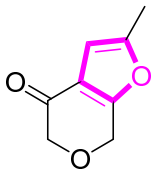
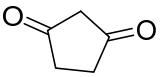
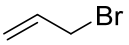
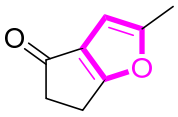
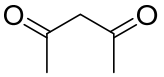
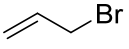
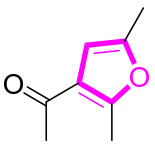
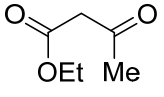
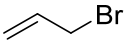
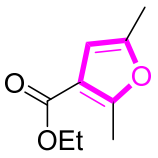
Exp.	Reactants		Product	Yield
	1,3-diketone	Allyl Halid		
1	 **1a**	 **2a**	 **3a**	94%
2	 **1b**	 **2a**	 **3b**	88%
3	 **1c**	 **2a**	 **3c**	25%
4	 **1d**	 **2a**	 **3d**	21%
5	 **1e**	 **2a**	 **3e**	71%
6	 **1f**	 **2a**	 **3f**	89%

Table 2. *Cont.*

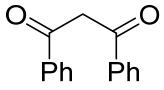
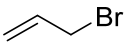
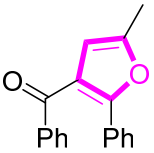
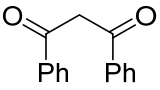
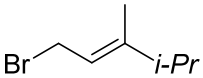
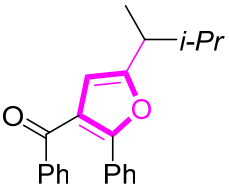
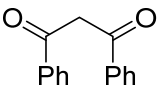
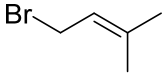
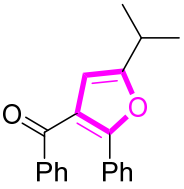
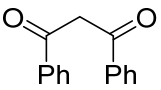
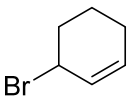
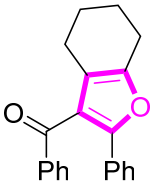
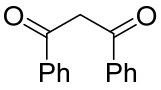
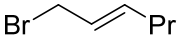
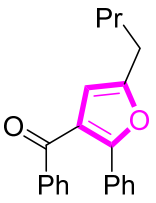
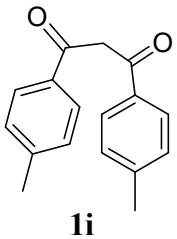
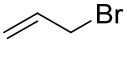
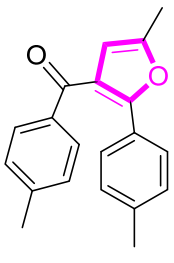
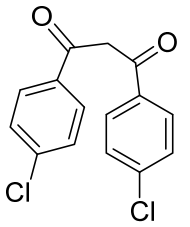
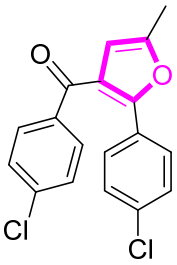
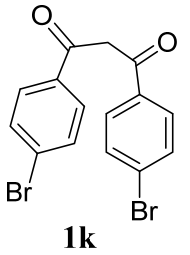
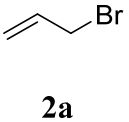
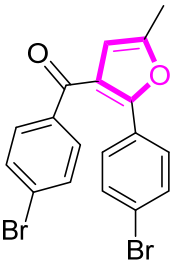
Exp.	Reactants		Product	Yield
	1,3-diketone	Allyl Halid		
7	 **1h**	 **2a**	 **3g**	80%
8	 **1h**	 **2b**	 **3h**	85%
9	 **1h**	 **2c**	 **3i**	81%
10	 **1h**	 **2d**	 **3j**	55%
11	 **1h**	 **2e**	 **3k**	72%
12	 **1i**	 **2a**	 **3l**	82%

Table 2. *Cont.*

Exp.	Reactants		Product	Yield
	1,3-diketone	Allyl Halid		
13	 **1g**	 **2a**	 **3m**	84%
14	 **1k**	 **2a**	 **3n**	86%

Experiment 3 successfully synthesized 2-Methyl-5*H*-furo [2,3-c]pyran-4(7*H*)-one (**3c**) from 2*H*-Pyran-3,5(4*H*,6*H*)-dione (**1c**) and allyl bromide (**2a**), although the yield was only 25%. This notably low yield may be due to the significant ring strain inherent in the 2H-Pyran dione structure. This strain may introduce steric or electronic hindrances during the cyclization process, making the formation of the furan ring less favorable and potentially compromising the reaction efficiency. Consequently, this may explain the reduced yield compared to the 94% achieved in Experiment 1.

Experiment 4 involved the reaction of Cyclopentane-1,3-dione (**1d**) with allyl bromide (**2a**) to produce 2-Methyl-5,6-dihydrocyclopenta[b]furan-4-one (**3d**). The reaction achieved a yield of only 21%, highlighting the inefficiency of the process, compared to Experiment 1. The reduced yield may be attributed to the substantial ring strain present in the smaller cyclopentane ring, which could introduce significant steric hindrance. This steric strain may make cyclization and furan ring formation less favorable, thereby reducing the overall reaction efficiency.

Experiment 5 involved the reaction of Pentane-2,4-dione (**1e**) with allyl bromide (**2a**) to produce 1-(2,5-Dimethylfuran-3-yl) ethanone (**3e**), achieving a commendable 71% yield. The reaction yielded a colorless oil, demonstrating that the Pentane-2,4-dione structure is more conducive to furan ring formation compared to the diketones used in Experiments 3 and 4. This improved yield is attributed to the relatively lower steric hindrance and ring strain of Pentane-2,4-dione, which facilitates a more efficient cyclization process. In contrast, Experiment 3 and Experiment 4, which involved 2*H*-Pyran-3,5(4*H*,6*H*)-dione and Cyclopentane-1,3-dione, respectively, suffered from increased ring strain, leading to diminished yields. This experiment underscores the critical role of diketone choice in optimizing furan synthesis, with reduced steric strain and ring strain leading to better reaction outcomes.

Experiment 6 involved the reaction of Ethyl 3-oxobutanoate with allyl bromide (**2a**) to synthesize Ethyl 2,5-dimethylfuran-3-carboxylate (**3f**), achieving an impressive yield of 89%. This high yield indicates the importance of the ester functionality in ethyl 3-oxobutanoate, which appears to stabilize the reaction intermediate and facilitate a more efficient furan ring formation. The presence of the ester group likely enhances the stability of the intermediate,

leading to a more favorable reaction pathway and resulting in a superior yield compared to other experiments.

Experiment 7 demonstrated the reaction of 1,3-Diphenylpropane-1,3-dione (**1h**) with allyl bromide (**2a**) to produce (5-Methyl-2-phenylfuran-3-yl)(phenyl)methanone (**3g**) with an 80% yield. This yield may be attributed to the stabilizing effects of the phenyl groups in the 1,3-diketone, which may facilitate the cyclization process. In contrast, Experiment 1 achieved a higher yield of 94% with a simpler alkenyl bromide. This comparison highlights that a less bulky alkenyl bromide, as used in Experiment 1, enhances cyclization efficiency more effectively.

Experiment 8 demonstrated the impact of alkenyl bromide substitution on furan synthesis efficiency. Reacting 1,3-Diphenylpropane-1,3-dione (**1h**) with (*E*)-1-Bromo-3,4-dimethylpent-2-ene (**2b**) yielded (5-(3-Methyl- butan-2-yl)-2-phenylfuran-3-yl)(phenyl)methanone (**3h**) with an impressive 85% yield. This result may highlight a significant improvement compared to Experiment 1, where a similar reaction achieved a 94% yield with a less complex alkenyl bromide. The enhanced yield in Experiment 8 is possibly due to the stabilizing effects of the branched alkenyl bromide, which may facilitate the cyclization process.

Experiment 9 involved reacting 1,3-Diphenylpropane-1,3-dione (**1h**) with 1-Bromo-3-methylbut-2-ene (**2c**) to produce (5-Isopropyl-2-phenylfuran-3-yl)(phenyl)methanone (**3i**), achieving an 81% yield. In comparison, Experiment 1 achieved a 94% yield with a simpler alkenyl bromide, suggesting that while branched alkyl groups may enhance stabilization, they could also introduce steric challenges that affect the overall efficiency of furan synthesis.

Experiment 10 involved reacting 1,3-Diphenylpropane-1,3-dione (**1h**) with 3-Bromocyclohex-1-ene (**2d**) to synthesize 3-Benzoyl-2-phenyl-6,7-dihydrobenzofuran-4(5H)-one (**3j**), achieving a 55% yield. This yield may be significantly lower compared to other reactions involving 1,3-Diphenylpropane-1,3-dione, possibly due to the substantial steric hindrance from the Cyclohex-1-ene substituent. In contrast to Experiment 1 (yield, 94%), the bulky cyclohexene ring may introduce considerable steric strain, complicating the cyclization process and possibly leading to reduced efficiency.

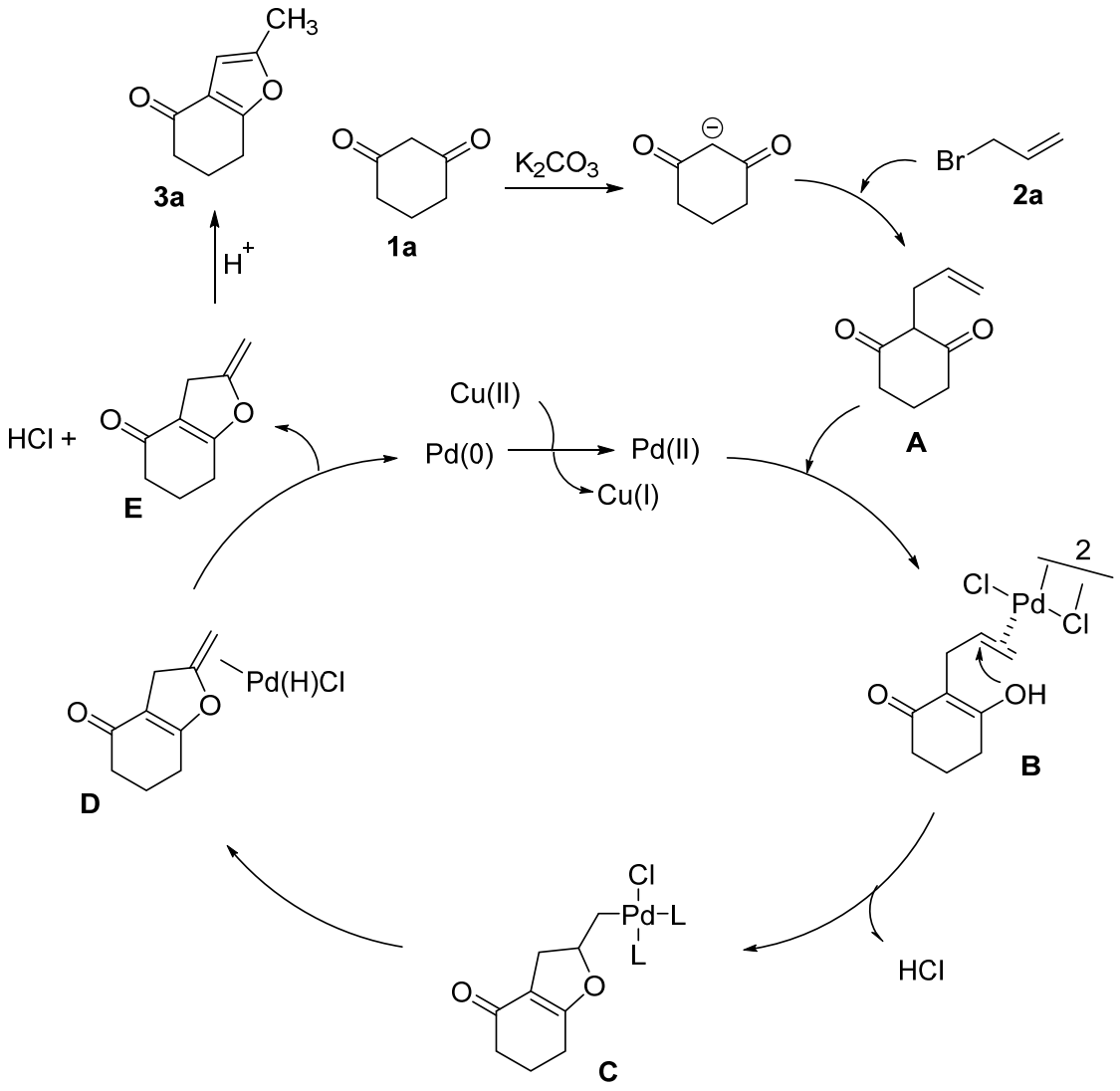
Experiment 11 involved reacting 1,3-Diphenylpropane-1,3-dione (**1h**) with (*E*)-1-Bromohex-2-ene (**2e**) to produce (5-Butyl-2-phenylfuran-3-yl)(phenyl)methanone (**3k**), resulting in a moderate yield of 72%. This yield is low compared to Experiment 1 (yield, 94%), potentially due to the steric hindrance introduced by the bulkier hex-2-ene. The size and branching of the alkenyl bromide may adversely impact the cyclization efficiency, highlighting the significance of substituent size and steric effects in furan synthesis.

In Experiments **12**, **13**, and **14**, 1,3-Dip-tolylpropane-1,3-dione (**1i**), 1,3-Bis(4-chlorophenyl) propane-1,3-dione (**1g**), and 1,3-Bis(4-bromophenyl)propane-1,3-dione (**1k**) were reacted with allyl bromide (**2a**) to produce (5-Methyl-2-p-tolylfuran-3-yl)(p-tolyl)methanone (**3l**, 82%), (4-Chlorophenyl)(2-(4-chlorophenyl)-5-methylfuran-3-yl)methanone (**3m**, 84%), and (4-Bromophenyl)(2-(4-bromophenyl)-5-methylfuran-3-yl)methanone (**3n**, 86%), respectively. These yields are higher compared to Experiment 7 (80% yield), where 1,3-Diphenylpropane-1,3-dione (**1h**) was reacted with allyl bromide (**2a**). The increased yields can be attributed to the enhanced reactivity of the 1,3-dicarbonyl compounds with electron-donating substituents such as methyl, chloro, or bromo groups on the benzene ring.

2.6. Hypothetical Mechanism

The proposed mechanism for the synthesis of substituted furans follows a plausible catalytic cycle based on known principles of palladium-catalyzed reactions (Scheme 2). The reaction is hypothesized to begin with a nucleophilic attack of the 1,3-diketone on the alkyl halide, leading to the formation of a 2-alkenyl-1,3-diketone intermediate. This intermediate coordinates with the palladium catalyst, forming a π-olefin–palladium (II) halide complex. In this complex, the olefin becomes susceptible to nucleophilic attack by the enolic oxygen atom, resulting in the formation of a palladium–carbon bond and the elimination of HCl. The resulting intermediate is believed to undergo β-hydride

elimination, forming a 2-methylene-2,3-dihydrofuran–palladium complex. This complex decomposes to give the substituted furan product, along with palladium (0) and HCl. The palladium (0) is subsequently reoxidized to palladium (II) by reoxidants, such as $CuCl_2$, allowing the catalyst to be regenerated and participate in additional catalytic cycles. This hypothetical mechanism accounts for the efficient production of various substituted furans under different reaction conditions and with a range of substrates. It highlights the critical role of the solvent, base, and reoxidant in optimizing the reaction's yield and minimizing by-products. While the proposed steps align with known palladium-catalyzed pathways, further experimental studies are required to confirm the precise intermediates and validate the mechanism.



Scheme 2. Proposed catalytic mechanism for the synthesis of substituted furans via palladium-catalyzed reactions.

3. Experimental Procedure

3.1. Reagents and Materials

All chemicals used in this study were supplied by Sigma-Aldrich (Saint Louis, MO, USA). The catalysts employed included palladium (II) dichloride (acetonitrile) [$PdCl_2(CH_3CN)_2$], palladium (II) dichloride (phenylacetonitrile) [$PdCl_2(PhCN)_2$], palladium (II) acetate [$Pd(OAc)_2$], and palladium (II) acetylacetonate [$Pd(acac)_2$]. The solvents used were acetone, dioxane, tetrahydrofuran (THF), and dimethylformamide (DMF). Bases included potassium carbon-

ate [K_2CO_3], potassium phosphate [K_3PO_4], cesium carbonate [Cs_2CO_3], potassium tert-butoxide [KO^tBu], sodium acetate [NaOAc], and triethylamine [Et_3N]. The oxidants used were copper (II) chloride [$CuCl_2$], 1,4-benzoquinone (BQ) [$C_6H_4O_2$], and 2-iodoxybenzoic acid (IBX) [$C_{11}H_7IO_5$]. The reactants used in the experiments included 1,3-diketones such as cyclohexane-1,3-dione, 5,5-dimethylcyclohexane-1,3-dione, 2H-pyran-3,5(4H,6H)-dione, cyclopentane-1,3-dione, pentane-2,4-dione, ethyl 3-oxobutanoate, 1,3-diphenylpropane-1,3-dione, 1,3-dip-tolylpropane-1,3-dione, 1,3-bis(4-chlorophenyl)propane-1,3-dione, and 1,3-bis(4-bromo- phenyl)propane-1,3-dione. The alkenyl bromides used in the experiments included allyl bromide, (E)-1-bromo-3,4-dimethylpent-2-ene, 1-bromo-3-methylbut-2-ene, 3-bromocyclohex-1-ene, and (E)-1-bromohex-2-ene.

3.2. One-Pot Synthesis of Functionalized Furans via Pd-Catalysis

The optimization of one-pot synthesis of functionalized furans was carried out by reacting 1 mmol of 1,3-Cyclohexanedione (**1a**) with 1 mmol of allyl bromide (**2a**) in a 50 mL round-bottom flask with a reflux condenser and vigorous stirring, under various reaction conditions. The sequence of addition was as follows: A total of 4 mL of solvent (e.g., dioxane or DMF) was added first, followed by 2 mmol of base (K_2CO_3, K_3PO_4, Cs_2CO_3, KOtBu, NaOAc, or Et_3N). Next, 0.01 mmol of catalyst ($PdCl_2(CH_3CN)_2$, $Pd(OAc)_2$, or $Pd(acac)_2$) was introduced, followed by 0.05 mmol of oxidant ($CuCl_2$, BQ, or IBX). Finally, 1 mmol of 1,3-Cyclohexanedione (**1a**) and 1 mmol of allyl bromide (**2a**) were added. The reactions were performed at 80 °C for durations of 2 to 12 h under reflux. After the reaction, the mixture was quenched with a saturated aqueous solution of ammonium chloride (NH_4Cl) and then extracted with diethyl ether (Et_2O). The combined organic extracts were washed with water and saturated brine, dried over anhydrous sodium sulfate (Na_2SO_4), and concentrated under vacuum. The resulting crude products were purified by column chromatography on silica gel using petroleum ether/ethyl acetate (15:1) as the eluent to afford the corresponding furans, with yields and conditions detailed in Table 1.

In the synthesis of functionalized furans, various 1,3-diketones were reacted with different alkenyl bromides under optimized conditions (Entry 1, Table 1). The reactions were conducted using 1 mmol of 1,3-diketones with 1 mmol of alkenyl bromide, $PdCl_2(CH_3CN)_2$ (0.01 mmol, 2.6 mg) as the catalyst, 4 mL of dioxane as the solvent, K_2CO_3 (2 mmol, 276.4 mg) as the base, and $CuCl_2$ (0.05 mmol, 2.5 mg) as the oxidant, with the mixture heated to 80 °C for 2 h. Table 2 summarizes the outcomes of these reactions, showcasing the synthesis of various functionalized furans.

3.3. Characteristics of the Reaction Product

The chemical structures of the products were confirmed using melting points, ^{1}H NMR, ^{13}C NMR, IR, and MS spectroscopy. The ^{1}H NMR and ^{13}C NMR spectra are provided in the supplementary information. The yield of the reaction was calculated using the following equation:

$$\text{Yield } (\%) = \frac{Actual\ Yield}{Theoretical\ Yiled} \times 100$$

where actual yield is the amount of product obtained from the reaction (usually measured in grams or milligrams). Theoretical yield is the maximum amount of product that could be formed from the given quantities of reactants, calculated based on stoichiometry.

2-Methyl-6,7-dihydrobenzofuran-4(5H)-one (**3a**). Colorless solid; yield: 141.17 mg (94%); mp = 37–38 °C. ^{1}H NMR (400 MHz, $CDCl_3$.,δ, ppm): 6.25 (d, *J* = 1.1 Hz, 1H, furyl-H), 2.84 (t, *J* = 6.3 Hz, 2H, CH_2), 2.54–2.43 (m, 2H, CH_2), 2.31 (d, *J* = 1.1 Hz, 3H, CH_3), 2.24–2.12 (m, 2H, CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 194.6, 166.0, 152.6, 122.0, 101.9, 37.6, 23.3, 22.7, 13.4. IR (νmax, cm^{-1}) 2964, 1664, 1639, 1581, 1427, 1379, 1305, 1217, 1049. $C_9H_{11}O_2$ *m*/*z*: 151.0780 $[M + H]^+$; found 151.0782 [36].

2,6,6-Trimethyl-6,7-dihydrobenzofuran-4(5H)-one (**3b**). White solid; yield: 156.84 mg (88%); mp = 121–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm,): δ 6.13 (d, *J* = 1.1 Hz, 1H, furyl-

H), 2.78 (s, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.32 (s, 2H, CH_2), 1.16 (s, 6H, $2CH_3$). ^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm= 192.0, 190.0, 164.8, 156.6, 140.4, 135.9, 132.3, 130.0, 127.9, 122.7, 119.6, 117.8, 52.4, 37.4, 35.5, 28.7, 13.1; IR (νmax, cm^{-1}) 2962, 2368, 2341, 1664, 1639, 1581, 1562, 1427, 1379, 1305, 1218, 1147, 1049, 927, 904, 750, 727. $C_{11}H_{15}O_2$ *m*/*z*: 179.1023 $[M + H]^+$; found 179.1025 [37].

2-Methyl-5H-furo[2,3-c]pyran-4(7H)-one (**3c**). Light yellow solid; yield: 38.04 mg (25%); mp = 105–106 °C. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.25 (d, *J* = 1.1 Hz, 1H, furyl-H), 4.85 (s, 2H, CH_2), 4.44 (s, 2H, CH_2), 2.20 (s, 3H, CH_3).^{13}C NMR (101 MHz): δ 194.6, 166.0, 152.6, 122.0, 101.9, 82.1,65.1 13.1; IR (νmax, cm^{-1}) 2964, 2368, 2343, 1664, 1639, 1581, 1562, 1427, 1379, 1305, 1217, 1147, 1049, 927, 904, 750, 729. HRMS (ESI) calcd for $C_8H_9O_3$ *m*/*z*: 153.1235 $[M + H]^+$; found 153.1238.

2-Methyl-5,6-dihydrocyclopenta[b]furan-4-one (**3d**). Light yellow solid; yield: 28.59 mg (21%); mp = 101–102 °C. ^{1}HNMR (400 MHz, $CDCl_3$, δ, ppm): δ 6.63 (d, *J* = 1.1 Hz, 1H, furyl-H), 2.86 (ddd, *J* = 15.17, 8.06, 4.17 Hz, 2H, CH_2), 2.50 (ddd, *J* = 15.14, 8.06, 4.17 Hz, 2H, $2CH_2$), δ 2.31 (3H, s). ^{13}C NMR (101 MHz): δ 13.4, 28.8, 37.6, 101.9, 122.0, 152.6, 166.0, 194.6. IR (νmax, cm-1) 2952, 2368, 2343, 1664, 1615, 1581, 1562, 1427, 1379, 1305, 1220, 1141, 1049, 927, 904, 750, 739. HRMS (ESI) calcd for $C_8H_9O_2$ *m*/*z*: 138.5037 $[M + H]^+$; found 138.5039.

1-(2,5-Dimethylfuran-3-yl)ethanone (**3e**). Colorless oil; yield: 98.10 mg (71%); 1H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.09 (s, 1H, furyl-H). 2.42 (s, 3H, $COCH_3$), 2.25 (s, 3H, CH_3), 2.21 (s, 3H, CH_3). ^{13}C NMR (101 MHz): δ 189.42, 159.14, 152.70, 124.40, 106.24, 34.65, 14.64, 13.42. IR (νmax, cm-1) 2962, 2368, 2341, 1664, 1639, 1581, 1305, 1218, 927, 904, 750, 727. HRMS (ESI) calcd for $C_8H_{11}O_2$ *m*/*z*: 139.1745 $[M + H]^+$; found 139.1747.

Ethyl 2,5-dimethylfuran-3-carboxylate (**3f**). Colorless oil; yield: 149.50 mg (89%); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 6.13 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 2.44 (s, 3H), 2.15 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz): δ 163.3, 156.5, 148.8, 113.0, 105.2, 58.9, 13.3, 12.6, 12.1. IR (νmax, cm^{-1}) 2962, 2368, 2341, 1664, 1650, 1581, 1305, 1218, 927, 904, 743, 730. HRMS (ESI) calcd for $C_9H_{13}O_3$ *m*/*z*: 169.0812 $[M + H]^+$; found 169.0815 [38].

(5-Methyl-2-phenylfuran-3-yl)(phenyl)methanone (**3g**). Colorless oil; yield: 209.85 mg (80%); ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.72 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.41–7.37 (m, 1H), 7.28–7.24 (m, 1H), 7.23–7.13 (m, 3H), 6.20 (d, *J* = 1.0 Hz, 1H), 2.29 (d, *J* = 1.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ/ppm = 190.9, 153.5, 150.1, 137.2, 131.6, 129.0, 128.6, 127.5, 127.18, 127.16, 126.2, 120.7, 108.7, 12.4. IR (νmax, cm^{-1}) 2930, 2360, 1675, 1649, 1579, 1495, 1450, 1434, 1407, 1378, 1320, 1304, 1232, 1211, 1043, 906, 761, 731, 690, 668. HRMS (ESI) calcd for $C_{18}H_{15}O_2$ m/z: 263.3133 $[M + H]^+$; found 263.3135.

(5-(3-Methylbutan-2-yl)-2-phenylfuran-3-yl)(phenyl)methanone (**3h**). Light yellow solid; yield: 270.66 mg (85%); mp = 110–111 °C. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.73 (d, *J* = 8.4 Hz, 2H), 7.57 (d, *J* = 8.1 Hz, 2H, ArH), 7.40–7.36 (m, 1H, ArH), 7.28–7.24 (m, 1H, ArH), 7.23–7.13 (m, 3H, ArH), 6.20 (d, *J* = 1.0 Hz, 1H, furyl-H), 3.18 (qd, *J* = 6.61, 2.77 Hz, 1H, CH), 2.29 (qqd, *J* = 6.94, 6.94, 2.77 Hz, 1H, CH), 1.47 (d, *J* = 6.61 Hz, 3H, CH_3), 1.23 (d, *J* = 6.61 Hz, 3H, CH_3), 1.06 (d, *J* = 6.61 Hz, 3H, CH_3). ^{13}C NMR (101 MHz): δ 13.4, 20.3, 20.4, 31.2, 35.2, 98.8, 106.9, 126.7, 128.1, 128.3, 128.5, 130.5, 134.0, 137.7, 158.0, 159.2, 196.0. IR (νmax, cm^{-1}) 2922, 2360, 1675, 1649, 1579, 1495, 1450, 1434, 1407, 1378, 1320, 1304, 1232, 1211, 1043, 906, 762, 731, 691, 668. HRMS (ESI) calcd for $C_{22}H_{23}O_2$ *m*/*z*: 319.2017 $[M + H]^+$; found 319.2020.

(5-Isopropyl-2-phenylfuran-3-yl)(phenyl)methanone (**3i**). Colorless solid; yield: 235.19 mg (81%); mp = 109–110 °C. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.40–7.39 (m, 2H, ArH), 7.14–7.06 (m, 3H, ArH), 7.04–6.85 (m, 5H, ArH), 6.13 (1H, s, CH), 3.35 (m, 1H, CH), δ 1.56 (6H, d, *J* = 6.70 Hz, $2CH_3$). ^{13}C NMR (101 MHz): δ 20.6, 25.6, 32.0, 98.3, 126.7, 126.7, 128.1, 128.3, 128.5, 130.5, 134.0, 137.7, 158.0, 159.2, 196.0. IR (νmax, cm^{-1}) 2912, 2360, 1675, 1649, 1580, 1495, 1450, 1435, 1410, 1378, 1320, 1304, 1232, 1211, 1043, 906, 762, 731, 692, 661. HRMS (ESI) calcd for $C_{20}H_{19}O_2$ *m*/*z*: 291.4561 $[M + H]^+$; found 291.4563.

3-Benzoyl-2-phenyl-6,7-dihydrobenzofuran-4(5H)-one (**3j**). White solid; yield: 166.30 mg (55%); mp 101−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.91 (m, 2H), 7.54 (m, 3H), 7.40 (t, 5.0 Hz, 2H), 7.30 (m, 3H), 3.03 (t, *J* = 4.0 Hz, 2H), 2.48 (t, *J* = 3.0 Hz, 2H), 2.26 (m, 2H).). ^{13}C NMR (101 MHz): δ 207.3, 192.8, 192.7, 165.9, 151.5, 137.3, 133.8, 129.6, 129.0, 128.9, 128.7, 125.9, 122.6, 117.5, 37.8, 31.1, 23.6, 22.5. IR (νmax, cm^{-1}) 2921, 2360, 1675, 1650, 1579, 1495, 1450, 1434, 1407, 1378, 1320, 1304, 1232, 1211, 1043, 907, 762, 730, 691, 668. HRMS (ESI) calcd for $C_{21}H_{19}O_2$ *m*/*z*: 303.3740 $[M + H]^+$; found 303.3742.

(5-Butyl-2-phenylfuran-3-yl)(phenyl)methanone (**3k**). White solid; yield: 219.16 mg (72%); mp 107−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 7.40–7.39 (m, 2H, ArH), 7.14–7.06 (m, 3H, ArH), 7.04–6.85 (m, 5H, ArH), 6.13 (1H, s, CH), 2.50 (t, *J* = 7.67 Hz, 2H, CH_2), 1.75 (tt, *J* = 7.67, 7.00 Hz, 2H, CH_2), 1.49 (tq, *J* = 7.00, 6.50 Hz, 2H, CH_2), δ 0.87 (t, *J* = 6.50 Hz, 3H, CH_3). ^{13}C NMR (101 MHz): δ 13.9, 20.9, 31.5, 35.1, 98.9, 126.7, 126.1, 128.1, 128.3, 128.5, 130.5, 134.0, 137.7, 152.2, 158.0, 196.0. IR (νmax, cm^{-1}) 2922, 2360, 1675, 1649, 1579, 1495, 1450, 1434, 1407, 1378, 1320, 1304, 1232, 1211, 1043, 906, 762, 731, 691, 668. HRMS (ESI) calcd for $C_{21}H_{21}O_2$ *m*/*z*: 305.3912 $[M + H]^+$; found 305.3915.

5-Methyl-2-p-tolylfuran-3-yl)(p-tolyl)methanone (**3l**)**.** Colorless oil; yield: 238.9 mg (82%); ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.66 (d, *J* = 8.2 Hz, 2H, ArH), 7.50 (d, *J* = 8.2 Hz, 2H, ArH), 7.10 (d, *J* = 8.0 Hz, 2H, ArH), 7.01 (d, *J* = 8.0 Hz, 2H, ArH), 6.17 (s, 1H, CH), 2.30 (s, 6H, $2CH_3$), 2.24 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 190.8, 154.3, 149.7, 142.4, 137.7, 134.7, 128.8, 127.8, 126.4, 126.2, 120.2, 108.6, 20.6, 20.3, 12.3. IR (νmax, cm^{-1}) 2930, 2360, 1678, 1649, 1579, 1495, 1450, 1424, 1407, 1378, 1320, 1304, 1231, 1211, 1043, 906, 761, 730, 690, 668. HRMS (ESI) calcd for $C_{20}H_{18}O_2$ *m*/*z* = 291.1380 $[M + H]^+$; found: 291.1382 [36].

4-Chlorophenyl)(2-(4-chlorophenyl)-5-methylfuran-3-yl)methanone (**3m**)**.** White solid; yield: 278.2 mg (84%); mp 108−109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm= 7.81 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.27 (s, 1H), 2.41 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm = 190.5, 153.6, 151.7, 140.1, 136.5, 134.7, 131.2, 128.8, 128.7, 128.5, 128.4, 121.8, 109.9, 13.3. IR (νmax, cm^{-1}) 2930, 2360, 1678, 1649, 1579, 1495, 1450, 1424, 1407, 1378, 1320, 1304, 1231, 1211, 1043, 906, 761, 742, 730, 704, 690, 668, 550. HRMS (ESI) calcd for $C_{18}H_{12}Cl_2O_2$ *m*/*z* = 331.0292 $[M + H]^+$; found: 331.0295 [36].

4-Bromophenyl)(2-(4-bromophenyl)-5-methylfuran-3-yl)methanone (**3n**)**.** Colorless solid; yield: 361.3 mg (86%); mp 114−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ/ppm = 7.70 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.58 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.6 Hz, 2H), 6.27 (s, 1H), 2.40 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ/ppm= 190.7, 153.6, 151.6, 136.8, 131.8, 131.6, 131.3, 128.8, 128.7, 128.1, 123.2, 121.8, 109.8, 13.4. IR (νmax, cm^{-1}) 2930, 2360, 1675, 1649, 1579, 1495, 1450, 1434, 1407, 1378, 1320, 1304, 1232, 1211, 1129, 1043, 906, 761, 731, 690, 668. HRMS (ESI) calcd for $C_{18}H_{12}Br_2O_2$ *m*/*z* = 418.9285 $[M + H]^+$; found: 418.9288 [36].

3.4. Characterization Techniques

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer. Samples were dissolved in deuterated chloroform ($CDCl_3$), and tetramethylsilane (TMS) was used as an internal standard for chemical shift calibration. Chemical shifts are reported in ppm (δ) and coupling constants (J) are given in Hz. Data were processed and analyzed using Mnova NMR Software; Mestrelab Research S.L.: Santiago de Compostela, Spain, 2020; Available online: https://mestrelab.com/software/mnova/ (accessed on 2 May 2020).

Infrared spectroscopy (FTIR) was performed using a Nicolet (Mountain, WI, USA) AVATAR 330 FTIR spectrometer. Samples were prepared as KBr pellets or thin films, depending on the sample's physical state, and spectra were recorded over a range of 4000 to 400 cm^{-1}. The resolution of the spectra was set to 4 cm^{-1}, and the data were analyzed to identify characteristic functional groups and bonding environments.

High-resolution mass spectra (MS) were acquired using an LC/MSD TOF (Time-of-Flight) mass spectrometer. For accurate mass determination, samples were introduced via

electrospray ionization (ESI) and analyzed in the positive ion mode. The mass range was set to cover potential molecular weights of the compounds of interest, and calibration was performed using standard solutions. Data were processed using Agilent MassHunter software.

Thin layer chromatography (TLC) was performed on pre-coated silica gel plates (YT257-85, 10–40 μm). The plates were developed using a solvent system appropriate for the separation of the target compounds, and spots were visualized under UV light (254 nm). Rf values were calculated for each compound, and a comparison with authentic samples was used to identify and confirm compounds.

Column chromatography was carried out using silica gel (ZCX II, 200–300 mesh) as the stationary phase. The elution was performed with a gradient of petroleum ether and ethyl acetate (15:1) to achieve separation of the target compounds. Fractions were monitored by TLC, and those containing the desired products were combined, concentrated, and further purified if necessary. The effectiveness of the separation was evaluated by the purity of the final compounds.

4. Conclusions

This study offers an in-depth evaluation of factors affecting the palladium-catalyzed one-pot synthesis of functionalized furans from 1,3-dicarbonyl compounds and alkenyl bromides. By systematically exploring parameters such as catalyst type, solvent, base, and oxidant, we identified $PdCl_2(CH_3CN)_2$ as the most effective catalyst, achieving a superior yield of 94%. This catalyst's high efficiency may be due to its favorable chemical structure, coordination environment, and stability, which contribute to enhanced reaction performance and yield. Palladium-based catalysts consistently outperformed other transition metals, with $PdCl_2(CH_3CN)_2$ showing exceptional catalytic activity. Optimal conditions were found to be $PdCl_2(CH_3CN)_2$ in dioxane at 80 °C with K_2CO_3 as the base and $CuCl_2$ as the oxidant. This setup highlights the critical impact of solvent choice and reaction temperature on reaction efficiency. This study demonstrated the method's versatility across a diverse array of 1,3-diketones and alkenyl bromides. It utilized various 1,3-diketones, including cyclohexane-1,3-dione, 5,5-Dimethylcyclohexane-1,3-dione, 2H-pyran-3,5(4H,6H)-dione, cyclopentane-1,3-dione, pentane-2,4-dione, ethyl 3-oxobutanoate, 1,3-diphenylpropane-1,3-dione, 1,3-dip-tolylpropane-1,3-dione, 1,3-bis(4-chlorophenyl)propane-1,3-dione, and 1,3-bis(4-bromo- phenyl)propane-1,3-dione. Each of these compounds influenced the reaction's outcome based on their chemical structure, showcasing the method's adaptability and effectiveness in varying chemical environments. Similarly, different alkenyl bromides such as allyl bromide, (*E*)-1-bromo-3,4-dimethylpent-2-ene, 1-Bromo-3-methylbut-2-ene, 3-bromocyclohex-1-ene, and (*E*)-1-bromohex-2-ene were tested, showcasing their ability to introduce diverse functional groups onto the furan scaffold. The nature of these substituents significantly impacted reactivity and selectivity, allowing for tailored synthetic applications and expanding the utility of this synthetic method.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/catal14100712/s1.

Author Contributions: Conceptualization, K.H. and A.B.; methodology, K.H. and A.B.; software, K.H., S.H. and A.B.; validation, K.H., S.H. and A.B.; formal analysis, K.H., S.H., M.B. and A.B.; investigation, K.H., S.H., M.B. and A.B.; resources, K.H., M.B. and A.B.; data curation, K.H., M.B. and A.B.; writing—original draft, K.H., S.H., H.A., M.B. and A.B.; writing—review and editing, K.H. and A.B.; visualization, H.A. and A.B.; supervision, A.B.; project administration, H.A. and A.B.; funding acquisition, H.A. and M.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: Data are contained within the article and Supplementary Materials.

Acknowledgments: Researchers Supporting Project number (RSPD2024R604), King Saud University, Riyadh, Saudi Arabia.

Conflicts of Interest: The authors declare that there are no financial or personal conflicts of interest that could potentially influence or bias the outcomes of this research work.

References

1. Deepthi, A.; Babu, B.P.; Balachandran, A.L. Synthesis of Furans—Recent Advances. *Org. Prep. Proced. Int.* **2019**, *51*, 409–442. [CrossRef]
2. Mortensen, D.S.; Rodriguez, A.L.; Carlson, K.E.; Sun, J.; Katzenellenbogen, B.S.; Katzenellenbogen, J.A. Synthesis and biological evaluation of a novel series of furans: Ligands selective for estrogen receptor α. *J. Med. Chem.* **2001**, *44*, 3838–3848. [CrossRef] [PubMed]
3. Gevrek, T.N.; Sanyal, A. Furan-Containing Polymeric Materials: Harnessing the Diels-Alder Chemistry for Biomedical Applications. *Eur. Polym. J.* **2021**, *153*, 110514. [CrossRef]
4. Banerjee, R.; Kumar, H.K.S.; Banerjee, M. Medicinal Significance of Furan Derivatives: A Review. *Int. J. Res. Phytochem. Pharmacol.* **2015**, *5*, 48–57.
5. Sahoo, S.S.; Kataria, P.; Kontham, R. Concise and Collective Total Syntheses of 2,4-Disubstituted Furan-Derived Natural Products from Hydroxyoxetanyl Ketones. *Org. Biomol. Chem.* **2024**, *22*, 1475–1483. [CrossRef]
6. Raczko, J.; Jurczak, J. Furan in the synthesis of natural products. *Stud. Nat. Prod. Chem.* **1995**, *16*, 639–685. [CrossRef]
7. Minetto, G.; Raveglia, L.F.; Sega, A.; Taddei, M. Microwave-Assisted Paal–Knorr Reaction—Three-Step Regiocontrolled Synthesis of Polysubstituted Furans, Pyrroles and Thiophenes. *Eur. J. Org. Chem.* **2005**, *24*, 5277–5288. [CrossRef]
8. Rao, H.S.P.; Jothilingam, S. Facile Microwave-Mediated Transformations of 2-Butene-1,4-diones and 2-Butyne-1,4-diones to Furan Derivatives. *J. Org. Chem.* **2003**, *68*, 5392–5394. [CrossRef]
9. Ghazvini, M.; Shahvelayati, A.S.; Sabri, A.; Nasrabadi, F.Z. Synthesis of Furan and Dihydrofuran Derivatives via Feist–Benary Reaction in the Presence of Ammonium Acetate in Aqueous Ethanol. *Chem. Heterocycl. Compd.* **2016**, *52*, 161–164. [CrossRef]
10. Efremov, I.; Paquette, L.A. First Synthesis of a Rearranged*neo*-Clerodane Diterpenoid. Development of Totally Regioselective Trisubstituted Furan Ring Assembly and Medium-Ring Alkylation Tactics for Efficient Access to (−)-Teubrevin G. *J. Am. Chem. Soc.* **2000**, *122*, 9324–9325. [CrossRef]
11. Rodriguez, A.; Moran, W.J. Furan Synthesis through $AuCl_3$-Catalysed Cycloisomerisation of β-Alkynyl β-Ketoesters. *Tetrahedron Lett.* **2011**, *52*, 2605–2607. [CrossRef]
12. Arcadi, A.; Cacchi, S.; Larock, R.C.; Marinelli, F. The palladium-catalysed synthesis of 2, 3, 5-trisubstituted furans from 2-propargyl-1, 3-dicarbonyl compounds and vinylic or aryl triflates or halides. *Tetrahedron Lett.* **1993**, *34*, 2813–2816. [CrossRef]
13. Zeni, G.; Larock, R.C. Synthesis of Heterocycles via Palladium π-Olefin and π-Alkyne Chemistry. *Chem. Rev.* **2004**, *104*, 2285–2310. [CrossRef]
14. Wang, W.K.; Tan, H.R.; Wang, N.N.; Ruan, H.L.; Zhao, S.Y. Copper(I)-catalyzed direct oxidative annulation of 1,3-dicarbonyl compounds with maleimides: Access to polysubstituted dihydrofuran derivatives. *J. Org. Chem.* **2022**, *87*, 2711–2720. [CrossRef] [PubMed]
15. Lou, J.; Wang, Q.; Wu, K.; Wu, P.; Yu, Z. Iron-catalyzed oxidative C–H functionalization of internal olefins for the synthesis of tetrasubstituted furans. *Org. Lett.* **2017**, *19*, 3287–3290. [CrossRef]
16. Colobert, F.; Castanet, A.S.; Abillard, O. Palladium-Catalyzed Suzuki Coupling with Terminal Alkynes—Application to the Synthesis of 2,3-Disubstituted Benzo[b]furans. *Eur. J. Org. Chem.* **2005**, *2005*, 3334–3341. [CrossRef]
17. Li, F.; Yuan, Y.; Lyu, D.; Yi, Y.; Zhang, J.; Sun, T.; Gao, G. Palladium-Catalyzed Domino Heck/Cross-Coupling Cyclization Reaction: Diastereoselective Synthesis of Furan-Containing Indolines. *J. Org. Chem.* **2024**, *89*, 7552–7560. [CrossRef]
18. Duan, X.H.; Liu, X.Y.; Guo, L.N.; Liao, M.C.; Liu, W.M.; Liang, Y.M. Palladium-Catalyzed One-Pot Synthesis of Highly Substituted Furans by a Three-Component Annulation Reaction. *J. Org. Chem.* **2005**, *70*, 6980–6983. [CrossRef]
19. Mohapatra, S.; Panda, J.; Mohapatra, S.; Nayak, S. Synthesis of Polysubstituted Furans: An Update Since 2019. *Asian J. Org. Chem.* **2023**, *12*, e202300304. [CrossRef]
20. Aljaar, N.; Malakar, C.C.; Conrad, J.; Strobel, S.; Schleid, T.; Beifuss, U. Cu-catalyzed reaction of 1,2-dihalobenzenes with 1,3-cyclohexanediones for the synthesis of 3,4-dihydrodibenzo[b,d]furan-1(2H)-ones. *J. Org. Chem.* **2012**, *77*, 7793–7803. [CrossRef]
21. Kumar, P.; Satbhaiya, S. Proline and proline-derived organocatalysts in the synthesis of heterocycles. In *Green Synthetic Approaches for Biologically Relevant Heterocycles*; Elsevier: Amsterdam, The Netherlands, 2021; pp. 215–251. [CrossRef]
22. Tian, Y.M.; Wang, H.; König, B. Photocatalytic synthesis of tetra-substituted furans promoted by carbon dioxide. *Chem. Sci.* **2024**, *15*, 3084–3213. [CrossRef] [PubMed]
23. Natarajan, P.; Bala, A.; Mehta, S.K.; Bhasin, K.K. Visible-Light Photocatalyzed Synthesis of 2-Aryl*N*-Methylpyrroles, Furans, and Thiophenes Utilizing Arylsulfonyl Chlorides as a Coupling Partner. *Tetrahedron* **2016**, *72*, 2521–2526. [CrossRef]
24. Han, X.; Widenhoefer, R.A. Palladium-Catalyzed Oxidative Alkoxylation of α-Alkenyl β-Diketones to Form Functionalized Furans. *J. Org. Chem.* **2004**, *69*, 1738–1740. [CrossRef] [PubMed]
25. Zhang, X.; Chang, M.; Xu, X.; Zhao, Q. Direct Access to Furan and Cyclopropane Derivatives via Palladium-Catalyzed C-H Activation/Alkene Insertion/Annulation. *Chem. Commun.* **2024**, *60*, 6769–6772. [CrossRef]
26. Arcadi, A.; Cerichelli, G.; Chiarini, M.; Di Giuseppe, S.; Marinelli, F. Sequential Alkylation/Transition Metal Catalyzed Annulation Reactions of 1,3-Dicarbonyl Compounds with Propargyl Bromide. *Tetrahedron Lett.* **2000**, *41*, 9195–9198. [CrossRef]

27. Zhu, C.F.; Gao, C.H.; Hao, W.J.; Zhu, Y.L.; Tu, S.J.; Wang, D.C.; Jiang, B. Synthesis of C_3-alkylated benzofurans via palladium-catalyzed regiocontrolled hydro-furanization of unactivated alkenes. *Org. Chem. Front.* **2021**, *8*, 247. [CrossRef]
28. Rossi, R.; Bellina, F.; Bechini, C.; Mannina, L.; Vergamini, P. Studies on the Transition Metal-Catalyzed Synthesis of Variously Substituted (E)-3-[1-(Aryl)Methylidene]- and (E)-3-(1-Alkylidene)-3H-Furan-2-Ones. *Tetrahedron* **1998**, *54*, 135–156. [CrossRef]
29. Hfaiedh, A.; Yuan, K.; Ben Ammar, H.; Ben Hassine, B.; Soulé, J.F.; Doucet, H. Eco-friendly solvents for palladium-catalyzed desulfitative C–H bond arylation of heteroarenes. *ChemSusChem* **2015**, *8*, 429. [CrossRef] [PubMed]
30. Cao, H.; Jiang, H.F.; Huang, H.W.; Zhao, J.W. Pd-catalyzed cyclization reaction: A convenient domino process for the synthesis of α-carbonyl furan derivatives. *Org. Biomol. Chem.* **2011**, *9*, 7313–7317. [CrossRef]
31. Huang, H.; Jiang, H.; Cao, H.; Zhao, J.; Shi, D. Palladium-Catalyzed One-Pot Synthesis of Polysubstituted Furans from Alkynoates and 2-yn-1-ols. *Tetrahedron* **2012**, *68*, 3135–3144. [CrossRef]
32. Nallagonda, R.; Reddy, R.R.; Ghorai, P. Palladium-Catalyzed Oxidative Cycloisomerization of 2-Cinnamyl-1,3-Dicarbonyls: Synthesis of Functionalized 2-Benzyl Furans. *Chem.–Eur. J.* **2015**, *21*, 14732–14736. [CrossRef] [PubMed]
33. Moran, W.J.; Rodríguez, A. Metal-Catalyzed Furan Synthesis. A Review. *Org. Prep. Proc. Int.* **2012**, *44*, 103–130. [CrossRef]
34. Guo, L.N.; Duan, X.H.; Liang, Y.M. Palladium-Catalyzed Cyclization of Propargylic Compounds. *Acc. Chem. Res.* **2011**, *44*, 111–122. [CrossRef]
35. Makarov, A.S.; Uchuskin, M.G.; Gevorgyan, V. Intramolecular Palladium-Catalyzed Oxidative Amination of Furans: Synthesis of Functionalized Indoles. *J. Org. Chem.* **2018**, *83*, 14010–14021. [CrossRef]
36. Liu, J.; Liu, Q.Y.; Fang, X.X.; Liu, G.Q.; Ling, Y. Preparation of Polysubstituted Dihydrofurans through a $PhI(OAc)_2$-Promoted Haloenolcyclization of Olefinic Dicarbonyl Compounds. *Org. Biomol. Chem.* **2018**, *16*, 7454–7460. [CrossRef] [PubMed]
37. Yusifov, N.N.; Ismayilov, V.M.; Sadigova, N.D.; Kopylovich, M.N.; Mahmudov, K.T. A Straightforward Synthesis of 2(3),6,6-Trimethyl-6,7-Dihydrobenzofuran-4(5H)-ones. *Mendeleev Commun.* **2013**, *23*, 292–293. [CrossRef]
38. Wang, G.-Q.; Guan, Z.; Tang, R.-C.; Ostojic, Z.; Jones, T.N.; Wu, T.-T.; He, Y.-H. A Simple Preparation of Ethyl 2,5-Dimethylfuran-3-Carboxylate and 2,5-Dimethylfuran-3,4-Dicarboxylic Acid from Diethyl 2,3-Diacetylsuccinate. *J. Heterocycl. Chem.* **2009**, *46*, 540–543. [CrossRef]