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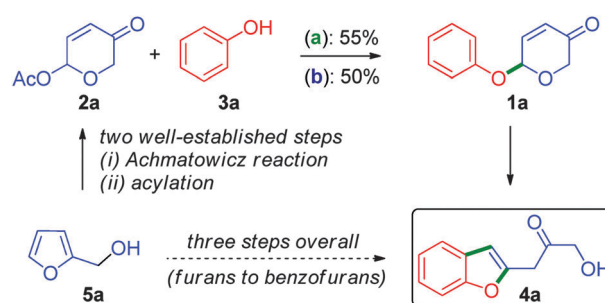
# Synthesis of benzofurans *via* an acid catalysed transacetalisation/Fries-type O → C rearrangement/Michael addition/ring-opening aromatisation cascade of β-pyrones†

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An unusual and facile approach for the synthesis of 2-benzofuranyl-3-hydroxyacetones from 6-acetoxy-β-pyrones and phenols is presented. The synthetic sequence involves a cascade transacetalisation, Fries-type O → C rearrangement followed by Michael addition and ring-opening aromatisation. The versatility of this method was further demonstrated *via* the synthesis of 4,4a-dihydropyrano[3,2-*b*]benzofuran-3-ones, furo[3,2-*c*]coumarins, and spiro[benzofuran-2,2'-furan]-4'-ones. The unexpected cascade event would also provide new possible considerations in the β-pyrone-involved organic synthesis.

Benzofurans are ubiquitous building blocks in many bioactive natural products and primary structural motifs in several pharmaceuticals and molecular electronics.<sup>1</sup> Furthermore, benzofurans are acclaimed privileged scaffolds in drug discovery.<sup>2</sup> These distinguished features stimulated the development of several efficient and concise strategies for the synthesis of diverse benzofuran derivatives.<sup>3</sup> However, owing to the limitations of the conventional approaches, such as the harsh reaction conditions, broad substrate scope and limited functional-group tolerability, there still exists ample scope for exploring new approaches for the synthesis of benzofurans. Herein, we report a new access to benzofurans *via* a Lewis acid catalysed one-pot cascade process.

Development of novel cascade processes has received great attention owing to their exceptional ability to rapidly assemble intricate molecular scaffolds.<sup>4</sup> As part of our recent efforts to develop new cascade approaches for the O,S-containing heterocycles, it necessitated us to have rapid and efficient access to 6-aryloxy-β-pyrones of the type **1a**.<sup>5</sup> For this purpose, the Lewis acid catalysed protocols of Gryniewicz<sup>6a</sup> and Feringa<sup>6b</sup> were tried with 6-acetoxy-β-pyrone **2a** and phenol **3a**, but the required



(a) Gryniewicz conditions: SnCl<sub>4</sub>, 1,2-dichloroethane, 0–5 °C, 10 min  
(b) Feringa conditions: BF<sub>3</sub>OEt<sub>2</sub>, 1,2-dichloroethane, 0–5 °C, 5 min

**Scheme 1** Unprecedented cascade reaction of 6-acetoxy-β-pyrones and phenols leading to the synthesis of 1-(2-benzofuranyl)-3-hydroxyacetones.

product **1a** was isolated in low yields, Scheme 1.<sup>7</sup> A detailed investigation revealed that the formation of a polar compound (on TLC) was responsible for the yield loss. Further study of the reaction under Feringa's conditions revealed that the concentration of the initially formed phenyl ether **1a** started diminishing and simultaneous build-up of the unanticipated product **4a** was observed. Thus, we have drawn the conclusion at this stage that the unexpected product **4a** formed *via* the intermediacy of **1a**. The structure of the unexpected product **4a** was deduced from <sup>1</sup>H and <sup>13</sup>C NMR data and was further confirmed by single-crystal X-ray diffraction analysis (*vide infra*).<sup>8</sup> Since the 6-acetoxy-β-pyrone **2a** can be accessed from furyl carbinol **5a** in two straightforward steps,<sup>5</sup> this protocol thus represents an unique three-step conversion of furans (of the type **5a**) to benzofurans (such as **4a**), Scheme 1.<sup>9</sup>

Having realised the significance of benzofurans especially generated under mild Lewis acidic conditions from readily accessible starting compounds, and considering the potential implications of this rearrangement in organic synthesis, we turned to optimising the reaction conditions. Towards this, various Lewis acid and solvent combinations were investigated, and few important results are shown in Table 1.

The reaction catalysed by La(OTf)<sub>3</sub> generated exclusively the 6-phenoxy-β-pyrone **1a** even after extended reaction times,

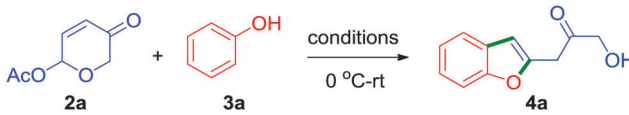
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Table 1 Optimisation of the reaction parameters<sup>a</sup>


Entry	Acid (10 mol %)	Solvent	Time (h)	Yield <sup>b</sup> (%)
1	La(OTf) <sub>3</sub>	DCE	48	74 <sup>c</sup>
2	SnCl <sub>4</sub>	DCE	3	50
3	BF <sub>3</sub> OEt <sub>2</sub>	DCE	18	55
4	FeCl <sub>3</sub>	DCE	18	45
5	In(OTf) <sub>3</sub>	DCE	20	48
6	Zn(OTf) <sub>3</sub>	DCE	20	45
7	Bi(OTf) <sub>3</sub>	DCE	20	61
8	AgOTf	DCE	21	40
9	<b>TMSOTf</b>	<b>DCE</b>	<b>20</b>	<b>74</b>
10 <sup>d</sup>	TMSOTf	DCE	20	47
11 <sup>e,f</sup>	TMSOTf	DCE	30	45
12 <sup>g</sup>	TMSOTf	DCE	72	—
13	TfOH	DCE	20	63
14	PTSA	DCE	20	51
15	TMSOTf	CH <sub>3</sub> CN	21	48
16	TMSOTf	Toluene	72	25
17	TMSOTf	THF	72	—

<sup>a</sup> A 5 mL glass vial was filled with **2a** (0.2 mmol), **3a** (0.22 mmol), and a solvent (1 mL). A catalyst (0.02 mmol) was then added at 0–5 °C. After stirring at the same temperature for about 30 min, the reaction continued at room temperature until **1a** and **2a** disappeared (by TLC).

<sup>b</sup> Isolated yield after column chromatography. <sup>c</sup> **1a** exclusively formed.

<sup>d</sup> 20 mol% TMSOTf was employed. <sup>e</sup> 5 mol% TMSOTf was employed.

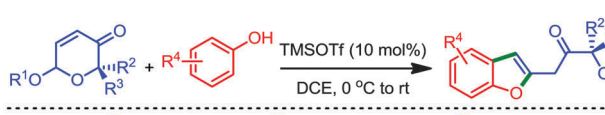
<sup>f</sup> **1a** and **2a** were also recovered. <sup>g</sup> In the presence of 2,6-di-*tert*-butyl-4-methylpyridine (1 equiv.).

thereby establishing a high-yielding method for its selective synthesis (Table 1, entry 1). Most of the Lewis acids employed during the screening otherwise furnished the desired product **4a** in varied yields, with TMSOTf giving the best result (entries 2–9). Reaction with higher TMSOTf loading (20 mol%) gave a poor result due to the formation of undesired side products (entry 10). On the other hand, reaction in the presence of 5 mol% TMSOTf was found to be sluggish (entry 11). So, 10 mol% TMSOTf loading was realised to be optimal for this transformation.

Interestingly, the reaction in the presence of a proton sponge such as 2,6-di-*tert*-butyl-4-methylpyridine completely inhibited the product formation, indicating most likely that catalytic amounts of TfOH generated *in situ* might be promoting this process (entry 12). However, despite repeated attempts, TfOH furnished the required product in lower yields when compared to TMSOTf (entry 13). Among few other Brønsted acids employed, PTSA generated **4a** in satisfactory yield (entry 14). So, TMSOTf was identified as the catalyst of choice for this study considering its mild nature and ease of handling. Brief solvent screening with TMSOTf offered no further improvement in the yield (Table 1, entries 15–17).

With the optimised reaction conditions in hand, the scope of the reaction was subsequently investigated, and the representative results are presented in Table 2. Since the 6-benzoyloxy-β-pyrones (**2b** and **2g**) afforded the respective products (**4b**, **4d**, **4l**, and **4m**) consistently in low yields under the optimised conditions, acetates of β-pyrones were preferred over benzoates during this study.

A variety of 6-acetoxy-β-pyrones (**2c–2f**, **2h–2j**) and phenols (**3b–3e**) conveniently generated the respective benzofurans **4b–4x** in good to

Table 2 Substrate scope<sup>a,b</sup>


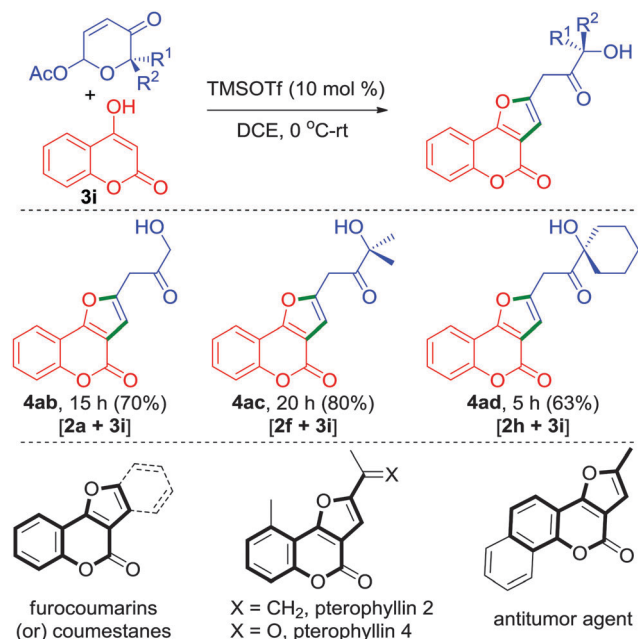
<b>2b</b> , R = Bz <b>2c</b> , R = <i>n</i> -Bu <b>2d</b> , R = Ph <b>2e</b> <b>2f</b> , R = Ac <b>2g</b> , R = Bz <b>2h</b> , n = 1 <b>2i</b> , n = 2 <b>2j</b>	<b>3b</b> , R = Me <b>3c</b> , R = Ph <b>3d</b> , R = OMe <b>3e</b> <b>3f</b> , X = F <b>3g</b> , X = Cl <b>3h</b> , X = Br	<b>4b</b> , R = Me, 2 h (85%) [ <b>2a</b> + <b>3b</b> ] <b>4b</b> , R = Me, 2 h (47%) [ <b>2b</b> + <b>3b</b> ] <b>4c</b> , R = Ph, 3 h (80%) [ <b>2a</b> + <b>3c</b> ] <b>4d</b> , R = OMe, 1.5 h (75%) [ <b>2a</b> + <b>3d</b> ] <b>4d</b> , R = OMe, 1 h (45%) [ <b>2b</b> + <b>3d</b> ] <b>4e</b> , R <sup>1</sup> = Me, R <sup>2</sup> = <i>n</i> -Bu, 6 h (78%) [ <b>2c</b> + <b>3b</b> ] <b>4f</b> , R <sup>1</sup> = Me, R <sup>2</sup> = Ph, 10 h (80%) [ <b>2d</b> + <b>3b</b> ] <b>4g</b> , R = H, 18 h (70%) [ <b>2f</b> + <b>3a</b> ] <b>4l</b> , R = Me, 2 h (74%) [ <b>2f</b> + <b>3b</b> ] <sup>c</sup> <b>4l</b> , R = Me, 1 h (40%) [ <b>2g</b> + <b>3b</b> ] <b>4m</b> , R = OMe, 2 h (70%) [ <b>2f</b> + <b>3d</b> ] <b>4m</b> , R = OMe, 1.5 h (32%) [ <b>2g</b> + <b>3d</b> ] <b>4n</b> , n = 1, R = H, 2 h (60%) [ <b>2h</b> + <b>3a</b> ] <b>4o</b> , n = 1, R = Me, 3 h (70%) [ <b>2h</b> + <b>3b</b> ] <b>4p</b> , n = 1, R = OMe, 2 h (66%) [ <b>2h</b> + <b>3d</b> ] <b>4q</b> , n = 2, R = Me, 5 h (75%) [ <b>2i</b> + <b>3b</b> ] <b>4r</b> , n = 2, R = OMe, 6 h (76%) [ <b>2i</b> + <b>3d</b> ] <b>4s</b> , R <sup>1</sup> = R <sup>2</sup> = H, 5 min (90%) [ <b>2a</b> + <b>3e</b> ] <b>4t</b> , R <sup>1</sup> = Me, R <sup>2</sup> = H, 2 h (90%) [ <b>2e</b> + <b>3e</b> ] <b>4u</b> , R <sup>1</sup> = R <sup>2</sup> = Me, 5 min (92%) [ <b>2f</b> + <b>3e</b> ] <b>4v</b> , R <sup>1</sup> = R <sup>2</sup> = Ph, 20 min (80%) [ <b>2j</b> + <b>3e</b> ] <b>4w</b> , n = 1, 7 min (90%) [ <b>2h</b> + <b>3e</b> ] <b>4x</b> , n = 2, 8 min (92%) [ <b>2i</b> + <b>3e</b> ] <b>4y</b> , X = F, 25 h (70%) [ <b>2a</b> + <b>3f</b> ] <b>4z</b> , X = Cl, 24 h (78%) [ <b>2a</b> + <b>3g</b> ] <b>4aa</b> , X = Br, 24 h (75%) [ <b>2a</b> + <b>3h</b> ]
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<sup>a</sup> A 5 mL glass vial was filled with **2** (0.2 mmol), **3** (0.22 mmol), and DCE (1 mL). TMSOTf (0.02 mmol) was then introduced at 0–5 °C. After stirring at the same temperature for 30 min, the reaction continued at room temperature until **1** and **2** disappeared (by TLC). <sup>b</sup> Isolated yield after column chromatography. <sup>c</sup> Structure confirmed by single crystal X-ray diffraction analysis, see the ESI for details.<sup>10</sup>

excellent yields.<sup>11</sup> A range of possible substitution patterns on the pyrones were considered that provided 2-benzofuranyl propanones possessing 1°, 2° and 3°-alcoholic centres. Notably, chiral hydroxyacetones such as **4g–4j** and **4t** can be easily assembled by employing this strategy. In particular, isolation of alcohols **4j** and **4t** in 98% and 93% ee, respectively, indicates the involvement of a non-racemising process during the transformation which in turn signifies the mildness of the reaction conditions.

Interestingly, the reaction of the pyrone **2a** with halogenated phenols **3f–3h** generated only the 4,4a-dihydropyrano[3,2-*b*]-benzofurans **4y**, **4z**, and **4aa**. Even prolonged reaction times



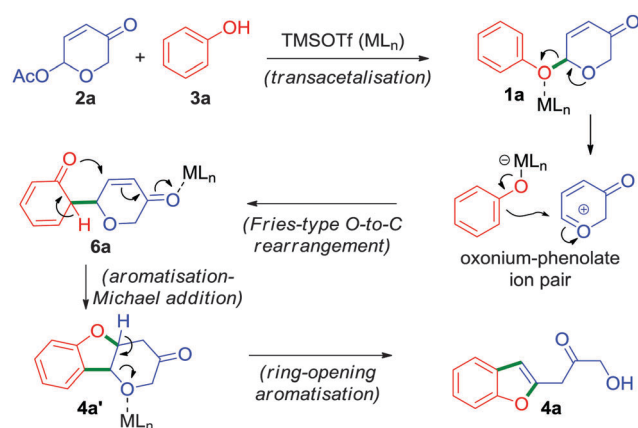


**Scheme 2** Unprecedented approach for the synthesis of furo[3,2-*c*]coumarins and a few representative bioactive furocoumarins.

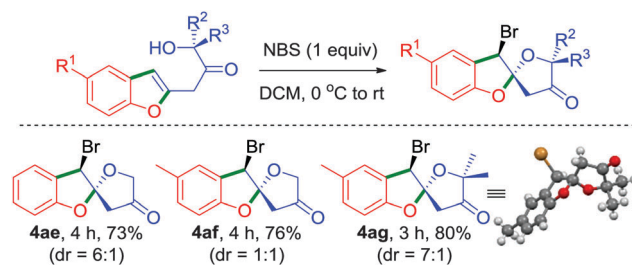
did not yield the expected 2-benzofuranyl-3-hydroxyacetones. This result has two-fold significance; it not only provided mechanistic insights into the conversion of 2 to 4, but also provided a new entry for the synthesis of pyrano[3,2-*b*]benzofuran-3-ones.<sup>12</sup>

Apart from phenols, strikingly, enol such as 4-hydroxycoumarin **3i** also proved to be a distinctive reactive partner in producing furocoumarins **4ab–4ad** in one simple step from 6-acetoxy- $\beta$ -pyrones, Scheme 2. Furocoumarins are part of several bioactive natural products and medicinally interesting compounds.<sup>13</sup> Most of the synthetic approaches have focused on the construction of coumestans. Only a few methods have been described for the synthesis of furo[3,2-*c*]coumarins.<sup>14</sup> In this regard, our approach depicted herein provides an unprecedented access for the synthesis of 2-alkylated furo[3,2-*c*]coumarins.

Based on the experimental observations, a plausible mechanism has been proposed in Scheme 3.<sup>15</sup> The cascade process



**Scheme 3** Plausible mechanism.



**Scheme 4** An unusual two-step synthetic approach for spiro[benzofuran-2,2'-furan]-4'-ones from  $\beta$ -pyrones.

begins with an acid catalysed transacetalisation<sup>6</sup> followed by an unusual Fries-type O  $\rightarrow$  C rearrangement<sup>16</sup> which leads to the formation of a neutral but unstable intermediate **6a** in a highly regio- and chemoselective manner.<sup>17</sup> Subsequently, **6a** undergoes aromatisation and concomitant oxa-Michael addition to form intermediate **4a'**. Furthermore, acid-induced ring-opening aromatisation of **4a'** affords the 2-benzofuranyl-3-hydroxyacetone **4a**.

To further illustrate the generality and synthetic utility of this methodology, we considered an elaboration, Scheme 4. We intended to exploit the presence of alcohol functionality in the side chain in an intramolecular haloetherification reaction which would potentially generate spiro[benzofuran-2,2'-furan]-4'-ones.<sup>18</sup> Accordingly, reaction of the keto-alcohols **4a**, **4b** and **4l** with NBS at room temperature conveniently furnished the respective 5,5-spiroketal **4ae–4ag** in excellent yields, thereby establishing a mere two-step unprecedented access from readily accessible 6-acetoxy- $\beta$ -pyrones. The relative stereochemistry of **4ae–4ag** was assigned based on the X-ray crystal analysis of **4ag**.<sup>19</sup> Prevalence of several bioactive natural products possessing the 5,5-spiroketal scaffold renders this an attractive strategy for their easy synthesis, Scheme 4.<sup>20</sup>

Finally, scalability and practicality of the cascade process were verified by conducting gram scale reactions of **2a**.<sup>8</sup>

In conclusion, we have described a cascade event of  $\beta$ -pyrones and phenols, originating out of serendipity, leading to the synthesis of 2-benzofuranyl-3-hydroxyacetones. The versatility of this strategy lies in its ability to establish unprecedented access for medicinally significant scaffolds such as 4,4a-dihydropyrano[3,2-*b*]benzofuran-3-ones, furo[3,2-*c*]coumarins, and spiro[benzofuran-2,2'-furan]-4'-ones in a short and efficient manner. Efforts to extend these methods for the total synthesis of natural products are in progress and will be communicated in due course.

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## Notes and references

- (a) B. H. Lipshutz, *Chem. Rev.*, 1986, **86**, 795; (b) T. Nagahara, Y. Yokoyama, K. Inamura, S. Katakura, S. Komoriya, H. Yamaguchi, T. Hara and M. Iwamoto, *J. Med. Chem.*, 1994, **37**, 1200; (c) J. R. Hanson, *Nat. Prod. Rep.*, 1995, **12**, 381; (d) X. L. Hou, H. Y. Cheung, T. Y. Hon, P. L. Kwan, T. H. Lo, S. Y. Tong and H. N. C. Wong, *Tetrahedron*, 1998, **54**, 1955; (e) T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2491;





- (f) M. Watanabe, W. T. Su, Y. J. Chang, T. H. Chao, Y. S. Wen and T. J. Chow, *Chem. – Asian J.*, 2012, **8**, 60; (g) S. O. Simonetti, E. L. Larghi, A. B. J. Bracca and T. S. Kaufman, *Nat. Prod. Rep.*, 2013, **30**, 941; (h) P. Han, X. Gong, B. Lin, Z. Jia, S. Ye, Y. Suna and H. Yang, *RSC Adv.*, 2015, **5**, 50098.
- (a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfield, *J. Med. Chem.*, 1988, **31**, 2235; (b) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893; (c) A. K. Ghosh, P. R. Sridhar, N. Kumaragurubaran, Y. Koh, I. T. Weber and H. Mitsuya, *ChemMedChem*, 2006, **1**, 939; (d) H. Sundén and R. Olsson, *Org. Biomol. Chem.*, 2010, **8**, 4831.
  - (a) T. Sakamoto, Y. Kondo and H. Yamanaka, *Heterocycles*, 1988, **27**, 2225; (b) D. Nematollahi, D. Habibi, M. Rahmati and M. Rafiee, *J. Org. Chem.*, 2004, **69**, 2637; (c) S. Cacchi, G. Fabrizi and A. Goggiamani, *Curr. Org. Chem.*, 2006, **10**, 1423; (d) M. Nagamochi, Y. Q. Fang and M. Lautens, *Org. Lett.*, 2007, **9**, 2955; (e) Y. Liu, M. Wang, H. Yuan and C. Liu, *Adv. Synth. Catal.*, 2010, **352**, 884; (f) S. Cacchi, G. Fabrizi and A. Goggiamani, *Org. Biomol. Chem.*, 2011, **9**, 641; (g) M. R. Kuram, M. Bhanuchandra and A. K. Sahoo, *Angew. Chem., Int. Ed.*, 2013, **52**, 4607; (h) U. Sharma, T. Naveen, A. Maji, S. Manna and D. Maiti, *Angew. Chem., Int. Ed.*, 2013, **52**, 12669; (i) Y. Gao, W. Xiong, H. Chen, W. Wu, J. Peng, Y. Gao and H. Jiang, *J. Org. Chem.*, 2015, **80**, 7456.
  - Few selected articles: (a) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed.*, 1993, **32**, 131; (b) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (c) S. Sato, M. Miura, T. Sekito and T. Kumazawa, *J. Carbohydr. Chem.*, 2008, **27**, 86; (d) D. B. Ramachary, C. Venkaiah and P. M. Krishna, *Chem. Commun.*, 2012, **48**, 2252; (e) R. A. Sheldon, *Chem. Soc. Rev.*, 2012, **41**, 1437; (f) L. Q. Lu, J. R. Chen and W. J. Xiao, *Acc. Chem. Res.*, 2012, **45**, 1278; (g) S. Dhiman and S. S. V. Ramasastry, *J. Org. Chem.*, 2013, **78**, 10427; (h) B. Satpathi, S. Dhiman and S. S. V. Ramasastry, *J. Agric. Food Chem.*, 2014, **62**, 8470; (i) L. Zhang, Y. Xia and D. G. Peterson, *J. Org. Chem.*, 2014, 2022; (j) S. Dhiman and S. S. V. Ramasastry, *Chem. Commun.*, 2015, **51**, 557; (k) S. Dhiman and S. S. V. Ramasastry, *Org. Lett.*, 2015, **17**, 5116; (l) D. H. Dethe and G. M. Murhade, *Chem. Commun.*, 2015, **51**, 10891.
  - (a) S. Kasare, S. K. Bankar and S. S. V. Ramasastry, *Org. Lett.*, 2014, **16**, 4284; (b) S. K. Bankar, R. P. Shirke and S. S. V. Ramasastry, *Adv. Synth. Catal.*, 2015, **357**, 3284.
  - (a) G. Grynkiewicz, B. Barszczak and A. Zamojski, *Synthesis*, 1979, 364; (b) J. Knol, J. F. G. A. Jansen, F. van Bolhuis and B. L. Feringa, *Tetrahedron Lett.*, 1991, **32**, 7465. For other outstanding contributions on this subject, see: (c) G. Grynkiewicz and A. Zamojski, *Z. Naturforsch.*, 1980, **35B**, 1024; (d) M. T. Reetz and H. Müller-Starke, *Liebigs Ann. Chem.*, 1983, 1726; (e) O. R. Martin, *Tetrahedron Lett.*, 1985, **26**, 2055; (f) T. Matsumoto, M. Katsuki, H. Jona and K. Suzuki, *Tetrahedron Lett.*, 1989, **30**, 6185; (g) K. Toshima, G. Matsuo, T. Ishizuka, M. Nakata and M. Kinoshita, *J. Chem. Soc., Chem. Commun.*, 1992, 1641; (h) K. Suzuki, *Pure Appl. Chem.*, 1994, **66**, 2175; (i) R. S. Babu and G. A. O'Doherty, *J. Am. Chem. Soc.*, 2003, **125**, 12406.
  - 1a** was obtained in <10% yield when the reaction was performed at room temperature as suggested in the original protocols of Grynkiewicz and Feringa. Reaction at reduced temperature (0–5 °C) afforded **1a** in reasonable yields.
  - See the ESI† for details.
  - For our recent work on the conversion of furans to benzofurans, see: R. P. Shirke, V. Reddy, R. V. Anand and S. S. V. Ramasastry, *Synthesis*, 2016, DOI: 10.1055/s-0035-1560432. For our work on an interesting transformation of benzofurans to furans, see ref. 4g.
  - X-ray crystallographic data of compound **4l** are provided in the ESI.† CCDC 1437901.
  - The observed regioselectivity (C-1 vs. C-3) during the Fries-type rearrangement of 2-naphthyl derivatives (**4s–4x**) is in agreement with literature reports, see: C. Cui, X. Wang and R. G. Weiss, *J. Org. Chem.*, 1996, **61**, 1962.
  - (a) S. J. Gharpure and V. Prasath, *Org. Biomol. Chem.*, 2014, **12**, 7397; (b) F. Wang, C. Luo, Y. Y. Shen, Z. D. Wang, X. Li and J. P. Cheng, *Org. Lett.*, 2015, **17**, 338.
  - For pterophyllins, see: (a) D. A. Mulholland, S. E. Iourine, D. A. H. Taylor and F. M. Dean, *Phytochemistry*, 1998, **47**, 1641. For medicinal significance of furocoumarins, see: (b) L. Santana, E. Uriarte, F. Roleira, N. Milhazes and F. Borges, *Curr. Med. Chem.*, 2004, **11**, 3239; (c) Y. Dong, Q. Shi, H. C. Pai, C. Y. Peng, S. L. Pan, C. M. Teng, K. Nakagawa-Goto, D. Yu, Y. N. Liu, P. C. Wu, K. F. Bastow, S. L. Morris-Natschke, A. Brossi, J. Y. Lang, J. L. Hsu, M. C. Hung, E. Y. H. P. Lee and K. H. Lee, *J. Med. Chem.*, 2010, **53**, 2299.
  - (a) G. Cheng and Y. Hu, *Chem. Commun.*, 2007, 3285; (b) G. Raffa, M. Rusch, G. Balme and N. Monteiro, *Org. Lett.*, 2009, **11**, 5254; (c) R. G. dos Santos, A. R. Jesus, J. M. Caio and A. P. Rauter, *Curr. Org. Chem.*, 2011, **15**, 128; (d) C.-J. Lee, C.-C. Tsai, S.-H. Hong, G.-H. Chang, M.-C. Yang, L. Möhlmann and W. Lin, *Angew. Chem., Int. Ed.*, 2015, **54**, 8502; (e) W. L. Zhang, S. N. Yue, Y. M. Shen, H. Y. Hu, Q.-H. Meng, H. Wu and Y. Liu, *Org. Biomol. Chem.*, 2015, **13**, 3602; (f) X. Y. Zhang, L. L. Hu, Z. Shen, Z. Z. Chen, Z. G. Xu, S. Q. Li, J. W. Xie and H. L. Cui, *Synlett*, 2015, 2821.
  - See the ESI† for additional experiments carried out to get insights into the mechanism.
  - (a) T. Kometani, H. Kondo and Y. Fujimori, *Synthesis*, 1988, 1005; (b) T. Matsumoto, M. Katsuki and K. Suzuki, *Tetrahedron Lett.*, 1988, **29**, 6935; (c) T. Matsumoto, T. Katsuki, H. Jona and K. Suzuki, *J. Am. Chem. Soc.*, 1991, **113**, 6982; (d) J. A. Mahling and R. R. Schmidt, *Synthesis*, 1993, 325; (e) C. Booma and K. K. Balasubramanian, *Tetrahedron Lett.*, 1995, **36**, 5807; (f) E. R. Palmacci and P. H. Seeberger, *Org. Lett.*, 2001, **3**, 1547; (g) E. R. Palmacci, O. J. Plante and P. H. Seeberger, *Eur. J. Org. Chem.*, 2002, 595; (h) C. G. Nasveschuk and T. Rovis, *Org. Biomol. Chem.*, 2008, **6**, 240; (i) C. Wiebe, C. Schlemmer, S. Weck and T. Opatz, *Chem. Commun.*, 2011, **47**, 9212; (j) X. H. Xu, M. Taniguchi, X. Wang, E. Tokunaga, T. Ozawa, H. Masuda and N. Norio Shibata, *Angew. Chem., Int. Ed.*, 2013, **52**, 12628; (k) C. N. Kona and C. V. Ramana, *Chem. Commun.*, 2014, **50**, 2152.
  - Intermediacy of an oxidopyrylium intermediate at this stage can be ruled out based on the fact that alcohols **4j** and **4t** were isolated in 98% and 93% ee, respectively.
  - (a) J. Sperry, Z. E. Wilson, D. C. K. Rathwell and M. A. Brimble, *Nat. Prod. Rep.*, 2010, **27**, 1117; (b) I. Sharma, J. M. Wurstand and D. S. Tan, *Org. Lett.*, 2014, **16**, 2474; (c) Z. Li and Y. Shi, *Org. Lett.*, 2015, **17**, 5752.
  - X-ray crystallographic data of compound **4ag** are provided in the ESI.† CCDC 1441109.
  - For aquilarinoside A, see: (a) J. Qi, J. J. Lu, J. H. Liu and B. Y. Yu, *Chem. Pharm. Bull.*, 2009, **57**, 134. For pinnatifinoside A, see: (b) P. C. Zhang and S. X. Xu, *Phytochemistry*, 2001, **57**, 1249. For other 5,5-spiroketal natural products, see: (c) Y. C. Hu, X. F. Wu, S. Gao, S. S. Yu, Y. Liu, J. Qu, J. Liu and Y. B. Liu, *Org. Lett.*, 2006, **8**, 2269; (d) R. Raju, O. Gromyko, V. Fedorenko, A. Luzhetskyy and R. Müller, *Org. Lett.*, 2013, **15**, 3487; (e) H. Wang, J. Hong, J. Yin, H. R. Moon, Y. Liu, X. Wei, D. C. Oh and J. H. Jung, *J. Nat. Prod.*, 2015, **78**, 2832.

