ORGANIC LETTERS

2012
Vol. 14, No. 15
4014–4017

Biomass Conversion to High Value Chemicals: From Furfural to Chiral Hydrofuroins in Two Steps

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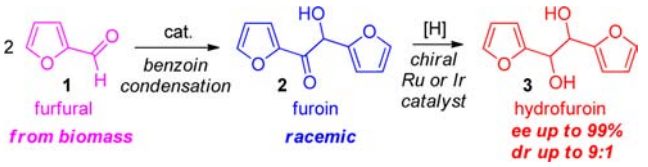
Received July 5, 2012

ABSTRACT



Catalytic asymmetric transfer hydrogenation of *rac*-furoin and furil produces hydrofuroin with up to 99% *ee* and 9:1 *dr*. This reaction provides an exceptionally easy access to optically active hydrofuroins in two straightforward steps from biomass-derived furfural (global production 200 000−300 000 t annually) using benzoin condensation.

The modern chemical industry is almost entirely based on petrochemical feedstock. As the limited natural supplies of crude oil run out fast, there is an increasing need to develop routes to chemicals, materials, and fuels from renewable feedstock such as biomass.[1] Although considerable progress has been made in the area of Green Chemistry, the development of new industrially feasible methods for efficient biomass conversion to useful fine chemicals remains a challenge that is being actively pursued.

Furfural (furan-2-carboxaldehyde; **1**)[2,3] is one of the most readily available individual organic compounds from nonedible biomass, including crop residues (e.g., corncobs) and waste aqueous hemicellulose solutions from the pulp and paper industry and cellulosic ethanol manufacturing. Current annual production of furfural amounts to approximately 200 000−300 000 t,[3a] and the global production capacity is estimated at 500 000 t. It has been noted[4] that the modern technologies using continuous two-zone biphasic reactors might produce furfural at $366 per t, just one-quarter of its current, already low selling price on the U.S. market.

All of the above makes furfural a particularly attractive candidate for use as a starting material for industrially viable chemical transformations. Although the chemistry of furfural is very well developed,[2] there is a significant need for new applications of this readily available simple aldehyde, especially for the preparation of high-value materials such as optically active compounds. Herein we report a highly efficient, chemo- and stereoselective synthesis of chiral hydrofuroins *via* asymmetric transfer hydrogenation of racemic furoin and furil that are easily prepared from furfural in one step.

Benzoin condensation of furfural is known[2,5] to give furoin (**2**) in up to quantitative yield. We hypothesized that asymmetric reduction of the carbonyl group of furoin

(1) For selected books, see: (a) Hood, E. E.; Nelson, P.; Powell, R., Eds. *Plant Biomass Conversion*; Wiley-Blackwell: Chichester, 2011. (b) Brown, R. C., Ed. *Thermochemical Processing of Biomass: Conversion into Fuels, Chemicals and Power*; John Wiley & Sons: Chichester, 2011. (c) Lancaster, M. *Green Chemistry: An Introductory Text*; RSC Publishing: Cambridge, U.K., 2010. (d) Clark, J. H., Deswarte, F., Eds. *Introduction to Chemicals from Biomass*; John Wiley & Sons: Chichester, 2008. (e) Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 1998.

(2) For a monograph, see: Zeitsch, K. J. *The Chemistry and Technology of Furfural and its Many By-Products*; Sugar Series, Vol. 13; Elsevier: Amsterdam, 2000.

(3) For selected most recent reviews, see: (a) Karinen, R.; Vilonen, K.; Niemelae, M. *ChemSusChem* **2011**, *4*, 1002. (b) Martel, F.; Estrine, B.; Plantier-Royon, R.; Hoffmann, N.; Portella, C. *Top. Curr. Chem.* **2010**, *294*, 79. (c) Corma, A.; Iborra, S.; Velty, A. *Chem. Rev.* **2007**, *107*, 2411. (d) Hoydonckx, H. E.; Van Rhijn, W. M.; Van Rhijn, W.; De Vos, D. E.; Jacobs, P. A. *Furfural and derivatives. Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weineheim, 2007.

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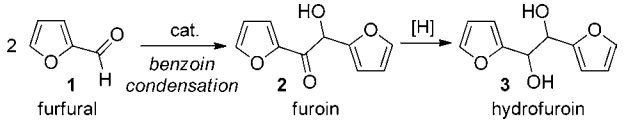
10.1021/ol3018402
Published on Web 07/25/2012

would produce chiral hydrofuroin (**3**), thereby providing an exceptionally easy entry to this valuable diol (Scheme 1). Note that optically active C_2-symmetric 1,2-diols are excellent chiral inducers in various types of asymmetric transformations.[6] While both (*R,R*)-(+)-hydrobenzoin and (*S,S*)-(−)-hydrobenzoin are commercially available and find numerous applications,[7] no practical synthetic methods have been reported for hydrofuroins of high optical purity. Thus, asymmetric pinacol coupling of furfural to hydrofuroin, catalyzed by chiral Ti[8] and V[9] complexes, provided an enantioselectivity of only 50% and 37%, respectively. The asymmetric reduction of furil with Me_2SBH_3 in the presence of a chiral oxazaborolidine furnished **3** with excellent *ee* > 99% (*de* = 78%).[10] However, a high chiral catalyst loading of 20 mol % was needed and the chemical yield achieved was only 70%.

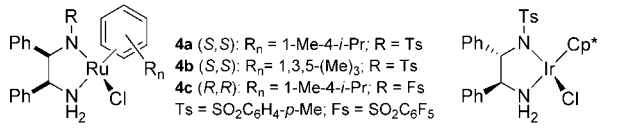
Scheme 1. Two-Step Synthesis of Hydrofuroin from Furfural



Among various methods for the synthesis of chiral 1,2-diols, metal-catalyzed Asymmetric Transfer Hydrogenation (ATH) of the corresponding prochiral α-diketones or α-hydroxy ketones is considered to be particularly convenient and efficient.[11] A highly efficient synthesis of (*R,R*)-hydrobenzoin from *rac*-benzoin (or benzil) has been developed[12] *via* ATH with a mixture of triethylamine (Et_3N; TEA) and formic acid (HCO_2H; FA), catalyzed by [RuCl(*p*-cymene)((*S,S*)-TsDPEN)] (**4a**; TsDPEN = *N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine). The lack of reports on a similar process involving furan derivatives is unsurprising, considering the well-recognized and long-established[13] fact that furan derivatives differ considerably from their benzene analogues in terms of chemical reactivity and stability. Furthermore, the presence in **2** and **3** of oxygen atoms in a potentially strongly chelating arrangement, along with the oxophilicity of ruthenium, casts serious doubts on the success of Ru-catalyzed ATH of furoin to hydrofuroin. Nonetheless, we attempted ATH of **2** to **3** and, to our delight, obtained results that surpassed our expectations.

We found that ATH of *rac*-furoin was efficiently catalyzed by Ru complex **4a** and its analogues **4b** and **4c**,[14] as well as by Ir complex **5** (Scheme 2). Results of these experiments are summarized in Table 1.

Scheme 2. Chiral Catalysts Used in this Work



In the commercially available azeotropic mixture TEAF (FA/TEA = 5:2 mol/mol), ATH of *rac*-**2** smoothly occurred in the presence of **4a** (0.5 mol %) to give hydrofuroin (+)-**3** in 97% isolated yield with 99% *ee* and 76% *de* after 2 h at 60 °C (Table 1, entry 1; for absolute configuration assignment, see below). This level of selectivity is apparently due to the dynamic kinetic resolution of *rac*-furoin, as in the previously reported ATH reactions of racemic benzoin[12b] and aryl-substituted α-hydroxy ketones.[15]

While nearly identical results were obtained with 0.4 mol % of **4a**, further catalyst loading reduction to 0.3 mol % under otherwise identical conditions significantly affected both the rate and stereoselectivity of the reaction (entries 2 and 3). A similar effect was observed when **4b** was employed as the catalyst (entries 5 and 6). Therefore, to achieve high chemical yields and stereoselectivity both **4b** and **4c** were used in the amount of 0.5 mol % (entries 5 and 7). It has been reported[12b,15] that ATH of aryl-substituted α-hydroxy ketones in a freshly prepared 3.1:2.6 (mol/mol) mixture of FA/TEA can efficiently proceed at 40 °C with as little as 0.1 mol % of **4a**. When we applied such conditions to the reduction of **2**, full conversion was reached after 24 h and the product with 99% *ee* and 80% *de* was isolated in 94% yield (entry 4).

(5) See, for example: (a) Stetter, H.; Raemsch, R. Y.; Kuhlmann, H. *Synthesis* **1976**, 733. (b) Lee, C. K.; Kim, M. S.; Gong, J. S.; Lee, I.-S. H. *J. Heterocycl. Chem.* **1992**, *29*, 149. (c) Miyashita, A.; Suzuki, Y.; Iwamoto, K.-i.; Higashino, T. *Chem. Pharm. Bull.* **1994**, *42*, 2633. (d) Enders, D.; Kallfass, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 1743. (e) Iwamoto, K.-i.; Hamaya, M.; Hashimoto, N.; Kimura, H.; Suzuki, Y.; Sato, M. *Tetrahedron Lett.* **2006**, *47*, 7175. (f) Iwamoto, K.-i.; Kimura, H.; Oike, M.; Sato, M. *Org. Biomol. Chem.* **2008**, *6*, 912. (g) Baragwanath, L.; Rose, C. A.; Zeitler, K.; Connon, S. J. *J. Org. Chem.* **2009**, *74*, 9214. (h) Ma, Y.; Xue, C. *Huaxue Xuebao* **2010**, *68*, 897. (i) Shimakawa, Y.; Morikawa, T.; Sakaguchi, S. *Tetrahedron Lett.* **2010**, *51*, 1786.

(6) (a) Kolb, H.; VanNieuwenhze, M.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Bhowmick, K. C.; Joshi, N. N. *Tetrahedron: Asymmetry* **2006**, *17*, 1901.

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(12) (a) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119. (b) Ikariya, T.; Hashiguchi, S.; Murata, K.; Noyori, R. *Org. Synth.* **2005**, *82*, 10.

(13) Dunlop, A. P.; Peters, F. N. *The Furans*; Reinhold Publishing Corporation: New York, 1953.

(14) (a) Catalysts **4a**−**c** are commercially available. Well-defined [RuCl(η^6-arene)(*N*-TsDPEN)]-type complexes have been extensively modified and found numerous applications.[14b] (b) For a recent review, see: Václavík, J.; Kačer, P.; Kuzma, M.; Červeny, L. *Molecules* **2011**, *16*, 5460.

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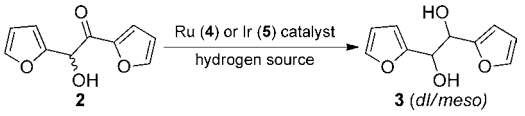
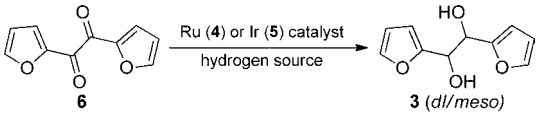
Table 1. ATH of Furoin, Catalyzed by Ru (**4a**–**c**) and Ir (**5**) Complexes[a]



entry	cat. (mol %)	method[b]	*t* (h)	yield (%)	*dl*/*meso*	*ee*, % (config)
1	**4a** (0.5)	**A**	2	97	88/12	99 (*S*,*S*)
2	**4a** (0.4)	**A**	4	96	88/12	99 (*S*,*S*)
3	**4a** (0.3)	**A**	24	86	68/32	93 (*S*,*S*)
4	**4a** (0.1)	**B**	24	94	90/10	99 (*S*,*S*)
5	**4b** (0.5)	**A**	2	93	87/13	99 (*S*,*S*)
6	**4b** (0.3)	**A**	48	7	85/15	98 (*S*,*S*)
7	**4c** (0.5)	**A**	2.5	92	81/19	95 (*R*,*R*)
8	**4a** (1.0)	**C** (5)	18	63	59/41	95 (*S*,*S*)
9	**5** (1.0)	**C** (1)	24	57	63/37	91 (*S*,*S*)
10	**5** (1.0)	**C** (2)	3	96	66/34	93 (*S*,*S*)
11	**5** (1.0)	**C** (3)	2	91	62/38	93 (*S*,*S*)
12	**5** (1.0)	**C** (5)	2	95	59/41	93 (*S*,*S*)
13	**5** (1.0)	**C** (7)	1	95	57/43	92 (*S*,*S*)
14[c]	**5** (1.0)	**C** (5)	20	86	56/44	94 (*S*,*S*)

[a] See the Supporting Information for details and specifics. [b] **A**: molar ratio **2**/FA/TEA = 1/10/4, 60 °C. **B**: molar ratio **2**/FA/TEA = 1/3.1/2.6, 40 °C. **C**: HCOONa (number of equiv in parentheses) in H_2O, 60 °C. [c] At 40 °C.

Table 2. ATH of Furil, Catalyzed by Ru (**4a**–**c**) and Ir (**5**) Complexes[a]



entry	cat. (mol %)	method[b]	*t* (h)	yield (%)	*dl*/*meso*	*ee*, % (config)
1	**4a** (0.5)	**A**	2	96	90/10	99 (*S*,*S*)
2	**4b** (0.5)	**A**	2	93	85/15	99 (*S*,*S*)
3	**4c** (0.5)	**A**	3	96	82/18	98 (*R*,*R*)
4	**4a** (1.0)	**B** (5)	48	24	74/26	98 (*S*,*S*)
5	**5** (1.0)	**B** (5)	0.7	89	81/19	97 (*S*,*S*)
6	**5** (0.8)	**B** (5)	0.7	87	82/18	97 (*S*,*S*)
7	**5** (0.6)	**B** (5)	1	93	82/18	97 (*S*,*S*)
8	**5** (0.2)	**B** (5)	1.5	91	86/14	97 (*S*,*S*)
9	**5** (0.2)	**B** (2)	24	63	87/13	97 (*S*,*S*)
10[c]	**5** (0.2)	**B** (5)	24	64	90/10	98 (*S*,*S*)
11	**5** (0.1)	**B** (5)	24	58	92/8	98 (*S*,*S*)

[a] See the Supporting Information for details and specifics. [b] **A**: molar ratio **6**/FA/TEA = 1/10/4, 60 °C. **B**: HCOONa (number of equiv in parentheses) in H_2O, 60 °C. [c] At 40 °C.

It has been recently shown[11c,16] that Ir-, Rh-, and Ru-TsDPEN complexes can catalyze ATH of simple aromatic ketones with sodium formate in water with excellent *ee* of up to 99%. These reports prompted us to examine both Ru (**4a**) and Ir (**5**) catalysts generated *in situ*[16b,c] for ATH of **2** with HCOONa in water. However, while chemical yields of up to 96% were obtained, these systems appeared inferior in terms of both *de* and *ee* even at a high catalyst loading (1 mol %) and in the presence of up to 7 equiv of HCOONa (Table 1, entries 8–14).

Under certain conditions, benzoin condensation of furfural coproduces furil (**6**),[2,13,17] apparently because of air oxidation of the primary product, furoin. Therefore, it was important to study ATH of **6** to demonstrate the applicability of the method not only to pure furoin but also to furil. We were pleased to find that like **2**, **6** can be cleanly and stereoselectively reduced to **3** under similar conditions (Table 2). For the Ru complexes **4a**–**c** in TEAF, the reaction smoothly proceeded with a substrate to a catalyst molar ratio of 200 to give hydrofuroin **3** in nearly quantitative yield with high stereoselectivity (entries 1–3). Enantiomerically pure (+)-**3** (99% *ee*) containing only 10% of the *meso* diastereomer was obtained using catalyst **4a** (entry 1). With complexes **4b** and **4c**, the reaction was also highly enantioselective, albeit the *dl* to *meso* ratio was lower (entries 2 and 3).

Similar to the **4a**-catalyzed ATH of **2** with aqueous sodium formate (Table 1, entry 8), the reduction of **6** under the same conditions occurred with high enantioselectivity (98% *ee*), yet considerably lower diastereoselectivity (48% *de*) and chemical yield (24%; Table 2, entry 4). The Ir complex (**5**) appeared more efficient in the reaction of furil.[18] With only 1.0–0.2 mol % of **5**, the reduction of **6** to **3** occurred in 63–93% chemical yield (entries 5–10) with 97–98% *ee* and up to 80% diastereoselectivity. The highest *de* of 84% was observed with only 0.1% of **5** in a slower reaction that produced **3** in 58% yield after 24 h (entry 11).

To demonstrate the generality of the method, we then reduced substituted *rac*-furoins **7a**–**d** to the corresponding hydrofuroins **8a**–**d** using the protocol developed for **2** (Table 3). With only 0.1 mol % of **4a** these reactions occurred with excellent enantioselectivity (99% *ee*) to produce the diols in 59–92% chemical yield. The diastereomeric ratio (*dl*/*meso*) varied from 90:10 for **8b** to 83:17 for **8d** bearing a more electron-deficient aryl substituent in the α-position of the furan ring.

While *dl*-**3** is a liquid at rt, its substituted analogues **8** are crystalline solids. Single-crystal X-ray diffraction of **8a** that was isolated enantiomerically pure (>99% *ee*) from the reduction of **7a** (Table 3) allowed for the determination of its absolute configuration. As shown in Figure 1, (+)-**8a** is (*S*,*S*) suggesting that this is the absolute configuration of

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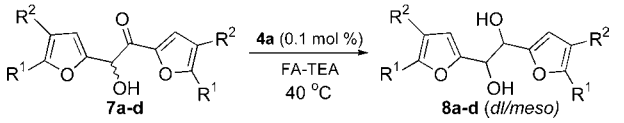
(17) For a recent example of coproduction of **6** in the formation of **2** from **1** in a study of hydrogenation of **1**, see: Strassberger, Z.; Mooijman, M.; Ruijter, E.; Alberts, A. H.; Maldonado, A. G.; Orru, R. V. A.; Rothenberg, G. *Adv. Synth. Catal.* **2010**, *352*, 2201.

(18) ATH of benzil with Ir/Rh-TsDPEN with formate in water to give hydrobenzoin with 97–99% *ee* and unspecified *de* has been reported.[16b]

Table 3. ATH of Furoins **7a**−**d**, Catalyzed by **4a**[a]



7	R^1	R^2	t (h)	yield (%)	*dl*/*meso*	*ee*, % (config)
7a	Me	H	24	92	89/11	99 (*S*,*S*)
7b	Me	Me	24	59	90/10	99 (*S*,*S*)
7c	Ph	H	40	85	87/13	99 (*S*,*S*)
7d	3-CF_3-C_6H_4	H	18	83	83/17	99 (*S*,*S*)

[a] Molar ratio **7**/FA/TEA = 1/3.1/2.6. See the Supporting Information for further details.

all (+)-hydrofuroins prepared in this work. Both the Flack[19] ($x = -0.05(17)$) and Hooft[20] ($y = 0.01(5)$) parameters were employed. The obtained values of x and its standard deviation are translated[21] into 99.59% probability for **8a** being (*S*,*S*) in the crystal. In fact, this probability is effectively 100%, as can be judged by the Hooft parameter. X-ray analysis of another single crystal from the same batch of enantiomerically pure (+)-**8a** confirmed its absolute configuration as (*S*,*S*).[22]

In conclusion, we have developed the first two-step synthesis of highly enantiomerically pure hydrofuroin from furfural that is readily available in large quantities from renewable resources. Furfural is first easily converted to *rac*-furoin using well-known benzoin condensation. The furoin product is then reduced to optically active hydrofuroin *via* asymmetric transfer hydrogenation in the presence of readily available, inexpensive chiral Ru catalysts (0.1−0.5 mol %). This asymmetric reduction occurs under mild conditions with 99% *ee* and up to 80% *de* to furnish (*R*,*R*)- or (*S*,*S*)-hydrofuroin that is easily isolated in >90% yield. Notably, furil that is often formed as a side product of benzoin condensation of furfural can also be converted to hydrobenzoin with similar chemo- and stereoselectivities under identical conditions and catalyst loadings. The use of formic acid as the reducing agent is particularly fitting, as HCOOH is a coproduct in the furfural production from biomass. Considering the importance of C_2-symmetric 1,2-diols as chiral inducers in a variety of asymmetric transformations, we hope that the easy access to chiral hydrofuroins described herein[23] will lead to new practicable developments in the area.

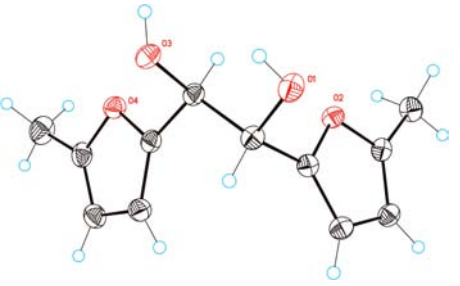


Figure 1. ORTEP drawing of (*S*,*S*)-(+)-**8a** with thermal ellipsoids drawn to the 50% probability level.

Acknowledgment. We thank the ICIQ Foundation and Consolider Ingenio 2010 (Grant CSD2006-0003) for support of this research.

Supporting Information Available. Full details of the synthetic procedures including spectral data (PDF) and crystallographic studies of **8a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Our crystallographic studies of (+)-**8a** suggest that the originally reported[10] and subsequently used[8] assignment of the (*S*,*S*) configuration to (−)-**3** might be incorrect. The literature assignment[10] was made by analogy with hydrobenzoin while apparently overlooking the fact that the formal replacement of the phenyls in (*S*,*S*)-PhCH(OH)CH(OH)Ph with 2-furyls without any other changes produces (*R*,*R*)-hydrofuroin, not the (*S*,*S*) form, as follows from the Cahn−Ingold−Prelog priority rules. It is also worth noting that although it has been reported[8,10] that **3** "deteriorates rapidly at ambient temperature", all diols obtained in our work, **3** included, are stable compounds exhibiting no signs of decomposition.

(23) Patent application (to ICIQ) filed.

The authors declare no competing financial interest.