Letter

Chemo-enzymatic Metathesis/Aromatization Cascades for the Synthesis of Furans: Disclosing the Aromatizing Activity of Laccase/TEMPO in Oxygen-containing Heterocycles

Caterina Risi, Fei Zhao, and Daniele Castagnolo

ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.9b02452 • Publication Date (Web): 05 Jul 2019

Chemo-Enzymatic Metathesis/Aromatization Cascades for the Synthesis of Furans: Disclosing the Aromatizing Activity of Laccase/TEMPO in Oxygen-Containing Heterocycles

Caterina Risi,‡ Fei Zhao‡ and Daniele Castagnolo*

School of Cancer and Pharmaceutical Sciences, King's College London, Franklin Wilkins Building, 150 Stamford Street, SE1 9NH London.

ABSTRACT: The unprecedented *Trametes versicolor* laccase/TEMPO catalyzed aromatization of 2,5-dihydrofurans to furans is described. A variety of furan derivatives have been synthesized in moderate to high conversions (21-99%) and yields (20-76%) under mild reaction conditions. This work reveals the aromatization ability of the *Trametes versicolor* laccase/TEMPO system in synthesizing oxygen-containing heterocycles. Moreover, the direct synthesis of furans from aliphatic diallyl ethers through a chemo-enzymatic metathesis/aromatization cascade which combines Grubbs' catalyzed ring-closing metathesis and laccase/TEMPO aromatization in the same reaction medium has been successfully developed.

KEYWORDS. Furan • Metathesis • Aromatization • Chemo-enzymatic cascade • Laccase • TEMPO

Furans are natural and synthetic five-membered heterocycles which find broad application in pharmaceutical, material and agrochemical industries.[1] As shown in Figure 1, the furan ring is a privileged scaffold in many pharmaceutical ingredients such as the best-selling drug Ranitidine **1**, the antiprotozoal agent Nifurtimox **2** and the muscle relaxant Dantrolene **3**. Flavouring agents such as the 2-furfurylthiol **4** and furfural **5,** which are responsible for the toasty smell of coffee or cooked meat, contain a furan nucleus as well.[2] Furans can be synthesised through different synthetic routes including the classical Paal-Knorr[3] and Feist-Bernary[4] reactions from 1,4-dicarbonyl compounds or the TFA mediated cyclization of β-keto-*tert*-butyl esters.[5] Other typical methods for furan synthesis include the metal-catalysed inter- or intra-molecular cyclization of alkynyl, allenyl or cyclopropyl ketones and alcohols under harsh reaction conditions,[6] and the aromatization of 2,5-dihydrofuran precursors[7] in the presence of stoichiometric ^{t}BuOOH[8], DDQ,[9] Shvo's catalyst[9] or TFA at high temperature.[10] Recently, a more sustainable method to synthesise furan derivatives by dehydration of renewable feedstock has also been described.[11] However, despite the remarkable achievements made in the last decades, no report on furan synthesis employing enzymes is known to date. This reflects the great challenge in developing enzymatic processes for the generation of furan compounds.

With the aim to develop alternative, greener and more sustainable methods for the synthesis of pharmaceutical and flavouring ingredients,[12-13] we started to explore novel biocatalytic and chemo-enzymatic approaches to generate aromatic heterocycles.[13] Biocatalysis represents a powerful and green technology for the synthesis of a wide variety of chiral molecules in enantiomerically pure form.[14] However, its use in the manufacturing of non-chiral flat heteroaromatic structures, which constitute the core of most drugs and pharmaceutical ingredients, has been poorly explored to date. Nevertheless, the synthesis of heteroaromatic compounds with enzymes offers a greener and more sustainable way as compared with chemical reagents. Within this context, we have recently demonstrated that enzymes can be successfully exploited in the synthesis of heteroaromatic molecules by replacing hazardous aromatizing reagents or oxidants, which are generally used in a stoichiometric amount at high temperature. We first disclosed the aromatizing properties of MAO-N biocatalysts in the synthesis of pyrroles **6** and pyridines **7**.[13] MAO-N enzymes are able to catalyse the aromatization of aliphatic precursors through the oxidation of their C-N bonds into imine/iminium intermediates followed by tautomerization. More recently, Turner's group described another chemo-enzymatic approach to pyrroles **9** and pyrazines **10** using transaminase (ATA) biocatalysts (Figure 1a).[15] However, due to the nature of the enzymes used, these methodologies are only limited to the synthesis of nitrogen-containing heterocycles and are not suitable for the synthesis of oxygen-containing heterocycles like furans.

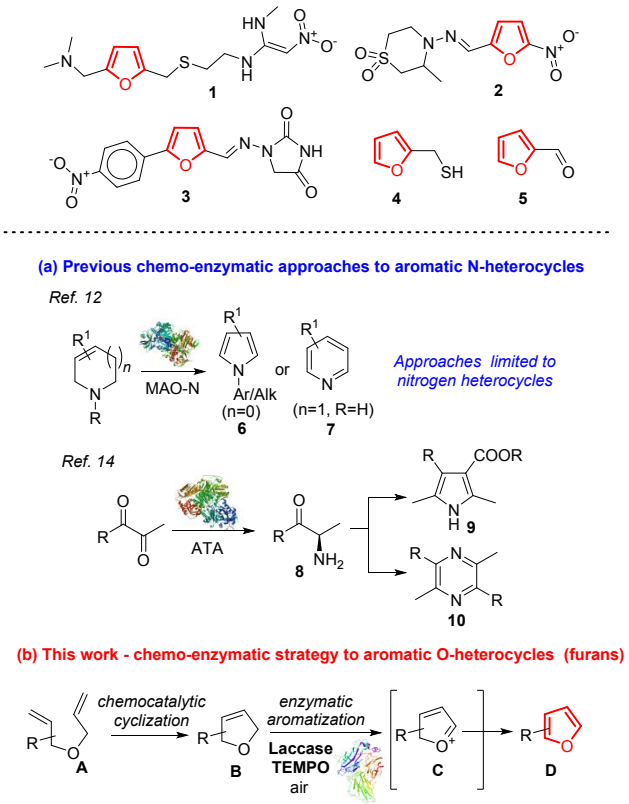
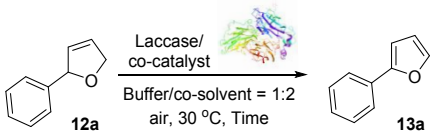


Figure 1. Representative drugs and flavouring agents with the furan motif. Previous works on chemo-enzymatic syntheses of nitrogen heterocycles and proposed chemo-enzymatic approach to furans.

Laccase enzymes are widely used in combination with O_2 or the oxy-radical TEMPO to catalyse the oxidation of alcohols to aldehydes or ketones.[16] Laccases can also promote the oxidative cleavage of ether bonds in lignine,[17] as well as the oxidation of nifedipine and tetrahydroquinazolines.[18]

Table 1. Aromatization of 2,5-dihdrofuran **12a** into furan **13a**. Screening and reaction optimization.

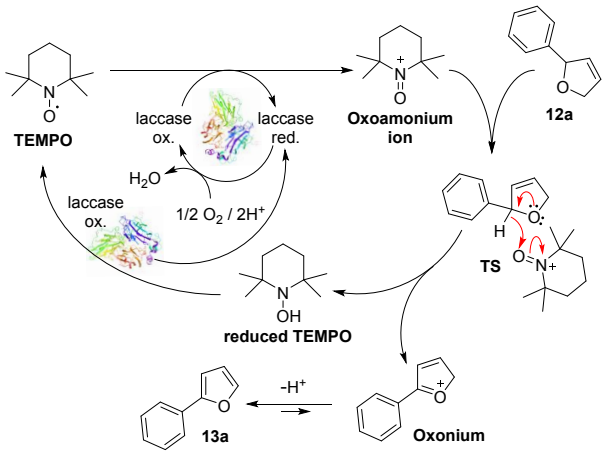


Entry	U Laccase[a]	Cocatalyst	Buffer[b]/ Cosolvent	Time (h)	Conv. (%)[c]
1	8.1	TEMPO (2 eq)	Acetate/ MTBE	24	>99
2	8.1	TEMPO (0.5 eq)	Acetate/ MTBE	24	>99
3	8.1	TEMPO (0.2 eq)	Acetate/ MTBE	24	40
4	8.1	TEMPO (0.2 eq)	Acetate/ MTBE	48	80
5	8.1	TEMPO (0.2 eq)	NaPBS/ MTBE	24	80
6	8.1	TEMPO (0.5 eq)	NaPBS/ MTBE	24	>99
7	8.1	TEMPO (0.2 eq)	NaPBS/ MTBE	30	>99[d]
8	7.5	TEMPO (0.2 eq)	NaPBS/ MTBE	36	>99[d], 68[e]
9	7.5	TEMPO (0.2 eq)	NaPBS/ isooctane	36	75
10	7.5	TEMPO (0.2 eq)	NaPBS/ CH_3CN	36	8
11	7.5	AZADO (0.2 eq)	NaPBS/ MTBE	24	8
12	7.5	AZADO (0.2 eq)	NaPBS/ MTBE	36	14
13	-	TEMPO (2 eq)	Acetate/ MTBE	24	<5
14	19	-	Acetate/ MTBE	48	0
15	-	-	Acetate/ MTBE	24	0

Reaction conditions: **12a** (13.7 μmol), Laccase/co-catalyst, buffer/co-solvent = 1:2 (420 μL), air, 30 °C, 24-48 h. [a] Units of laccase per 13.7 μmol **12a**. Commercially available *Trametes versicolor* laccase (0.94 U/mg of crude lyophilized enzyme powder). [b] Buffer acetate = HOAc/NaOAc (pH = 4.5, 0.05 M); Buffer NaPBS = Na_2HPO_4/NaH_2PO_4 (pH = 6.5, 0.05 M). [c] Calculated by ^{1}H-NMR integration. [d] Calculated by HPLC. [e] Isolated yield of **13a** when the reaction was scaled up to 0.35 mmol of **12a**; MTBE = *tert*-butyl methyl ether.

Inspired by these transformations, we envisaged that laccases could also catalyse the oxidation of the ether bond in 2,5-dihdrofuran substrates **B**, thus leading to the formation of the oxonium intermediates **C** which tautomerize to the aromatic furans **D**. In the present work, we describe a novel chemo-enzymatic aromatization strategy to furan heterocycles **D** from 2,5-dihdrofuran precursors **B** exploiting the laccase/TEMPO catalytic system (Figure 1b). To the best of our knowledge, this is the first example to date of aromatization reactions of oxygen heterocycles exploiting enzymes.

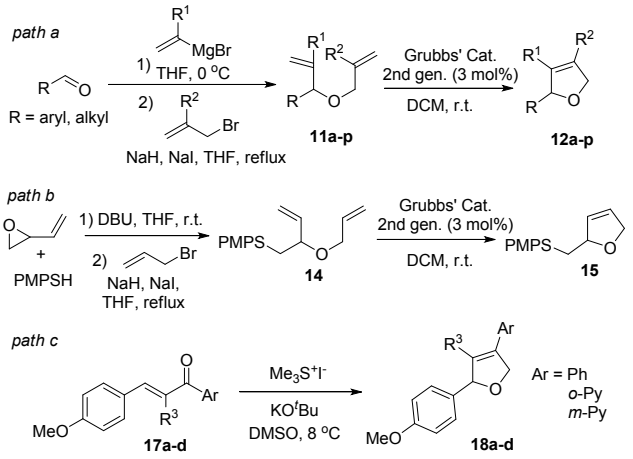
The aromatization of the 2,5-dihdrofuran **12a** (13.7 μmol) was first investigated (Table 1). Substrate **12a** was suspended in a 1:2 mixture of buffer acetate (pH = 4.5)[16] and *tert*-butyl methyl ether (MTBE) (total volume 420 μL) and then treated with the enzyme laccase (8.1 U) and an excess of TEMPO co-catalyst (2 eq) at 30 °C under air atmosphere. The aromatic furan **13a** was obtained with an excellent conversion (>99%) in 24 h (*entry 1*), clearly confirming the aromatization ability of laccase/TEMPO system. In order to make the biotransformation greener, the same reaction was carried out with 0.5 equivalent of TEMPO. To our delight, a full conversion was also observed in 24 h (*entry 2*). However, only an 80% conversion was observed, even after 48 h, when 0.2 equivalent of TEMPO was used (*entry 4*). A further optimization disclosed that changing the buffer solution proved to be beneficial. In fact, when NaPBS buffer solution (pH = 6.5) was used, substrate **12a** was completely converted into product **13a** in the presence of 0.2 equivalent of TEMPO after 30 h (*entry 7*). In addition, an attempt to reduce the loading of laccase to 7.5 U per 13.7 μmol **12a** turned out to be successful, even though a slightly longer time (36 h) was required to obtain a full conversion (*entry 8*). The replacement of MTBE with other co-solvents such as isooctane or CH_3CN (*entries 9-10*), and the use of the AZADO[19] co-catalyst instead of TEMPO (*entries 11-12*) adversely affected the enzymatic reaction, leading to lower conversions. Finally, in order to determine if the aromatization was truly catalysed by the laccase/TEMPO system rather than promoted by only one of them or by spontaneous air, a set of blank experiments, in which the enzyme or the co-catalyst was selectively removed from the reaction, were performed. As a result, no or negligible formation of the product **13a** was observed even in the presence of a higher loading of the single enzyme or co-catalyst (*entries 13 and 14*). Besides, when laccase and TEMPO were both removed from the reaction, the desired product was not detected at all (*entry 15*), indicating that the air itself cannot promote this transformation. These results clearly confirmed the crucial catalytic role of the laccase/TEMPO system in the aromatization of **12a**.



Scheme 1. Proposed mechanism for the laccase/TEMPO aromatization of 2,5-dihydrofuran **12a** into furan **13a**.

A plausible mechanism for the enzymatic aromatization of 2,5-dihydrofuran **12a** is proposed in Scheme 1. The TEMPO is oxidised into the oxoamonium ion intermediate by laccase, which can be regenerated by atmospheric O_2. The oxoamonium ion can react with the 2,5-dihydrofuran **12a** to form a 5-membered transition state **TS** in which a hydrogen transfer occurs to generate the reduced TEMPO and an oxonium ion. The latter is converted into the desired product **13a** by deprotonation. Finally, the reduced TEMPO can be oxidised into TEMPO by the laccase enzyme.

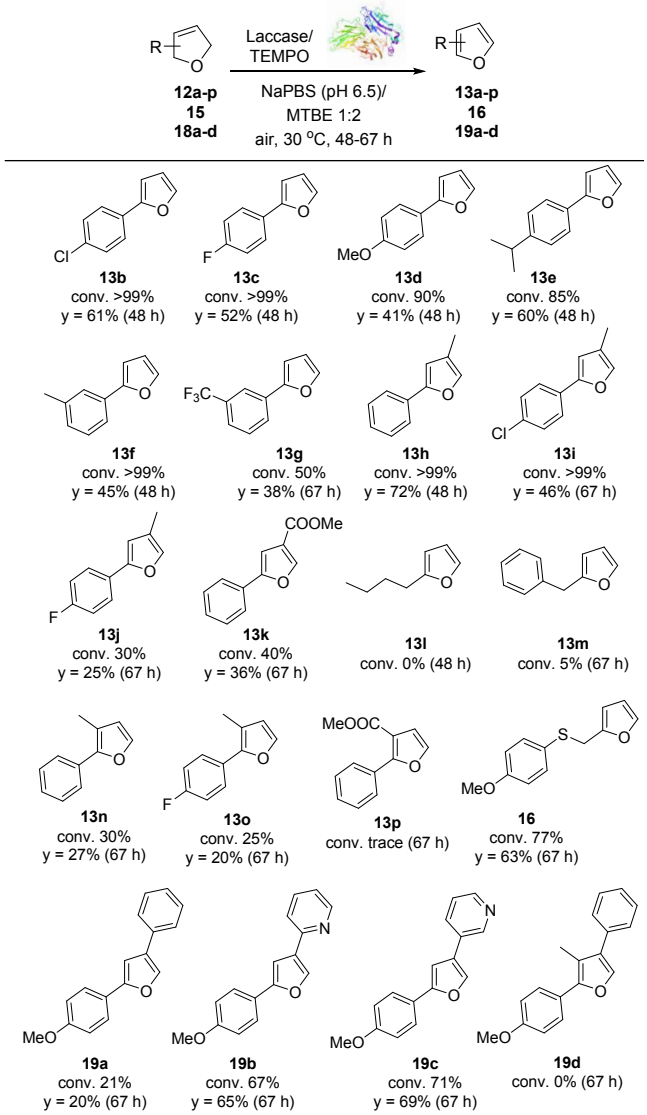
Once the reaction conditions were optimised, we began to explore the substrate scope of the chemo-enzymatic transformation. At first, a set of substituted 2,5-dihydrofuran substrates were synthesised. As illustrated in Scheme 2, precursors **12a-p** and **15** were synthesised via ring-closing metathesis (RCM) reactions from appropriate diallyl ethers **11a-p** and **14,** respectively. Ethers **11a-o** were obtained from appropriate aldehydes through Grignard reaction with vinyl magnesium bromide followed by alkylation with an appropriate allyl bromide. Ether **11p** was obtained through a slightly different approach as described in the literature[19]. The furan **15** was synthesised from 2-vinyloxirane through ring opening by thiol, alkylation of the resulting alcohol and the final RCM. Attempts to prepare **18a-d** through the RCM (path a) proved to be unsuccessful.[20] On the other hand, chalcones **17a-d**, which are readily available from appropriate aldehydes and ketones, were promptly converted into **18a-d** in good yields using $Me_3S^+I^-$ in the presence of KO^{t}Bu.[21]



Scheme 2. Synthesis of 2,5-dihydrofuran precursors **12a-p**, **15** and **18a-d**.

All the 2,5-dihydrofurans **12a-p** were then subjected to the laccase/TEMPO catalytic system as shown in Table 2. Generally, good to excellent conversions (up to 99%) and isolated yields (up to 72%) were observed for most of the substrates **12**.[22] For instance, substrates **12b-g** bearing diverse phenyl groups at the C2 position were converted into the corresponding products **13b-g** in good to high conversions (50-99%) and good yields (38-61%). The aromatization of 2-aryl-5-methyl substituted substrates **12h-i** also took place smoothly, providing the desired products **13h-i** in full conversions and good yields (46-72%). Lower conversions (30-40%) and yields (25-36%) were observed with the fluorinated derivative **12j** as well as furan **12k** bearing an ester moiety. This may be attributed to the electron withdrawing effects of the substituents. The 2-alkyl substituted substrates **12l-m** were fully consumed within 48-67 h when treated with laccase/TEMPO, but no desired furans **13l-m** were detected and only degradation products were observed by ^{1}H NMR. It has been recently reported that some 2,5-dialkylsubstituted furans can be deconstructed into diketones by the laccase/TEMPO system in the presence of atmospheric oxygen.[23] Even if the mechanism for this transformation is not fully clear, the presence of an alkyl substituent at both position C2 and C5 of the furan ring seems to be essential. We thus hypothesised that furans **13l-m** could have been formed during the aromatization reaction, but then immediately degraded by the same catalytic system into volatile side-products.[23b] The 2,3-disubstituted substrates **12n-p** proved to be more resistant to the oxidation, affording desired furans **13n-p** in lower conversions and yields. Finally, the 2,5-dihydrofurans **15** and **18a-c** were aromatized into the corresponding furans **16** and **19a-c** in moderate to good yields (20-69%), respectively, while no conversion was observed for the bulkier 2,3,4-trisubstituted substrate **18d**.

Table 2. Laccase/TEMPO aromatization of 2,5-dihyrofurans[a]



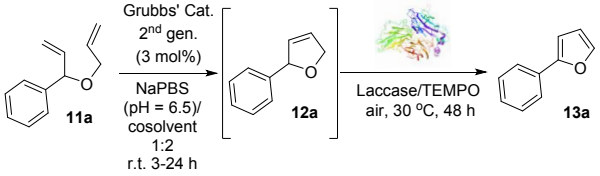
Reaction conditions: substrates **12a-m**, **15**, **18a-d** (0.14 mmol), laccase (75 U of 0.94 U/mg *T. versicolor* laccase lyophilized powder), TEMPO (0.028 mmol), NaPBS/MTBE = 1:2 (4.2 mL), air, 30 °C, 48-67 h. [a] Conversions were calculated by ^{1}H-NMR integration, "y" refers to isolated yield.

With the aim to develop a more straightforward methodology avoiding multi-step synthesis and purification, the possibility to access furans **13** directly from diallyl ethers **11** through a chemo-enzymatic cascade reaction was then investigated. A one-pot two-step cascade reaction was initially set up (Table 3, *entry 1*). Ether **11a** was dissolved in a 1:2 mixture of NaPBS buffer and MTBE and then treated with 3 mol% of Grubbs' catalyst. After 24 h, the laccase/TEMPO catalytic system was added to the metathesis reaction mixture. This led to the formation of furan **13a** with a disappointing conversion (14%). Even if Grubbs' catalyst tolerates a variety of solvents including MTBE and water, the reaction rates and yields of RCM reactions can be affected by different reaction media.[24] In fact, when the RCM cyclization of **11a** was carried out

in NaPBS/MTBE (1:2), the 2,5-dihydrofuran intermediate **12a** was obtained with only 60% conversion after 24 h, while a full conversion (98%) was observed when isooctane was used as the co-solvent under the same conditions (*entries 2-3*). Moreover, the co-existence of Grubbs' catalyst and enzymes in chemo-enzymatic cascade reactions may be problematic because of the mutual inactivation of the enzymes and the ruthenium carbene, thus leading to a significant decrease in the reaction yield. However, as previously demonstrated, the use of biphasic systems with low mass transfer, which contains isooctane as the co-solvent, can prevent the Grubbs'-enzyme deactivation in chemo-enzymatic transformations.[25,13] Therefore, a one-pot two-step metathesis/aromatization cascade of **11a** was carried out in NaPBS/isooctane (1:2) media. This afforded furan **13a** with an 81% conversion (*entry 5*). It is noteworthy that it is preferable to add the laccase/TEMPO catalyst as soon as the RCM reaction was completed after 3 h, since a longer reaction time resulted in lower conversion (*entry 4*), probably due to the formation of side products.

Once the best reaction media was identified, the combination of the RCM reaction and the enzymatic aromatization in a one-pot cascade was attempted (Table 4). Ether **11a** was suspended in a 1:2 NaPBS/isooctane mixture and simultaneously treated with Grubbs' catalyst (3 mol%) and laccase/TEMPO, leading to furan **13a** with 56% conversion after 24 h (*entry 1*). Increasing the reaction time up to 65 h proved to be beneficial, providing a remarkable improvement in the conversion **(**93%) and yield (62%) of **13a** (*entry 3*). The chemo-enzymatic cascade was then extended to other ether substrates **11b-j**, which were all converted into the corresponding furans **13b-j** in moderate to good yields (*entries 4-9*).

Table 3. Reaction optimization of the one-pot two-step chemo-enzymatic cascade.

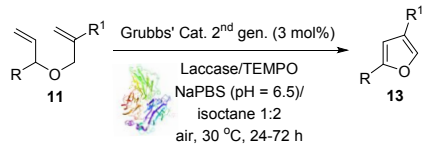


Entry	Cosolvent	Time (h)	Conv. **12a**[a] (%)	Conv. **13a**[a] (%)
1	MTBE	24+48	n.d.[c]	14
2[b]	MTBE	24	60[d]	-
3[b]	isooctane	5	98	-
4	isooctane	16+48	n.d.[c]	71
5	isooctane	3+48	n.d.[c]	81

Reaction conditions: compound **11a** (0.08 mmol), Grubbs' catalyst (0.0024 mmol, 3 mol%), NaPBS (pH = 6.5)/cosolvent = 1/2 (2 mL), room temperature, 3-24 h, then laccase (67 U), TEMPO (0.016 mmol), air, 30 °C, 48 h. [a] Conversion was calculated by ^{1}H-NMR integration or HPLC. [b] The reaction was stopped after the RCM reaction was completed (monitored by TLC). [c] Not determined. [d] When the same reaction was carried out in 100% DCM medium, a >95% conversion (67% yield) was observed by ^{1}H NMR after 24 h.

In summary, a novel green and enzymatic methodology for the aromatization of 2,5-dihydrofurans into furans exploiting the laccase/TEMPO system under mild and aqueous conditions has been developed.

Table 4. One-pot chemo-enzymatic cascade for the synthesis of furans **13** from diallyl ethers **11**.



Entry	Ether substrate	Time (h)	Furan	Conv. (%)[a]	Yield (%)[b]
1		24		56	31
2	**11a**	48	**13a**	74	-[c]
3		65		93	62
4	**11b**	65	**13b**	36	-[c]
5	**11c**	65	**13c**	55	28
6	**11d**	72	**13d**	92	76
7	**11f**	72	**13f**	68	36
8	**11h**	72	**13h**	82	52
9	**11j**	72	**13j**	61	40

Reaction conditions: substrates **11** (0.08 mmol), Grubbs' catalyst (0.0024, 3 mol%), laccase (67 U), TEMPO (0.016 mmol), NaPBS (pH = 6.5)/isooctane = 1/2 (2 mL), air, 30 °C, 24-72 h. [a] Conversion was calculated by ^{1}H-NMR integration. [b] Isolated yields are reported. [c] Not calculated

The approach described in this work reveals the previously undisclosed aromatization ability of laccase/TEMPO in synthesising oxygen-containing heterocycles like furans. In general, 2-aryl substituted dihydrofurans were aromatized with good to excellent conversions and moderate to good isolated yields, while 2-alkyl-substituted and 2,3,4-trisubstituted substrates proved to be less reactive. The low yields observed in some cases could be ascribable to the volatility of the furan products as well as instability of the laccase in the reaction system.[26] Finally, a chemo-enzymatic cascade reaction to furan derivatives directly from diallyl ethers has also been developed through the combination of Grubbs' catalyst and laccase/TEMPO in the same reaction medium, affording a variety of furan derivatives with good conversions and yields. This work represents the first example of a chemo-enzymatic synthesis of aromatic oxygen heterocycles like furans and a robust, alternative and sustainable method for the industrial synthesis of furans.

AUTHOR INFORMATION

Corresponding Author

*daniele.castagnolo@kcl.ac.uk

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡Co-first authors; these authors contributed equally.

Funding Sources

EPSRC King's College Strategic Fund. K.C. Wong Education Foundation.

ASSOCIATED CONTENT

Experimental details, procedures and copies of spectra are reported in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

ACKNOWLEDGMENT

EPSRC KCL Strategic Fund is acknowledged for funding. CR acknowledges the University of Siena for a PhD period of leave. FZ and DC acknowledge K.C. Wong Education Foundation for financial support. Dr Francesca Mazzacuva at Mass Spectrometry Facility at King's College London is gratefully acknowledged for HRMS experiments.

REFERENCES

1) a) Lukevits, É.; Demicheva, L. Biological Activity of Furan Derivatives (Review). *Chem. Heter. Comp.* **1993**, *29*, 243–267; b) Gubina, T. I.; Kharchenko, V. G. Furan and its Derivatives in the Synthesis of Other Heterocycles (Review). *Chem. Heter. Comp.* **1995**, *31*, 900–916; c) Maier, M. Furan as a Building Block in Synthesis. In *Organic Synthesis Highlights II* (ed. H. Waldmann), VCH Verlagsgesellschaft mbH, Weinheim, **2008**, 231-242. d) Keay, B. A.; Dibble, P. W. Furans and their Benzo Derivatives: Applications. In *Comprehensive Heterocyclic Chemistry II, Vol. 2* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Elsevier, Oxford, **1997**, 395–436; e) Hou, X. L.; Yang, Z.; Wong, H. N. C. Five-Membered Ring Systems: Furans and Benzofurans. In *Progress in Heterocyclic Chemistry, Vol. 15* (Eds.: G. W. Gribble, T. L. Gilchrist) Pergamon, Oxford, **2003**, 167-205; f) Lipshutz, B. H. Five-Membered Heteroaromatic Rings as Intermediates in Organic Synthesis. *Chem. Rev.* **1986**, 86, 795–819.

2) a) Blanchard, L.; Tominaga, T.; Dubourdieu, D. Formation of Furfurylthiol Exhibiting a Strong Coffee Aroma During Oak Barrel Fermentation from Furfural Released by Toasted Staves. *J. Agric. Food Chem.* **2001**, *49*, 4833–4835; b) Schoenauer, S.; Schieberle, P. Structure-Odor Correlations in Homologous Series of Mercapto Furans and Mercapto Thiophenes Synthesized by Changing the Structural Motifs of the Key Coffee Odorant Furan-2-ylmethanethiol. *J. Agric. Food Chem.* **2018**, *66*, 4189–4199.

3) Khaghaninejad, S.; Heravi, M. M. Paal–Knorr Reaction in the Synthesis of Heterocyclic Compounds. In *Advances in Heterocyclic Chemistry, Vol. 111* (Eds.: A. R. Katritzky) Elsevier Academic Press Inc.: San Diego, **2014**, 95−146.

4) Feist, F. Studien in der Furan-und Pyrrol-Gruppe. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1537.

5) Stauffer, F.; Neier, R. Synthesis of Tri- and Tetrasubstituted Furans Catalyzed by Trifluoroacetic Acid. *Org. Lett.* **2000**, *2*, 3535–3537.

6) a) Hou, X. L.; Cheung, H. Y.; Hon, T. Y.; Kwan, P. L.; Lo, T. H.; Tong, S. Y.; Wong, H. N. C. Regioselective Syntheses of Substituted Furans. *Tetrahedron*, **1998**, *54*, 1955–2020; b) Duan, X.; Liu, X.; Guo, L.; Liao, M.; Liu, W.; Liang, Y. Palladium-Catalyzed One-Pot Synthesis of Highly Substituted Furans by a Three-Component Annulation Reaction. *J. Org. Chem.* **2005**, *70*, 6980–6983; c) Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. Cross-Coupling of Heteroarenes by C-H Functionalization: Recent Progress Towards Direct Arylation and Heteroarylation Reactions Involving Heteroarenes Containing One Heteroatom. *Adv. Synth. Catal.* **2014**, *356*, 17–117; d) Mei, S.-T.; Liang, H.-W.; Teng, B.; Wang, N.-J.; Shuai, L.; Yuan, Y.; Chen, Y.-C.; Wei, Y. Spirocyclic Sultam and Heterobiaryl Synthesis Through Rh-Catalyzed Cross-Dehydrogenative Coupling of N-Sulfonyl Ketimines and Thiophenes or Furans. *Org. Lett.* **2016**, *18*, 1088–1091; e) Dey, A.; Ali, M. A.; Jana, S.; Hajra, A. Copper-Catalyzed Regioselective Synthesis of Multisubstituted Furans By Coupling Between Ketones and Aromatic Olefins. *J. Org Chem.* **2017**, *82*, 4812–4818; f) Brown, R. C. D. Developments in Furan Syntheses. *Angew. Chem., Int. Ed.* **2005**, *44*, 850–852; g) Pridmore, S. J.; Slatford, P. A.; Taylor, J. E.; Whittlesey, M. K.; Williams, J. M. J. Synthesis of Furans, Pyrroles and Pyridazines by a Ruthenium-Catalysed Isomerisation of Alkynediols and In Situ Cyclisation. *Tetrahedron* **2009**, *65*, 8981–8986; h) Feng, X.; Tan, Z.; Chen, D.; Shen, Y.; Guo, C.-G.; Zhu, J. X. C. Synthesis of Tetrasubstituted Furans via In-Catalyzed Propargylation of 1,3-Dicarbonyl Compounds-Cyclization Tandem Process. *Tetrahedron Lett.* **2008**, *49*, 4110–4112.

7) Donohoe, T. J.; Bower, J. F.; Basutto, J. A. Olefin Cross-Metathesis–Based Approaches to Furans: Procedures for the Preparation of Di- And Trisubstituted Variants. *Nature Protoc.* **2010**, *5*, 2005–2010.

8) Schmidt, B.; Krehl, S.; Jablowski, E. Assisted Tandem Catalytic RCM-Aromatization in the Synthesis of Pyrroles and Furans. *Org. Biomol. Chem.* **2012**, *10*, 5119–5130.

9) Schmidt, B.; Geißler, D. Ru-and Pd-Catalysed Synthesis of 2-Arylfurans by One-Flask Heck Arylation/Oxidation. *Eur. J. Org. Chem.* **2011**, 4814 – 4822.

10) Donohoe, T. J.; Orr, A. J.; Gosby, K.; Bingham, M. A Metathesis Approach to Aromatic Heterocycles. *Eur. J. Org. Chem.* **2005**, 1969–1971.

11) 11) a) Jeong, G-Y.; Singh, A. K.; Sharma, S.; Kim, D. One-Flow Syntheses of Diverse Heterocyclic Furan Chemicals Directly from Fructose via Tandem Transformation Platform. *NPG Asia Materials* **2015**, *7*, e173; b) Agirrezabal-Telleria, I.; Guo, Y.; Hemmann, F.; Arias, P. L.; Kemnitz, E. Dehydration of Xylose and Glucose to Furan Derivatives Using Bifunctional Partially Hydroxylated MgF_2 Catalysts and N_2-Stripping. *Catal. Sci. Technol.* **2014**, *4*, 1357-1368. c) Liu, B.; Gou, Z.; Liu, A.; Zhang, Z. Synthesis of Furan Compounds from HMF and Fructose Catalyzed by Aluminum-Exchanged K-10 Clay. *J. Ind. Eng. Chem.* **2015**, *21*, 338-339.

12) Lauder, K.; Toscani, A.; Qi, Y.; Lim, J.; Charnock, S. J.; Korah, K.; Castagnolo, D. Photo-Biocatalytic One-Pot Cascades for the Enantioselective Synthesis of 1,3-Mercaptoalkanol Volatile Sulfur Compounds. *Angew. Chem., Int. Ed.* **2018**, *57*, 5803-5807.

13) a) Toscani, A.; Risi, C.; Black, G. W.; Brown, N. L.; Shaaban, A.; Turner, N. J.; Castagnolo, D. Monoamine oxidase (MAO-N) Whole Cell Biocatalyzed Aromatization of 1,2,5,6-Tetrahydropyridines into Pyridines. *ACS Catal.* **2018**, *8*, 8781-8787; b) Scalacci, N.; Black, G. W.; Mattedi, G.; Brown, N. L.; Turner, N. J.; Castagnolo, D. Unveiling the Biocatalytic Aromatizing Activity of Monoamine Oxidases MAO-N and 6-HDNO: Development of Chemoenzymatic Cascades for the Synthesis of Pyrroles. *ACS Catal.* **2017**, *7*, 1295-1300.

14) a) Sheldon, R. A.; Woodley, J. M. Role of Biocatalysis in Sustainable Chemistry. *Chem. Rev.* **2018**, *118*, 801–838; b) Albarrán-Velo, J.; González-Martínez, D.; Gotor-Fernández, V. Stereoselective Biocatalysis: A Mature Technology for the Asymmetric Synthesis of Pharmaceutical Building Blocks. *Biocat. Biotrans.* **2018**, *36*, 102-130.

15) Xu, J.; Green, A. P.; Turner, N. J. Chemo-Enzymatic Synthesis of Pyrazines and Pyrroles. *Angew. Chem., Int. Ed.* **2018**, *57*, 16760-16763.

16) a) Riva, S. Laccases: Blue Enzymes for Green Chemistry. *Trends Biotechnol.* **2006**, *24*, 219–226; b) Coutoand, S. R.; Herrera, J. L. T. Industrial and Biotechnological Applications of Laccases: A Review. *Biotechnol. Adv.* **2006**, *24*, 500–513; c) Witayakran, S.; Ragauskas, A. J. Synthetic Applications of Laccase in Green Chemistry. *Adv. Synth. Catal.* **2009**, *351*, 1187–1209; d) Kudanga, T.; Nyanhongo, G. S.; Guebitz, G. M.; Burton, S. Potential Applications of Laccase-Mediated Coupling and Grafting Reactions: A Review. *Enzyme Microb. Technol.* **2011**, *48*, 195–208; e) Díaz-Rodríguez, A.; Lavandera, I.; Kanbak-Aksu, S.; Sheldon, R. A.; Gotor, V.; Gotor-Fernández, V. From Diols to Lactones Under Aerobic Conditions Using a

Laccase/TEMPO Catalytic System in Aqueous Medium. *Adv. Synth. Catal.* **2012**, *354*, 3405–3408; f) Kedziora, K.; Díaz-Rodríguez, A.; Lavandera, I.; Gotor-Fernández, V.; Gotor, V. Laccase/TEMPO-Mediated System for the Thermodynamically Disfavored Oxidation of 2,2-Dihalo-1-Phenylethanol Derivatives. *Green Chem*. **2014**, *16*, 2448-2453; g) Tromp, S.A.; Matijošytė, I.; Sheldon, R.A.; Arends, I.W.C.E.; Mul, G.; Kreutzer, M.T.; Moulijn, J.A.; de Vries, S. Mechanism of Laccase–TEMPO-Catalyzed Oxidation of Benzyl Alcohol. *ChemCatChem* **2010**, *2*, 827-833.

17) a) Kawai, S.; Nakagawa, M.; Ohashi, H. Degradation Mechanisms of a Nonphenolic β-O-4 Lignin Model Dimer by *Trametes Versicolor* Laccase in the Presence of 1-Hydroxybenzotriazole. *Enzyme Microb. Technol.* **2002**, *30*, 482–489; b) Christopher, L. P.; Yao, B.; Ji, Y. Lignin Biodegradation with Laccase-Mediator Systems. *Front. Energy Res.* **2014**, *2*, 1-13.

18) a) Wells, A.; Teria, M.; Eve, T. Green Oxidations with Laccase–Mediator Systems. *Biochem. Soc. Trans.* **2006**, *34*, 304–308; b) Saadati, S.; Ghorashi, N.; Rostami, A.; Kobarfard, F. Laccasebased Oxidative Catalytic Systems for The Aerobic Aromatization of Tetrahydroquinazolines And Related N-Heterocyclic Compounds Under Mild Conditions. *Eur. J. Org. Chem.* **2018**, 4050-4057.

19) Kim, J. K.; Lee, K. Y.; Lee, S.; Kim, J. N. Ring-Closing Metathesis Toward the Synthesis of 2,5-Dihydrofuran and 2,5-Dihydropyrrole Skeletons from Baylis–Hillman Adducts *Tetrahedron Lett.* **2004**, *45,* 2805-2808.

20) Attempts to alkylate allyl alcohols generated via Grignard reaction with 2-aryl-allyl bromides were unsuccessful and the starting alcohols were recovered from the reaction mixture.

21) Zhu, C.; Zhang, Z.; Ding, W.; Xie, J.; Chen, Y.; Wu, J.; Chen, X.; Ying, H. A Mild and Highly Efficient Laccase-Mediator System for Aerobic Oxidation of Alcohols. *Green Chem.* **2014**, *16*, 1131-1138.

22) The low isolated yields observed in some cases can be ascribable to the volatility of the furan compounds which can be partially lost during the purification process and vacuum drying.

23) a) Asta, C.; Conrad, J.; Mika, S.; Beifuss, U. Laccase-Catalyzed Stereoselective Oxidative Ring Opening of 2,5-Dialkylfurans into 2-Ene-1,4-diones Using Air as an Oxidant. *Green Chem.* **2011**, *13*, 3066-3069; b) Furans **13l-m** are probably converted by laccase/TEMPO into α,β-unsaturated aldehydes which could be further decomposed into volatile derivatives.

24) a) Adjiman, C. S.; Clarke, A. J.; Cooper, G.; Taylor, P.C. Solvents for Ring-Closing Metathesis Reactions. *Chem. Commun.* **2008**, 2806-2808; b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. Mechanism and Activity of Ruthenium Olefin Metathesis Catalysts. *J. Am. Chem. Soc.* **2001**, *123*, 6543-6554.

25) a) Denard, C. A.; Bartlett, M. J.; Wang, Y.; Lu, L.; Hartwig, J. F.; Zhao, H. Development of a One-Pot Tandem Reaction Combining Ruthenium-Catalyzed Alkene Metathesis and Enantioselective Enzymatic Oxidation to Produce Aryl Epoxides. *ACS Catal.* **2015**, *5*, 3817−3822; b) Denard, C. A.; Huang, H.; Bartlett, M. J.; Lu, L.; Tan, Y.; Zhao, H.; Hartwig, J. F. Cooperative Tandem Catalysis by an Organometallic Complex and a Metalloenzyme. *Angew. Chem., Int. Ed.* **2014**, *53*, 465−469.

26) a) Rodakiewicz-Nowak, J.; Kasture, S.M.; Dudek, B; Haber, J. Effect of Various Organic Solvents on Enzymatic Activity of Fungal Laccases. *J. Mol. Catal. B Enzym*. **2000** *11*, 1-11. b) Wan, Y.Y.; Lu, R.; Xiao, L.; Du, Y.M.; Miyakoshi, T.; Chen, C.L.; Knill, C.J.; Kennedy, J.F. Effects of Organic Solvents on the Activity of Free and Immobilised Laccase from Rhus Vernicifera. *Int. J. Biol. Macromol.* **2010**, *47*, 488-95.

SYNOPSIS TOC.