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Enantioselective Carbonyl Allylation, Crotylation, and *tert*-Prenylation of Furan Methanols and Furfurals via Iridium-Catalyzed Transfer Hydrogenation

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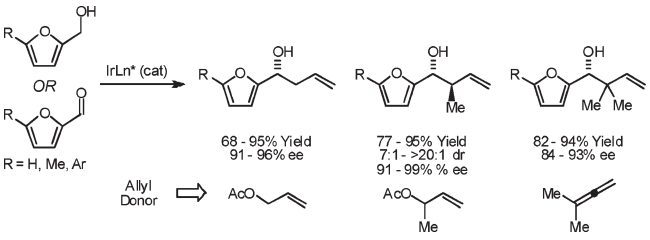

5-Substituted-2-furan methanols **1a**−**c** are subject to enantioselective carbonyl allylation, crotylation and *tert*-prenylation upon exposure to allyl acetate, α-methyl allyl acetate, or 1,1-dimethylallene in the presence of an *ortho*-cyclometalated iridium catalyst modified by (*R*)-Cl,MeO-BIPHEP, (*R*)-C3-TUNEPHOS, and (*R*)-C3-SEGPHOS, respectively. In the presence of 2-propanol, but under otherwise identical conditions, the corresponding substituted furfurals **2a**−**c** are converted to identical products of allylation, crotylation, and *tert*-prenylation. Optically enriched products of carbonyl allylation, crotylation, and reverse prenylation **3b**, **4b**, and **5b** were subjected to Achmatowicz rearrangement to furnish the corresponding γ-hydroxy-β-pyrones **6a**−**c**, respectively, with negligible erosion of enantiomeric excess.

In the course of studies on C−C bond-forming hydrogenations and transfer hydrogenations,[1] we found that cyclometalated iridium *C*,*O*-benzoates modified by chiral phosphine ligands are effective catalysts for the enantioselective reductive coupling of allyl acetate, α-methyl allyl acetate, and 1,1-dimethylallene to carbonyl electrophiles to furnish products of carbonyl allylation,[2a,b,e−h] crotylation,[2c,f] and *tert*-prenylation,[2d,f] respectively. For such "*C−C bond forming transfer hydrogenations*", 2-propanol serves as the terminal reductant for additions to preformed aldehyde electrophiles. Remarkably, primary alcohols serve dually as hydrogen donors and aldehyde precursors, enabling asymmetric carbonyl allylation, crotylation, and *tert*-prenylation directly from the alcohol oxidation level. Here, hydrogen exchange between an alcohol−unsaturate redox pair enables generation of an electrophile−nucleophile pair. In this way, nonstabilized carbanion equivalents are generated in the absence of stoichiometric metallic reagents. This strategy for carbonyl allylation differs significantly from conventional carbonyl allylation protocols, which exploit stoichiometric quantities of allylmetal reagents or metallic reductants.[3−5]

In connection with studies toward the syntheses of the mitochondrial electron-transport inhibitors ajudazols A and B,[6] one of the present authors required a highly enantioselective method for the crotylation of a substituted furfural. Although the enantioselective allylation of furfurals has been achieved using stoichiometric allylmetal reagents,[7] Denmark reports the only catalytic methods for enantioselective crotylation and reverse prenylation of furfural.[7f,o] Given the broad utility of furans as building blocks in organic synthesis,[8] we sought to further evaluate the scope of our emergent

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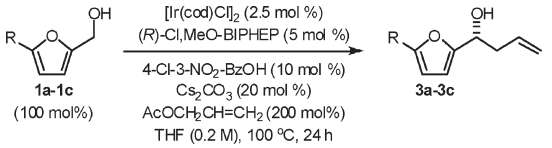
allylation methodology in a systematic study of allylation, crotylation and reverse prenylation of substituted furfurals from both the alcohol and aldehyde oxidation levels. Here, we disclose that 5-substituted-2-furan methanols **1a**−**c** are subject to highly enantioselective carbonyl allylation, crotylation, and reverse prenylation upon exposure to allyl acetate, α-methyl allyl acetate, or 1,1,-dimethylallene, respectively, in the presence of an *ortho*-cyclometalated iridium catalyst modified by (*R*)-Cl,MeO-BIPHEP, (*R*)-C3-TUNEPHOS, and (*R*)-C3-SEGPHOS, respectively. Under nearly identical conditions, but in the presence of 2-propanol, the corresponding substituted furfurals are converted to identical products of allylation, crotylation, and reverse prenylation. Achmatowicz rearrangement of the 5-methyl-2-furan methanol adducts **3b**, **4b**, and **5b** is described.[9]

In an initial set of experiments, 5-substituted-2-furan methanols **1a**−**c** were subjected to conditions for enantioselective iridium-catalyzed carbonyl allylation employing an *ortho*-cyclometalated catalyst generated in situ from $[Ir(cod)Cl]_2$, (*R*)-Cl,MeO-BIPEHP, and 4-chloro-3-nitrobenzoic acid.[2a,b,e−h] Use of the preformed complex provided comparable yields and selectivities. The products of carbonyl allylation **3a**−**c** are formed in good isolated yield with uniformly high levels of optical purity using only 2 equiv of allyl acetate as the allyl donor (Table 1). Under the same conditions, but in the presence of 2-propanol, the corresponding 5-substituted 2-furfurals **2a**−**c** are converted to an identical set of carbonyl allylation products **3a**−**c** in good to excellent isolated yields with uniformly high levels of enantioselectivity. Notably, the parent furans **1a** and **2a** provide slightly lower yields of the homoallylic alcohol **3a**, presumably due to volatility or sensitivity of the furan nucleus with respect to acid-promoted degradation during isolation by silica gel chromatography (Table 2).

Enantioselective crotylation of 5-substituted 2-furan methanols **1a**−**c** was explored next.[2c,f] Here, the preformed *ortho*-cyclometalated complex generated from $[Ir(cod)Cl]_2$, (*R*)-C3-TUNEPHOS, and 4-cyano-3-nitrobenzoic acid provided enhanced yields and selectivities. A further increase in isolated yield resulted from the use of tribasic potassium phosphate as base in the presence of water. Under these conditions, the 5-substituted 2-furan methanols **1a**−**c** were converted to the products of crotylation **4a**−**c** in good to excellent isolated yield with high levels of *anti*-diastereoselectivity and uniformly high levels of enantioselectivity, as determined by HPLC analysis (Table 3). Under the same conditions, but in the presence of 2-propanol, the corresponding 5-substituted 2-furfurals **2a**−**c** are converted to an identical set of carbonyl crotylation products **4a**−**c** with

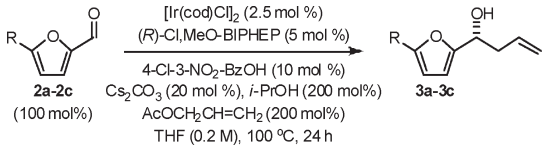
TABLE 1. Enantioselective Carbonyl Allylation of Furan Methanols via Iridium-Catalyzed Transfer Hydrogenation[a]



entry	furan methanol	product	isolated yield (%)	ee (%)
1	R = H, **1a**	**3a**	69	92 (*R*)
2	R = Me, **1b**	**3b**	75	95 (*R*)
3	R = Ar, **1c**	**3c**	79	94 (*R*)

[a]Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary-phase HPLC analysis. For compound **1c**, Ar = 3-chloro-4-methoxyphenyl. See the Supporting Information for additional details.

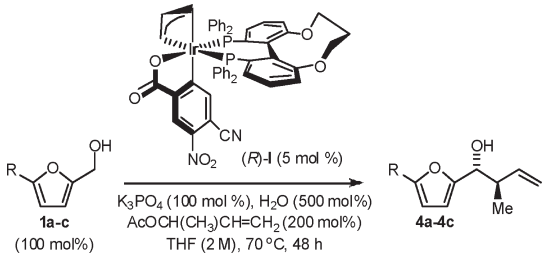
TABLE 2. Enantioselective Carbonyl Allylation of Furfurals via Iridium-Catalyzed Transfer Hydrogenation[a]



entry	furan methanol	product	isolated yield (%)	ee (%)
1	R = H, **1a**	**3a**	70	97 (*R*)
2	R = Me, **1b**	**3b**	82	95 (*R*)
3	R = Ar, **1c**	**3c**	94	97 (*R*)

[a]As described for Table 1.

TABLE 3. Enantioselective Carbonyl Crotylation of Furan Methanols via Iridium-Catalyzed Transfer Hydrogenation[a]



entry	furan methanol	product	isolated yield (%), dr	ee (%)
1	R = H, **1a**	**4a**	77, 10:1	92 (*R*,*R*)
2	R = Me, **1b**	**4b**	76, 7:1	91 (*R*,*R*)
3	R = Ar, **1c**	**4c**	95, 10:1	95 (*R*,*R*)

[a]As described for Table 1.

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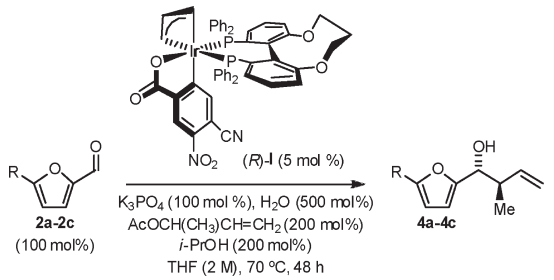
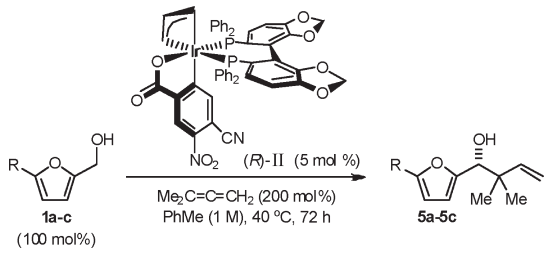
TABLE 4. Enantioselective Carbonyl Crotylation of Furfurals via Iridium-Catalyzed Transfer Hydrogenation[a]



entry	furan methanol	product	isolated yield (%), dr	ee (%)
1	R = H, **1a**	**4a**	72, >20:1	97 (*R*,*R*)
2	R = Me, **1b**	**4b**	79, >20:1	94 (*R*,*R*)
3	R = Ar, **1c**	**4c**	94, >20:1	99 (*R*,*R*)

[a]As described for Table 1.

TABLE 5. Enantioselective Carbonyl *tert*-Prenylation Furan Methanols via Iridium Catalyzed Transfer Hydrogenation[a]



entry	furan methanol	product	isolated yield (%)	ee (%)
1	R = H, **1a**	**5a**	82	87 (*R*)
2	R = Me, **1b**	**5b**	84	84 (*R*)
3	R = Ar, **1c**	**5c**	91	85 (*R*)

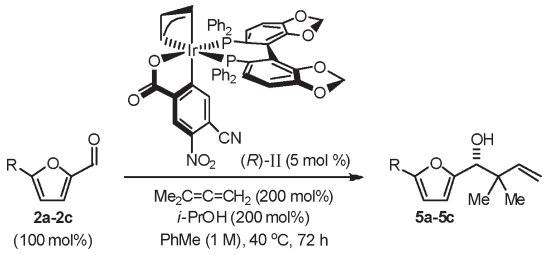
[a]As described for Table 1.

notably enhanced levels of *anti*-diastereo- and enantioselectivity (Table 4).

Finally, the enantioselective *tert*-prenylation of 5-substituted-2-furan methanols **1a**−**c** was explored using the isolated the *ortho*-cyclometalated catalyst generated from $[Ir(cod)Cl]_2$, (*R*)-SEGPHOS, and 4-cyano-3-nitrobenzoic acid.[2d,f] Under remarkably mild conditions, good to excellent isolated yields of **5a**−**c** were attended by good levels of asymmetric induction (Table 5). Slightly improved isolated yields and enantioselectivities were observed when the *tert*-prenylated adducts **5a**−**c** were generated from the corresponding aldehydes **2a**−**c** (Table 6). Thus, allylation, *anti*-crotylation, and *tert*-prenylation are achieved from either the alcohol or aldehyde oxidation level with roughly equal facility using 5-substituted 2-furan methanols **1a**−**c** or 5-substituted-2-furfurals **2a**−**c**, respectively.

The Achmatowicz rearrangement of substituted furan methanols is frequently employed in the total synthesis of natural products.[9b] Accordingly, the optically enriched products of allylation, crotylation, and *tert*-prenylation **3b**, **4b**, and **5b**, respectively, were subjected to conditions for Achmatowicz rearrangement employing *N*-bromosuccinimide as the oxidant. The corresponding γ-hydroxy-β-pyrones **6a**−**c** were formed as diastereomeric mixtures at the lactol center. However, negligible erosion of

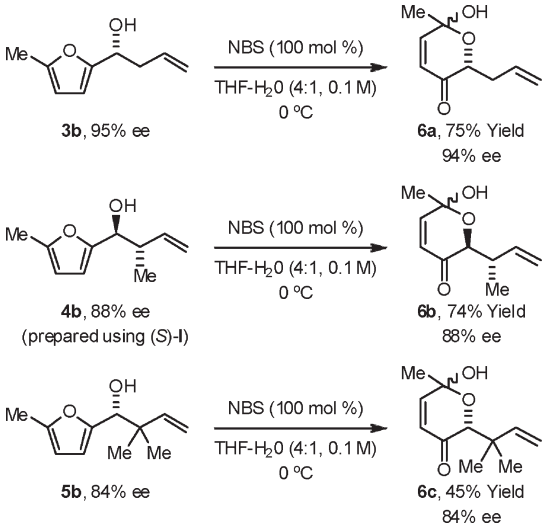
TABLE 6. Enantioselective Carbonyl *tert*-Prenylation of Furfurals via Iridium Catalyzed Transfer Hydrogenation[a]



entry	furan methanol	product	isolated yield (%)	ee (%)
1	R = H, **1a**	**5a**	82	88 (*R*)
2	R = Me, **1b**	**5b**	89	89 (*R*)
3	R = Ar, **1c**	**5c**	94	93 (*R*)

[a]As described for Table 1.

SCHEME 1. Achmatowicz Rearrangement of Optically Enriched Adducts 3b, 4b, and 5b[a]



[a]Yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary-phase HPLC analysis.

enantiomeric excess was observed at preexisting stereocenters, as determined by chiral stationary-phase HPLC analysis (Scheme 1).

In summary, we report that 5-substituted-2-furan methanols **1a**−**c** are subject to enantioselective carbonyl allylation, crotylation, and *tert*-prenylation upon exposure to allyl acetate, α-methyl allyl acetate, or 1,1,-dimethylallene in the presence of an *ortho*-cyclometalated iridium catalyst modified by (*R*)-Cl,MeO-BIPHEP, (*R*)-C3-TUNEPHOS, and (*R*)-SEGPHOS, respectively. In the presence of 2-propanol, but under otherwise identical conditions, the corresponding substituted furfurals **2a**−**c** are converted to identical products of allylation, crotylation, and *tert*-prenylation. Optically enriched products of carbonyl allylation, crotylation and reverse prenylation **3b**, **4b**, and **5b** engage in Achmatowicz rearrangement to furnish the corresponding γ-hydroxy-β-pyrones in good yield and with negligible erosion of enantiomeric excess at the preexisting stereocenters.

Experimental Section

General Procedure for the Preparation of Adducts 3a−c from Furan Methanols 1a−c. To a flame-dried resealable reaction tube purged with argon and containing a magnetic stirrer were added $[Ir(cod)Cl]_2$ (6.7 mg, 0.010 mmol, 2.5 mol %), (*R*)-Cl, MeO-BIPHEP (13.0 mg, 0.020 mmol, 5 mol %), 3-nitro-4-chlorobenzoic acid (8.1 mg, 0.040 mmol 10 mol %), Cs_2CO_3 (26.1 mg, 0.080 mmol, 20 mol %), and the furan methanol (0.40 mmol, 100 mol %). THF (2.0 mL, 0.2 M concentration with respect to the furan methanol) and allyl acetate (86 μL, 0.80 mmol, 200 mol %) were added, and the reaction mixture was allowed to stir at 100 °C for 24 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2) to furnish the corresponding products of allylation **3a−c**.

General Procedure for the Preparation of Adducts 3a−c from Furfurals 2a−c. To a flame-dried resealable reaction tube purged with argon and containing a magnetic stirrer were added $[Ir(cod)Cl]_2$ (6.7 mg, 0.010 mmol, 2.5 mol %), (*R*)-Cl,MeO-BIPHEP (13.0 mg, 0.020 mmol, 5 mol %), 3-nitro-4-chlorobenzoic acid (8.1 mg, 0.040 mmol 10 mol %), Cs_2CO_3 (26.1 mg, 0.080 mmol, 20 mol %), and the furfural (0.40 mmol, 100 mol %). THF (2.0 mL, 0.2 M concentration with respect to the furfural), *i*-PrOH (61 μL, 0.80 mmol, 200 mol %), and allyl acetate (86 μL, 0.80 mmol, 200 mol %) were added, and the reaction mixture was allowed to stir at 100 °C for 24 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2) to furnish the corresponding products of allylation **3a−c**.

General Procedure for the Preparation of Adducts 4a−c from Furan Methanols 1a−c. To a flame-dried resealable reaction tube purged with argon and containing a magnetic stirrer were added (*R*)-Ir-complex **I** (20.4 mg, 0.020 mmol, 5 mol %), K_3PO_4 (84.9 mg, 0.40 mmol, 100 mol %), and the corresponding furan methanol (0.40 mmol, 100 mol %). THF (0.2 mL, 2 M concentration with respect to the alcohol), H_2O (36 μL, 2.0 mmol, 500 mol %), and α-methyl allyl acetate (86 μL, 0.80 mmol, 200 mol %) were added, and the reaction mixture was allowed to stir at 70 °C for 48 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2) to furnish the corresponding products of crotylation **4a−c**.

General Procedure for the Preparation of Adducts 4a−c from Furfurals 2a−c. To a flame-dried resealable reaction tube purged with argon and containing a magnetic stirrer were added (*R*)-Ir-complex **I** (20.4 mg, 0.020 mmol, 5 mol %), K_3PO_4 (84.9 mg, 0.400 mmol, 100 mol %), and the corresponding furfural (0.40 mmol, 100 mol %). THF (0.2 mL, 2 M concentration with respect to the aldehyde), H_2O (36 μL, 2.0 mmol, 500 mol %), *i*-PrOH (61 μL, 0.80 mmol, 200 mol %), and α-methyl allyl acetate (86 μL, 0.80 mmol, 200 mol %) were added, and the reaction mixture was allowed to stir at 70 °C for 48 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2), under the conditions noted, to furnish the corresponding products of crotylation **4a−c**.

General Procedure for the Preparation of Adducts 5a−c from Furan Methanols 1a−c. To a flame-dried resealable reaction tube purged with nitrogen and containing a magnetic stirrer were added (*R*)-Ir-complex **II** (5 mol %) and the corresponding furan methanol (100 mol %). Toluene (1 M concentration with respect to the alcohol), 1,1-dimethylallene (200 mol %), and propionaldehyde (5 mol %) were added, and the reaction mixture was allowed to stir at 40 °C for 72 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2) to furnish the corresponding products of *tert*-prenylation **5a−c**.

General Procedure for the Preparation of Adducts 5a−c from Furfurals 2a−c. To a flame-dried resealable reaction tube purged with nitrogen and containing a magnetic stirrer were added (*R*)-Ir-complex **II** (5 mol %) and the corresponding furfural (100 mol %). Toluene (1 M concentration with respect to the aldehyde), 1,1-dimethylallene (200 mol %), and *i*-PrOH (200 mol %) were added, and the reaction mixture was allowed to stir at 40 °C for 72 h. The reaction mixture was concentrated in vacuo and purified by flash column chromatography (SiO_2) to furnish the corresponding products of *tert*-prenylation **5a−c**.

General Procedure for the Achmatowicz Rearrangement of Adducts 3b, 4b, and 5b. Alcohol **3b**, **4b**, or **5b** (100 mol %) was dissolved in aqueous THF (THF/H_2O, 4:1, 0.1 M), and the solution was cooled to 0 °C. *N*-Bromosuccinimide (100 mol %) was added portionwise while a temperature of 0 °C was maintained. After the reaction had gone to completion as determined by TLC analysis, the reaction mixture was diluted with dichloromethane and washed with KI (10% aqueous solution), $Na_2S_2O_4$ (15% aqueous solution), $NaHCO_3$ (10% aqueous solution), and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatography (SiO_2) to furnish the corresponding pyrones **6a**, **6b**, or **6c**, respectively.

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Supporting Information Available: Spectral data for all new compounds, including scanned images of ^1H and ^{13}C NMR spectra. Scanned images of chiral stationary-phase HPLC data. Single-crystal X-ray diffraction data for the Ir(BIPHEP)-(η-C_3H_5)(*C,O*-$O_2C_6H_3NO_2$). This material is available free of charge via the Internet at http://pubs.acs.org.