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Ru- and Pd-Catalysed Synthesis of 2-Arylfurans by One-Flask Heck Arylation/Oxidation

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2,5-Disubstituted furans were synthesized by one-flask Heck arylation/oxidation sequences. The starting materials are 2-substituted 2,3-dihydrofurans, conveniently available by RCM/isomerization sequences, and arenediazonium salts. These react in ligand-free Heck reactions to afford 2,5-disubstituted 2,5-dihydrofurans, which are oxidized to the corresponding furans without isolation or intermediate workup. The oxidation is conveniently achieved with chloranil or DDQ, depending on the substrate.

Introduction

2-Substituted and 2,5-disubstituted furans are important substructures of several drugs currently in clinical use.[1] Some of these, such as the diuretic furosemide (**1**, Figure 1) or the peptic ulcer therapeutic ranitidine (**2**), are best synthesized from cheap and conveniently available furans such as furan-2-carbaldehyde, furfuryl alcohol or furfurylamine, with use of electrophilic Mannich-type alkylation reactions[2] for the introduction of their second side chains. For the synthesis of 2-arylfurans different methods are required. The muscle relaxant dantrolene (**3**), commonly used for the treatment of life-threatening complications during anaesthesia,[3] for instance, has been synthesized from furfural and an arenediazonium salt[4] through a Cu-catalysed Meerwein arylation.[5] Formation of the quinazoline–furan C–C bond in the anticancer agent lapatinib (**4**), a tyrosine kinase inhibitor, was achieved through a Suzuki–Miyaura coupling between a 2-furylboronic acid and an appropriately substituted quinazolinyl iodide (Figure 1).[6]

Apart from these clinically approved drugs, numerous other 2-aryl-, 2-alkyl-5-aryl- and 2,5-diarylfurans have been investigated as drug candidates in medicinal chemistry studies over the past decade. These compounds (Figure 2) were tested for diverse applications, such as activity against several cancer cell lines (compounds **5** and **6**),[7] cardioprotective activity through inhibition of Na^+/H^+ exchangers (**7**),[8,9] activity as an HIV-integrase inhibitor (**8**),[10,11] activity against *Mycobacterium tuberculosis* (**9**)[12] or as potential therapeutics for smoking cessation (**10**).[13]

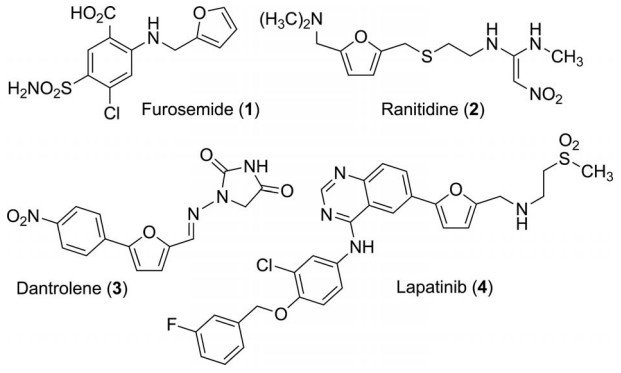

Figure 1. Approved drugs containing furan substructures.

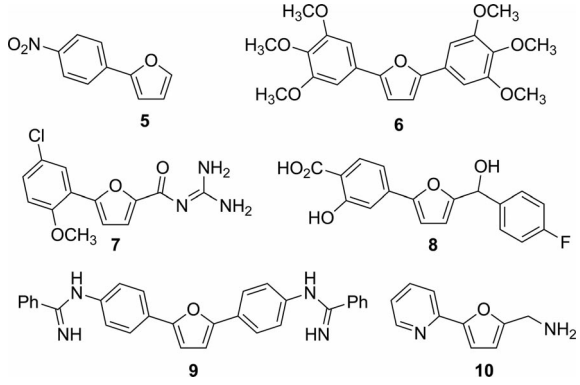

Figure 2. Examples of drug candidates containing arylfuran moieties.

Because of the low to moderate yields normally observed for Meerwein arylation reactions of furans, this method is restricted to cheap or conveniently available starting materials. For certain substrates, the Ti^{III}-mediated arylation of furans with diazonium salts might have potential as a useful alternative.[14] It has been reported, though, that Meerwein-

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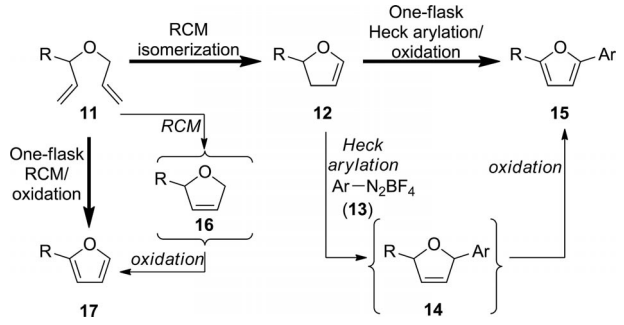
type arylation reactions cannot be applied to the synthesis of 2,5-diarylfurans such as **6** or **9**,[7] which have instead been synthesized from symmetrical 2,5-distannylfurans[15] in double Stille couplings. The disadvantages of this method include potential contamination of the products with organostannane residues, as well as selectivity issues arising when the method is adopted for the synthesis of unsymmetrical 2,5-diarylfurans. To overcome these drawbacks we sought an alternative route not based on furan cross-coupling reactions. Inspired by recent research in our group directed towards the synthesis of centrolobines[16] and related diarylheptanoids[17] through Heck coupling reactions of dihydropyrans and arenediazonium salts,[18] we decided to investigate the feasibility of a synthesis as outlined in Scheme 1.



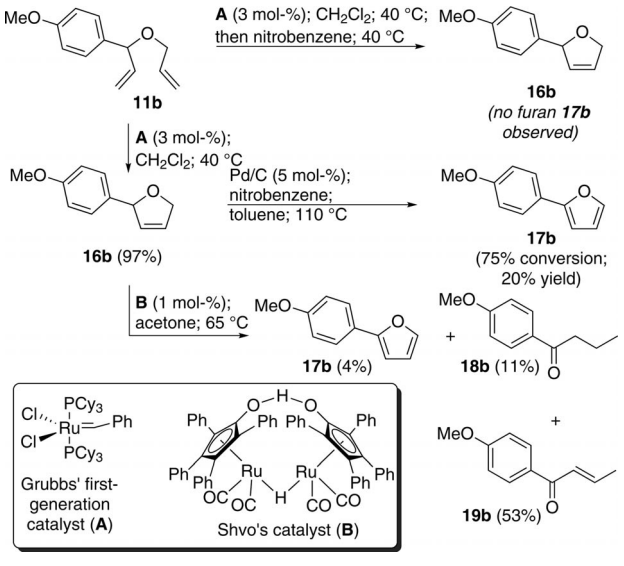
Scheme 1. RCM/Heck reaction/oxidation approach to furans.

Accordingly, the diallyl ethers **11**, conveniently available with a variety of R substituents, were envisaged as starting materials. Subjection of these diallyl ethers to an RCM/isomerization sequence[19–22] should yield the 2-substituted 2,3-dihydrofurans **12**, which should react with the arenediazonium salts **13** under Pd-catalysis conditions[23–25] to afford the 2,5-disubstituted 2,5-dihydrofurans **14**.[18] Oxidation or dehydrogenation of these intermediates should give the desired 2,5-disubstituted furans **15**. Similarly, the 2-substituted furans **17** should be obtainable from the same precursors **11** through RCM and subsequent oxidation/dehydrogenation of the intermediate 2-substituted 2,5-dihydrofurans **16**. For synthetic purposes, it should be most convenient to combine the transition-metal-catalyzed step and the aromatization step in a one-flask sequence, and we therefore decided to investigate this option.

Results and Discussion

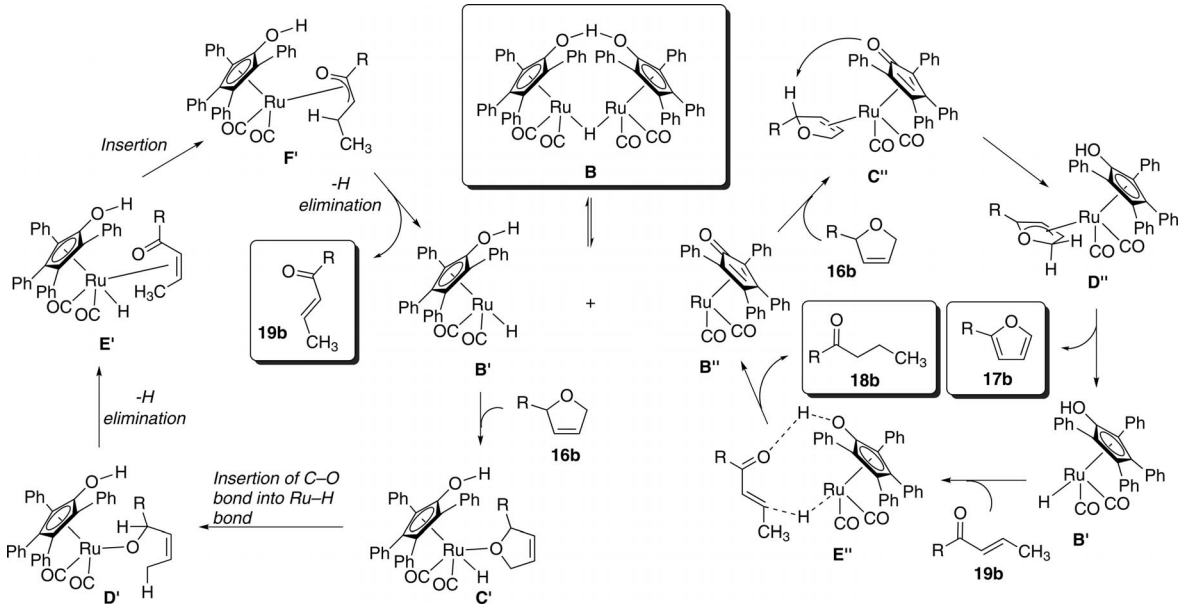
Assisted tandem[26] RCM/aromatization sequences,[27,28] characterized by the use of a single Ru precatalyst that undergoes an organometallic conversion to a dehydrogenation catalyst in situ, are scarce.[29–31] In most cases the heteroaromatic product is obtained in minor quantities as a side product, or the reaction is not general and difficult to reproduce. In this respect, an orthogonal tandem catalytic sequence originally developed for the synthesis of pyrroles from diallylamines through the use of Ru–carbenes for the metathesis step and $RuCl_3$ to promote the subsequent dehydrogenation step appeared advantageous.[32] Alternatively, a one-flask RCM/oxidation sequence that uses stoichiometric amounts of benzoquinones as oxidants has been developed for the same transformation.[33] In the furan series, we are aware of one example of such a sequence.[34] Benzoquinones – DDQ in particular – have also been used in a few cases for the oxidation of 2,5-disubstituted 2,5-dihydrofurans to the corresponding furans.[35–37] Spontaneous oxidation of 2,5-dihydrofurans by air[38] and their dehydrogenation catalysed by Pd/C[39] appear to be less general and therefore only of limited use.

Inspired by a protocol developed by Cossy and Belotti for the Pd/C-catalysed aromatisation of enamines to anilines,[40] we tested nitrobenzene as a hydrogen acceptor in the Ru-catalysed RCM of the diallyl ether **11b** (Scheme 2). Under these conditions, only the expected RCM product **16b** was observed, but no furan **17b**. However, application of Cossy's conditions to **16b** indeed resulted in the formation of the desired furan with 75% conversion and good selectivity. Unfortunately, though, separation of the product from unreacted nitrobenzene turned out to be very difficult, resulting in a reduced yield of only 20%. We then examined Shvo's catalyst (**B**)[41] for the dehydrogenation of the dihydrofuran **16b**, using acetone as a solvent and hydrogen acceptor. Although it had previously been demonstrated that this catalyst is efficient for the dehydrogenation of secondary alcohols,[42] to the best of our knowledge it has not been used for dehydrogenative aromatization reactions.[43] Upon treatment of **16b** with Shvo's catalyst (**B**) in acetone, we were indeed able to isolate the furan **17b** from the reaction mixture in 4% yield, along with an 11% yield of the saturated ketone **18b** and a 53% yield of the α,β-unsaturated ketone **19b** (Scheme 2).



Scheme 2. Unsuccessful dehydrogenation experiments.

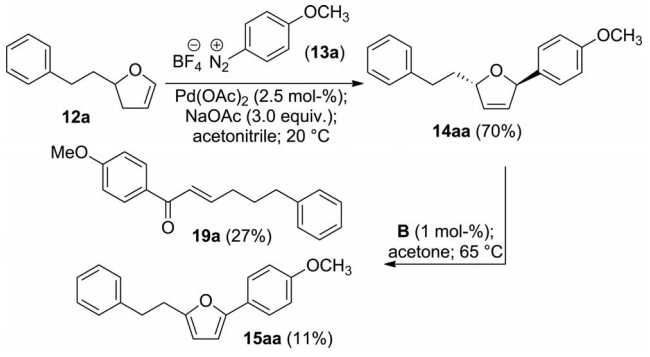
The mechanism proposed in Scheme 3 would explain the formation of all three products **17b**, **18b** and **19b**. Initially, the catalyst **B** might dissociate into the reducing species **B′**



Scheme 3. Proposed mechanism for the ring cleavage of dihydrofurans.

and the oxidizing species **B′′**.[41] We assume that the former is responsible for the preferred pathway, leading to the ketone **19b**. Presumably, the dihydrofuran **16b** could coordinate to the Ru atom through the ring oxygen atom, giving the complex **C′**. This could undergo insertion of the sterically less hindered C–O bond into the Ru–H bond (Ru–alkoxide **D′**), followed by β-hydride elimination to give **E′**. The two following steps could result in an isomerization of the initially formed (*Z*)-enone to the thermodynamically more stable (*E*)-enone. This isomerization might involve a migratory insertion, giving the Ru–enolate **F′**, and a final β-hydride elimination to afford (*E*)-**19b** and the catalytically active species **B′**. An important clue for understanding the formation of **17b** and **18b** was provided by examination of the ^{1}H NMR spectra of the crude reaction mixture. These products are present in a ratio of approximately 1:1, suggesting that their formation is not independent, but that **19b** serves as a hydrogen acceptor for the starting material **16b**, which is simultaneously dehydrogenated to afford the furan **17b**. We propose a mechanism involving coordination of the dihydrofuran **16b** to the oxidizing Ru species **B′′**, probably through the C–C double bond. Migration of a proton in the η^2-alkene complex **C′′** to the carbonyl group of the cyclopentadienone ligand could give the η^3-allyl–Ru complex **D′′**, which could undergo β-hydride elimination to afford the furan **17b** and the reducing catalyst **B′**. Regeneration of the oxidizing catalyst **B′′** could occur either through hydrogenation of the enone **19b** to afford the ketone **18b**, as outlined in Scheme 3, or through hydrogenation of the acetone solvent (not shown). Because **17b** and **18b** are formed in equimolar amounts, it appears likely that the enone **19b** is a much better hydrogen acceptor than acetone, which is present in a large excess.

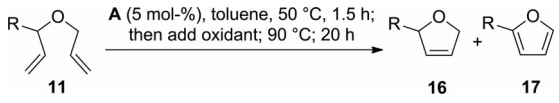
A similar result was observed for the attempted aromatization of the 2,5-disubstituted dihydrofuran **14aa** (Scheme 4). This substrate was synthesized from **12a** and **13a** by means of a Heck reaction[18] and, after purification, was treated with Shvo's catalyst in acetone at reflux. Together with recovery of the starting material **14aa** (46%), we isolated the enone **19a** (27%) and the desired 2,5-disubstituted furan **15aa** in 11% yield. Unlike in the analogous reaction of the monosubstituted dihydrofuran **16b**, no saturated ketone **18a**, resulting from hydrogen transfer to the ring-opening product **19a**, was observed. Presumably, acetone is a better hydrogen acceptor than **19a** in this case.



Scheme 4. Ring-opening versus dehydrogenation reactions of the 2,5-disubstituted dihydrofuran **14aa** catalysed by Shvo's catalyst.

In view of these rather unsatisfactory results, we investigated the potential of one-flask sequences consisting of a transition-metal-catalysed step and a benzoquinone-mediated oxidation step. To this end, the metathesis precursors **11a** and **11b** (Table 1) were treated with first-generation Grubbs catalyst (**A**) at slightly elevated temperature, and after completion of the RCM step the oxidant was added, without intermediate purification or exchange of solvents.

Table 1. One-flask RCM/oxidation.



Entry	11	R	Oxidant [equiv.]	Ratio of 16/17[a]	Product (yield)
1	**11a**	$PhCH_2CH_2$	CA[b] (1.2)	>19:1	n.d.
2	**11a**	$PhCH_2CH_2$	DDQ (1.2)	1:3.5	n.d.
3	**11a**	$PhCH_2CH_2$	DDQ (2.0)	<1:19	**17a** (51%)
4	**11b**	4-$MeOC_6H_4$	CA[b] (1.2)	<1:19	**17b** (61%)

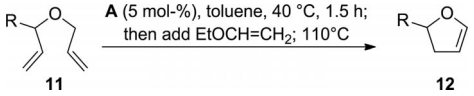
[a] Ratios were determined by ^1H NMR spectroscopy of the crude reaction mixture. [b] CA = chloranil.

An important result of these experiments is the finding that chloranil (CA)[44] cannot be used for the one-flask conversion of the alkyl-substituted diallyl ether **11a** into the corresponding furan **17a**. Instead, the intermediate RCM product **16a** was isolated quantitatively (Table 1, Entry 1). With DDQ[45] (1.2 equiv.) under otherwise identical conditions, approximately 75% conversion to the desired furan **17a** was observed (Entry 2). With an increase in the amount of DDQ to 2.0 equiv. the reaction went to completion, and **17a** was isolated in 51% yield (Entry 3). In the case of the 4-methoxyphenyl-substituted diallyl ether **11b** the oxidation step proceeded much more smoothly: for this substrate 1.2 equiv. of chloranil was sufficient to achieve quantitative oxidation to the furan **17b** (Entry 4). Oku et al. showed by measurement of the redox potentials in acetonitrile that DDQ is a significantly stronger oxidant than chloranil,[46] which is consistent with these results.

We next investigated the synthesis of the various 2,5-disubstituted furans **15** by a one-flask Heck arylation/oxidation sequence as outlined in Scheme 1. The starting materials required for this route – the 2-substituted 2,3-dihydrofurans **12** – were synthesized from the diallyl ethers **11** by the tandem RCM/isomerization sequence. As we have previously reported, ethyl vinyl ether is the best additive for this particular ring size, because competing transfer hydrogenation[47] is excluded.[22] The diallyl ethers **11a**–**d** were thus treated with the first-generation Grubbs catalyst **A**. After completion of the RCM step, ethyl vinyl ether was added, and the reaction mixture was heated to reflux. Under these conditions, the propagating species of the metathesis reaction is converted into a rutheium hydride, as described previously by Louie and Grubbs,[48] which catalyses the double-bond migration (Table 2).

The diazonium salts **13a**–**e** were tested as coupling partners. Compounds **13a**–**c** and **13e** were synthesized from the corresponding acetanilides. As we have described previously, the required diazonium salts were obtained in higher purities by this route, which has been found to be beneficial for their application in Pd-catalysed coupling reactions.[49] The trimethoxy-substituted diazonium salt **13d** could be synthesized from the corresponding aniline by a literature procedure (Figure 3).[50]

Table 2. Synthesis of the 2-substituted 2,3-dihydrofurans **12** used in this study.



Entry	Starting material	R	Product	Yield	Ref.
1	**11a**	$PhCH_2CH_2$	**12a**	68%	[22]
2	**11b**	4-$MeOC_6H_4$	**12b**		this work
3	**11c**	Ph	**12c**	60%	this work
4	**11d**	$BnOCH_2$	**12d**	59%	this work

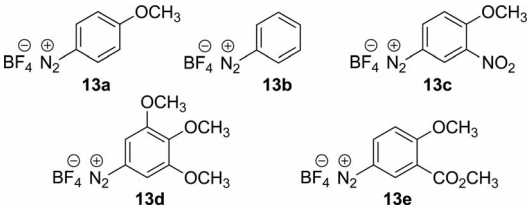
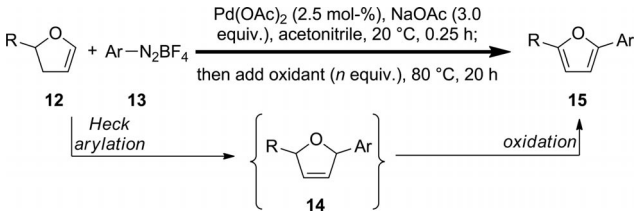


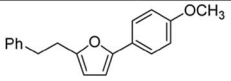
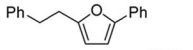
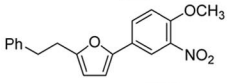
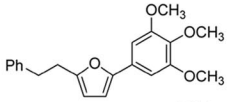
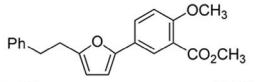
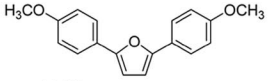
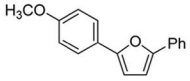
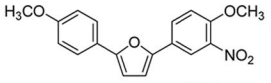
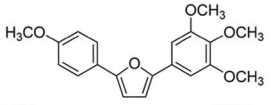
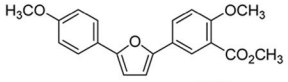
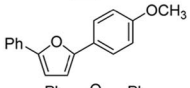
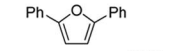
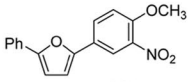
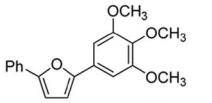
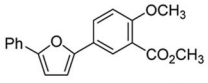
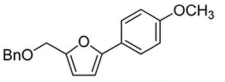
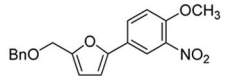
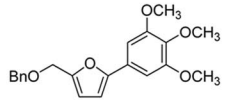
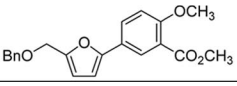
Figure 3. Arenediazonium salts used for the one-flask Heck arylation/oxidation sequence.

Previous investigations into Heck reactions with arenediazonium salts had found acetonitrile to be the best solvent for arylations of cyclic enol ethers[18] and enamides.[51] Methanol, although commonly used for Pd-catalysed coupling reactions of diazonium salts and electron-deficient alkenes, is less suitable for these substrates, because competing acetal formation poses a major problem.[52] For these reasons, the previously optimized conditions for intermolecular Heck arylations of cyclic enol ethers, as described in Scheme 4 for the synthesis of **14aa**, were adopted for the envisaged one-flask sequences. The Pd-catalysed coupling reactions are normally fast, and their completion is easily recognized when the evolution of nitrogen ceases. Afterwards, the appropriate oxidants were added, and the reaction mixtures were heated at 80 °C for 20 h (Scheme 5). The results are listed in Table 3: remarkably, even the Heck coupling products resulting from the 2-alkyl-substituted 2,3-dihydrofuran **12a** underwent oxidation to the corresponding furans **15aa**–**15ae** smoothly in the presence of the milder oxidant chloranil, whereas DDQ was required for the oxidation of the dihydrofuran **16a**, without an aromatic substituent directly attached to the heterocycle. In those cases in which the conversion was incomplete with 1.2 equiv. of oxidant (Entries 2, 4, 5 and 8) the remaining amount of



Scheme 5. One-flask Heck arylation/oxidation sequence. See Table 3 for results.

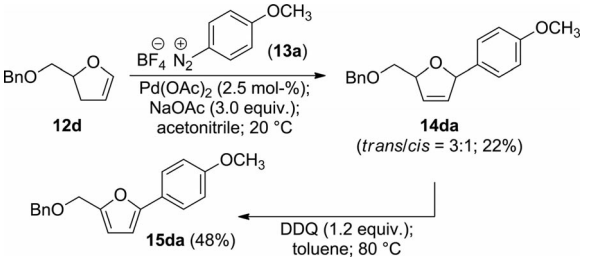
Table 3. One-flask Heck arylation/oxidation sequence for the synthesis of the 2,5-disubstituted furans **15** (see Scheme 5 for reaction details).

Entry	2,3-Dihydrofuran	Diazonium salt	Oxidant	Oxidant [equiv.]	Conversion[a]	Structure of product	Furan	Yield
1	**12a**	**13a**	chloranil	1.2	> 95%		**15aa**	45%
2[b]	**12a**	**13b**	chloranil	1.2	50%		**15ab**	n. d.
3	**12a**	**13b**	chloranil	2.0	> 95%		**15ab**	50%
4[b]	**12a**	**13c**	chloranil	1.2	50%		**15ac**	n. d.
5[b]	**12a**	**13c**	chloranil	2.5	66%		**15ac**	n. d.
6	**12a**	**13c**	chloranil	3.7	> 95%		**15ac**	77%
7	**12a**	**13d**	chloranil	1.2	> 95%		**15ad**	52%
8[b]	**12a**	**13e**	chloranil	1.2	66%		**15ae**	n. d.
9	**12a**	**13e**	chloranil	2.5	> 95%		**15ae**	67%
10	**12b**	**13a**	chloranil	1.2	> 95%		**15ba**	65%
11	**12b**	**13b**	chloranil	1.2	> 95%		**15bb**[c]	53%
12	**12b**	**13c**	chloranil	1.2	> 95%		**15bc**	71%
13	**12b**	**13d**	chloranil	1.2	> 95%		**15bd**	71%
14	**12b**	**13e**	chloranil	1.2	> 95%		**15be**	66%
15	**12c**	**13a**	chloranil	1.2	> 95%		**15ca**[c]	59%
16	**12c**	**13b**	chloranil	1.2	> 95%		**15cb**	53%
17[b]	**12c**	**13c**	chloranil	1.2	50%		**15cc**	n. d.
18[b]	**12c**	**13c**	chloranil	2.5	75%		**15cc**	n. d.
19	**12c**	**13c**	chloranil	3.7	> 90%		**15cc**	72%
20	**12c**	**13d**	chloranil	1.2	> 95%		**15cd**	78%
21	**12c**	**13e**	chloranil	1.2	66%		**15ce**	54%
22	**12c**	**13e**	chloranil	2.5	> 95%		**15ce**	64%
23[d]	**12d**	**13a**	chloranil	1.2	> 95%		**15da**	n. d.
24[d]	**12d**	**13a**	DDQ	1.2	> 95%		**15da**	n. d.
25	**12d**	**13b**	DDQ	1.2	33%		**15db**	18%
26[b]	**12d**	**13b**	DDQ	2.0	33%		**15db**	n. d.
27[b]	**12d**	**13c**	DDQ	1.2	66%		**15dc**	n. d.
28	**12d**	**13c**	DDQ	2.5	> 95%		**15dc**	57%
29	**12d**	**13d**	DDQ	1.2	> 95%		**15dd**	22%
30	**12d**	**13e**	DDQ	1.2	77%		**15de**	65%
31	**12d**	**13e**	DDQ	2.5	> 95%		**15de**	< 5%

[a] Refers to conversion of the oxidation step. Determined by ^{1}H NMR spectroscopy of the crude reactions mixture. [b] Reaction mixtures consist only of the furan **15** and the Heck arylation product **14**. [c] Compounds **15bb** and **15ca** are identical. Different notations are used to distinguish between the two different approaches to their synthesis. [d] Complex mixture of products was observed by ^{1}H NMR spectroscopy.

material is the unreacted dihydrofuran **14**. With an increase in the amount of oxidant to 2.0–3.7 equiv., full conversion into the corresponding furans **15ab**, **15ac** and **15ae** was achieved (Entries 3, 6 and 9).

Very similar reactivity was observed for the 2-phenyl-substituted derivatives (Table 3, Entries 15–22). Again, Heck coupling products of electron-rich arenediazonium salts (Entries 15, 16, 20) were smoothly oxidized to the corresponding furans **15ca**, **15cb** and **15cd** with 1.2 equiv. of chloranil, whereas larger amounts of the oxidant were required for **15cc** and **15ce** (Entries 17–19 and 21–22). It is in line with these observations that 1.2 equiv. of chloranil are sufficient for quantitative oxidation of all Heck coupling products derived from the *p*-methoxyphenyl-substituted 2,3-dihydrofuran **12b** (Table 3, Entries 10–14). Rather disappointing results were obtained for most derivatives bearing benzyloxymethyl substituents at their 2-positions (Entries 23–31). Admittedly, these transformations should be quite challenging, in view of the well-documented sensitivity of benzyl protecting groups towards oxidizing agents such as DDQ.[53] In a first experiment, **12d** and the diazonium salt **13a** were subjected to the standard conditions, with chloranil (1.2 equiv.) as the oxidant. Under these conditions, the intermediate Heck arylation product, the dihydrofuran **14da**, was fully consumed, but a complex mixture of products was observed in the ^{1}H NMR spectrum of the crude reaction mixture. After replacement of chloranil with DDQ, the desired furan **15da** was detected in small amounts in the crude mixture, but it could be isolated only in yields below 5%. This particularly difficult example was therefore investigated in some detail, by conducting the two steps separately (Scheme 6).

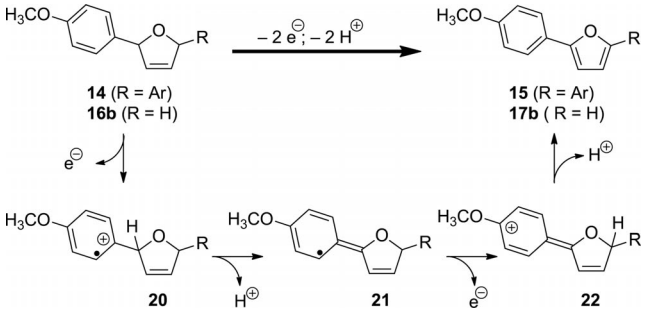


Scheme 6. Two-step synthesis of **15da**.

The reaction between **12d** and **13a** under the standard conditions established for this transformation afforded the intermediate **14da** only in 22% yield. NMR spectroscopy of the crude reaction mixture revealed that the Pd-catalysed step proceeded somewhat sluggishly, with the formation of small amounts of unidentified byproducts. In particular, a notable amount of the *cis* diastereomer, not normally observed under these coupling reactions, was detected. A thoroughly purified 3:1 mixture of *trans*/*cis*-**14da** was then treated with DDQ (1.2 equiv.) in toluene. Under these conditions, the furan **15da** was isolated in 48% yield.

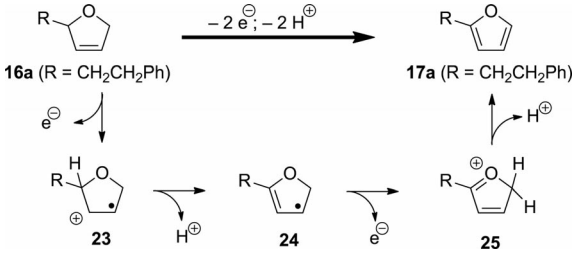
Similarly, very low isolated yields of the desired furans **15db** and **15dd** were obtained by the one-flask protocol. However, in those cases in which an electron-deficient aromatic substituent was introduced in the Heck arylation step (Entries 27/28 and 30/31), preparatively useful yields of the furans **15dc** and **15de** were isolated. Notably, the rate of conversion can be improved only to a very limited extent by increasing the amount of oxidant: in the case of the furan **15de**; for instance, 77% conversion was obtained with 1.2 equiv. of DDQ, resulting in a yield of 65%, whereas with 2.5 equiv. of DDQ full conversion was observed, but the isolated yield was lower than 5%, due to extensive decomposition.

The more facile oxidation of substrates bearing electron-rich aromatic substituents is most probably a consequence of their higher HOMO energies. In these cases, slight excesses of chloranil are sufficient to oxidize the aromatic systems to the radical cations **20** (Scheme 7), which are deprotonated to afford the radicals **21**. These are in turn oxidized to the stabilized carbenium ions **22**. Second deprotonations yield the furans **15** (R = Ar) or **17b** (R = H).



Scheme 7. Sequential oxidation/deprotonation mechanism for aryl-substituted derivatives.

Dihydrofurans bearing either phenyl substituents or aromatic substituents with electron-withdrawing groups are less prone to oxidation. It might be that in these cases the oxidations proceed through removal of single electrons from the C–C double bonds, which should require a stronger oxidant. This might explain why DDQ is required for the one-flask conversion of the diallyl ether **11a** into the corresponding furan **17a** (Table 1): presumably, the RCM product **16a** (Scheme 8) is first oxidized to the radical cation **23**, which undergoes deprotonation to give the allyl radical **24**. This radical is then oxidized to the carbocation **25**, and final deprotonation gives the furan **17a**.



Scheme 8. Sequential oxidation/deprotonation mechanism for alkyl-substituted derivatives.

Conclusions

We have established a one-flask method for the synthesis of furans, ultimately starting from simple diallyl ethers. The

sequence consists of transition-metal-catalysed C–C bond-forming reactions, such as RCM and the Heck reaction, and subsequent oxidative aromatization through the use either of chloranil or of DDQ. In particular, our method is well suited for the synthesis of 2,5-disubstituted furans, including unsymmetrical 2,5-diaryl furans, which play an increasingly important role in medicinal chemistry and drug discovery.

Experimental Section

General Remarks: All experiments were conducted in dry reaction vessels under dry nitrogen. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained with a Bruker DRX 300 spectrometer at 300 MHz in $CDCl_3$ with $CHCl_3$ (δ = 7.26 ppm) as an internal standard. Coupling constants (J) are given in Hz. Signal assignments refer to numbering schemes detailed in the Supporting Information. ^{13}C NMR spectra were recorded with a Bruker DRX 300 spectrometer at 75 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.0 ppm) as an internal standard. IR spectra were recorded with a Nicolet Impact 400 D instrument as films on NaCl or KBr plates or as KBr discs. Wavenumbers ($\tilde{\nu}$) are given in cm^{-1}. Mass spectra were obtained at 70 eV with a GC-TOF micromass spectrometer (Micromass Manchester Waters Inc.) for EI. ESI mass spectra were obtained with a Q-TOF micromass spectrometer (Micromass Manchester Waters Inc.).

General Procedure for One-Flask RCM/Oxidation: Catalyst **A** (41 mg, 5 mol-%) was added to a solution of the appropriate diallyl ether **11** (1.0 mmol) in dry and degassed toluene (20 mL). The solution was stirred at 50 °C for 90 min, and the appropriate oxidant was then added. The mixture was heated to 90 °C for 20 h, allowed to cool to ambient temperature and diluted with water. The organic layer was separated, and the aqueous layer was extracted with MTBE. The combined organic extracts were dried with $MgSO_4$ and filtered, and the solvents were evaporated. The residue was purified by column chromatography on silica.

2-Phenethylfuran (17a): This compound was obtained by the General Procedure, from the diallyl ether **11a** (304 mg, 1.5 mmol) and DDQ (685 mg, 3.0 mmol, 2.0 equiv.). Yield of **17a**: 132 mg (0.8 mmol, 51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34 (dd, J = 1.8, 0.8 Hz, 1 H, 1-H), 7.32–7.17 (5 H, Ph), 6.29 (dd, J = 3.1, 1.9 Hz, 1 H, 2-H), 5.98 (dd, J = 3.1, 0.7 Hz, 1 H, 3-H), 2.93–3.01 (4 H, 5-H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.4, 141.2, 140.9, 128.4, 128.3, 126.0, 110.1, 105.1, 34.4, 29.9 ppm.

2-(4-Methoxyphenyl)furan (17b): This compound was obtained by the General Procedure, from the diallyl ether **11b** (202 mg, 1.0 mmol) and chloranil (293 mg, 1.2 mmol, 1.2 equiv.). Yield of **17b**: 83 mg (0.5 mmol, 48%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, J = 9.0 Hz, 2 H, 6-H), 7.44 (dd, J = 1.8, 0.8 Hz, 1 H, 1-H), 6.94 (d, J = 9.0 Hz, 2 H, 7-H), 6.52 (dd, J = 3.3, 0.8 Hz, 1 H, 3-H), 6.46 (dd, J = 3.3, 1.8 Hz, 1 H, 2-H), 3.82 (s, 3 H, 9-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 154.0, 141.4, 125.3, 124.1, 114.1, 111.5, 103.4, 55.4 ppm.

General Procedure for the One-Flask Heck Arylation/Oxidation Sequence: NaOAc (3.0 equiv.), $Pd(OAc)_2$ (5 mol-%) and the appropriate diazonium salt **13** (1.0 equiv.) were added to a solution of the appropriate dihydrofuran **12** (1.0 equiv.) in acetonitrile (10 mL per mmol of **12**). The reaction mixture was stirred at ambient temperature until the evolution of nitrogen had ceased (approx. 15 min), and the appropriate oxidant was added. The reaction mixture was then heated at 80 °C for 20 h. After completion of the reaction, the mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and brine, dried with $MgSO_4$ and filtered, and the solvents were evaporated. The residue was purified by column chromatography on silica gel with hexane/MTBE mixtures as eluents to give the desired furans **15**.

2-(4-Methoxyphenyl)-5-phenethylfuran (15aa): This compound was obtained by the General Procedure, from **12a** (227 mg, 1.3 mmol), the diazonium salt **13a** (289 mg, 1.0 mmol) and chloranil (397 mg, 1.6 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica gel with a mixture of hexane/MTBE (20:1) as eluent. Yield of **15aa**: 163 mg (0.6 mmol, 45%), m.p. 75–78 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.58 (d, J = 8.9 Hz, 2 H, 4-H), 7.37–7.18 (5 H, Ph), 6.93 (d, J = 8.9 Hz, 2 H, 3-H), 6.41 (d, J = 3.2 Hz, 1 H, 7-H/8-H), 6.04 (d, J = 3.2 Hz, 1 H, 8-H/7-H), 3.84 (s, 3 H, 1-H), 2.98–3.07 (4 H, 10-H, 11-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.7, 154.4, 152.4, 141.2, 128.4, 128.3, 126.0, 124.8, 124.4, 114.1, 107.3, 104.0, 55.3, 34.5, 30.1 ppm. IR (KBr disc): $\tilde{\nu}$ = 1717, 1600, 1578, 1553, 1498, 1454, 1294, 1248, 1174, 1110, 1029, 831, 781, 750, 698 cm^{-1}. LRMS (EI): m/z (%) = 91 (26), 115 (13), 135 (22), 144 (18), 187 (100), 188 (13), 278 (13) [M]$^+$. HRMS (EI): calcd. for $C_{19}H_{18}O_2$ [M]$^+$ 278.1307; found 278.1320.

2-(4-Methoxyphenyl)-5-phenylfuran (15bb): This compound was obtained by the General Procedure, from **12b** (228 mg, 1.3 mmol), the diazonium salt **13b** (250 mg, 1.3 mmol) and chloranil (398 mg, 1.6 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica gel with a mixture of hexane/MTBE (50:1) as eluent. Yield of **15bb**: 172 mg (0.7 mmol, 53%), m.p. 115–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (dd, J = 8.5, 1.3 Hz, 2 H, 3-H), 7.68 (d, J = 8.9 Hz, 2 H, 10-H), 7.41 (dd, J = 7.4, 6.5 Hz, 2 H, 2-H), 7.25 (dd, J = 8.5, 7.4 Hz, 1 H, 1-H), 6.95 (d, J = 8.9 Hz, 2 H, 11-H), 6.72 (d, J = 3.5 Hz, 1 H, 6-H/7-H), 6.61 (d, J = 3.5 Hz, 1 H, 7-H/6-H), 3.85 (s, 3 H, 13-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.1, 153.5, 152.7, 130.9, 128.7, 127.1, 125.2, 123.9, 123.6, 114.2, 107.2, 105.7, 55.3 ppm. IR (KBr disc): $\tilde{\nu}$ = 1602, 1499, 1485, 1440, 1297, 1250, 1178, 1114, 1028, 928, 833, 787, 760, 692 cm^{-1}. LRMS (EI): m/z (%) = 77 (15), 125 (14), 178 (21), 207 (15), 235 (70), 236 (13), 250 (100) [M]$^+$. HRMS (EI): calcd. for $C_{17}H_{14}O_2$ [M]$^+$ 250.0994; found 250.0985. $C_{17}H_{14}O_2$ (250.29): C 81.6, H 5.6; found C 81.3, H 5.4.

2-(4-Methoxy-3-nitrophenyl)-5-(4-methoxyphenyl)furan (15bc): This compound was obtained by the General Procedure, from **12b** (240 mg, 1.4 mmol), the diazonium salt **13c** (366 mg, 1.4 mmol) and chloranil (419 mg, 1.6 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica gel with a mixture of hexane/MTBE (3:1) as eluent. Yield of **15bc**: 316 mg (1.0 mmol, 71%), m.p. 128–130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, J = 2.2 Hz, 1 H, 4′-H), 7.85 (dd, J = 8.8, 2.2 Hz, 1 H, 4-H), 7.66 (d, J = 9.0 Hz, 2 H, 11-H), 7.12 (d, J = 8.8 Hz, 1 H, 3-H), 6.95 (d, J = 9.0 Hz, 2 H, 12-H), 6.69 (d, J = 3.5 Hz, 1 H, 7-H/8-H), 6.60 (d, J = 3.5 Hz, 1 H, 8-H/7-H), 4.00 (s, 3 H, 14-H), 3.85 (s, 3 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 154.1, 151.2, 150.1, 139.9, 128.8, 125.2, 124.1, 123.4, 120.6, 114.3, 111.9, 107.7, 105.7, 56.7, 55.4 ppm. IR (KBr disc): $\tilde{\nu}$ = 1624, 1596, 1524, 1499, 1352, 1280, 1251, 1177, 1024, 868, 833, 784, 688 cm^{-1}. LRMS (EI): m/z (%) = 59 (15), 310 (17), 325 (100) [M]$^+$, 326 (18) [M + H]$^+$. HRMS (EI): calcd. for $C_{18}H_{15}O_5N$ [M]$^+$ 325.0950; found 325.0935.

2-Phenyl-5-(3,4,5-trimethoxyphenyl)furan (15cd): This compound was obtained by the General Procedure, from **12c** (188 mg,

1.2 mmol), the diazonium salt **13d** (363 mg, 1.3 mmol) and chloranil (393 mg, 1.5 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica gel with a mixture of hexane/MTBE (7:1) as eluent. Yield of **15cd**: 313 mg (1.0 mmol, 78%), m.p. 85–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (dd, J = 8.6, 1.3 Hz, 2 H, 11-H), 7.42 (dd, J = 7.4, 6.5 Hz, 2 H, 12-H), 7.28 (ddm, J = 7.1, 5.6 Hz, 1 H, 13-H), 6.96 (s, 2 H, 4-H), 6.74 (d, J = 3.5 Hz, 1 H, 7-H/8-H), 6.67 (d, J = 3.5 Hz, 1 H, 8-H/7-H), 3.95 (s, 6 H, 14-H), 3.89 (s, 3 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.6, 153.2, 153.2, 138.0, 130.7, 128.7, 127.3, 126.5, 123.7, 107.3, 106.9, 101.3, 60.9, 56.2 ppm. IR (KBr disc): $\tilde{\nu}$ = 1591, 1497, 1463, 1417, 1342, 1248, 1173, 1127, 1025, 1005, 966, 923, 834, 787, 759, 691 cm^{-1}. LRMS (EI): m/z (%) = 105 (10), 140 (9), 155 (10), 181 (17), 295 (70), 296 (13), 310 (100) $[M]^+$. HRMS (EI): calcd. for $C_{19}H_{18}O_4$ $[M]^+$ 310.1205; found 310.1217.

Methyl 5-[5-(Benzyloxymethyl)furan-2-yl]-2-methoxybenzoate (15de): This compound was obtained by the General Procedure, from **12d** (148 mg, 0.8 mmol), the diazonium salt **13e** (219 mg, 0.8 mmol) and DDQ (213 mg, 0.9 mmol, 1.2 equiv.). The crude product was purified by column chromatography on silica gel with a mixture of hexane/MTBE (5:1) as eluent. Yield of **15de**: 177 mg (0.7 mmol, 65%; 84% based on recovered **14de**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, J = 2.3 Hz, 1 H, 4′-H), 7.78 (dd, J = 8.7, 2.3 Hz, 1 H, 4-H), 7.40–7.27 (5 H, aryl), 7.00 (d, J = 8.8 Hz, 1 H, 3-H), 6.54 (d, J = 3.3 Hz, 1 H, 7-H/8-H), 6.40 (d, J = 3.3 Hz, 1 H, 8-H/7-H), 4.59 (s, 2 H, 11-H), 4.54 (s, 2 H, 10-H), 3.94 [s (br), 3 H, 17-H/1-H], 3.93 (br. s, 3 H, 1-H/17-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.4, 158.4, 153.2, 151.2, 137.9, 128.8, 128.4, 127.9, 127.7, 127.3, 123.5, 120.4, 112.4, 111.6, 104.9, 71.9, 63.9, 56.2, 52.1 ppm. IR (neat): $\tilde{\nu}$ = 129, 1488, 1454, 1535, 1312, 1273, 1229, 1182, 186, 1069, 1021, 820, 785, 737, 697, 603 cm^{-1}. LRMS (EI): m/z (%) = 59 (15), 77 (14), 91 (46), 115 (13), 172 (13), 245 (100), 246 (28), 352 (33) $[M]^+$. HRMS (EI): calcd. for $C_{21}H_{20}O_5$ $[M]^+$ 352.1311; found 352.1307. $C_{21}H_{20}O_5$ (352.38): C 71.6, H 5.7; found C 71.6, H 5.7.

Supporting Information (see footnote on the first page of this article): Experimental details for attempted dehydrogenation reactions with Shvo's catalyst including characterization data for the ring-cleavage products **18** and **19**, full analytical data for all furans **15** and **17**, numbering schemes for signal assignment and copies of ^{1}H and ^{13}C NMR spectra for all compounds.

Acknowledgments

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