Synthetic Methods

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Enantioselective Allylation, Crotylation, and Reverse Prenylation of Substituted Isatins: Iridium-Catalyzed C–C Bond-Forming Transfer Hydrogenation**

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3-Substituted 3-hydroxy-oxindoles appear as substructures within a fascinating array of natural products, including the convulutamydines,[1a,b] maremycins,[1c,d] donaxaridines,[1e,f] dioxibrassinins,[1g,h,i] celogentin K,[1j] hydroxyglucoisatisins,[1k] and TMC-95A-D (Figure 1).[1l] Whereas catalytic asymmetric

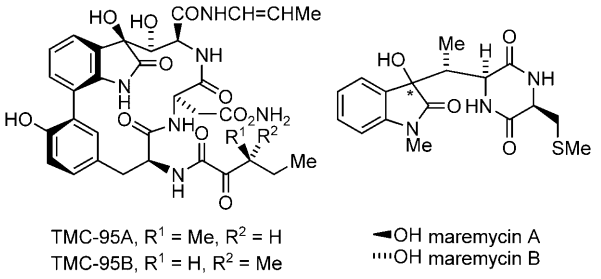

Figure 1. Examples of naturally occurring 3-substituted 3-hydroxy-oxindoles.

additions to isatins are known,[2–6] highly enantioselective catalytic allylation, crotylation, and reverse prenylation of isatins have remained elusive. In the course of developing hydrogen-mediated C–C couplings beyond hydroformylation,[7–15] chiral *ortho*-cyclometalated iridium *C*,*O*-benzoates were found to catalyze highly enantioselective carbonyl allylation,[14a,b] crotylation,[14c] and reverse prenylation[12d] under transfer-hydrogenation conditions. In contrast to classical allylation procedures which employ stoichiometric organometallic reagents,[16] transfer-hydrogenation protocols exploit allyl acetate, α-methyl allyl acetate, and 1,1-dimethylallene as precursors to transient allyl–, crotyl–, and prenyl–metal intermediates, respectively.[12,14a–c] To further evaluate the scope of this emergent methodology, catalytic enantioselective additions to ketones were explored.[17,18] In this account, we report that activated ketones in the form of substituted isatins are subject to highly enantioselective carbonyl allylation, crotylation, and reverse prenylation, constituting a convenient synthesis of optically enriched 3-substituted 3-hydroxy-oxindoles.

Our initial studies focused on the allylation of *N*-benzyl isatin (**1a**). Using the cyclometalated *C*,*O*-benzoate generated in situ from $[\{Ir(cod)Cl\}_2]$, biphep (biphep = 2,2′-bis(diphenylphosphino)biphenyl), and 4-chloro-3-nitrobenzoic acid,[14b] the coupling of allyl acetate (1000 mol%) to **1a** at 100 °C in tetrahydrofuran (0.2 M) delivered the tertiary homoallyl alcohol **2a** in 42% yield upon isolation. At lower loadings of allyl acetate (200 mol%) and with further optimization of reaction temperature, time, and concentration, the yield of homoallyl alcohol **2a** was increased to 77%. An assay of chelating chiral phosphine ligands was undertaken, which revealed dramatic enhancement in the level of asymmetric induction at lower reaction temperatures. However, lower temperatures also diminished conversion. This impasse was resolved by increasing the loading of isopropanol from 200 mol% to 400 mol%, which enabled conversion of *N*-benzyl isatin (**1a**) to the homoallyl alcohol **2a** in 73% yield and 91% enantiomeric excess using cth-(*R*)-p-phos (cth-(*R*)-p-phos = (*R*)-(+)-2,2′,6,6′-tetramethoxy-4,4′-bis(diphenylphosphino)-3,3′-bipyridine) as the ligand. Notably, under analogous reaction conditions employing our initially disclosed iridium catalyst modified by 3-nitrobenzoic acid,[14a,b] **2a** was obtained in 61% yield and 90% enantiomeric excess. These data further illustrate how catalyst performance is enhanced through structural variation of the *C*,*O*-benzoate moiety. Data pertaining to the optimization of the catalytic enantioselective allylation of *N*-benzyl isatin (**1a**) is tabulated in the Supporting Information.

Optimal reaction conditions identified for the conversion of *N*-benzyl isatin (**1a**) to the hydroxy oxindole **2a** were applied to substituted isatins **1a**–**1g** (Table 1). To our delight, the products of ketone allylation, **2a**–**2g**, were produced in moderate to excellent yields upon isolation (65–92%) with uniformly high levels of optical enrichment (91–96% *ee*). The absolute stereochemical assignments of the adducts **2a**–**2g** are based upon that determined for the 5-bromo derivative **2b** by single-crystal X-ray diffraction analysis using the anomalous dispersion method.

Given these favorable results, the crotylation of substituted isatins **1a**–**1g** was attempted under identical conditions employing α-methyl allyl acetate as the crotyl donor (Table 2). The products of ketone crotylation, **3a**–**3g**, were produced in moderate to excellent yields upon isolation (64–

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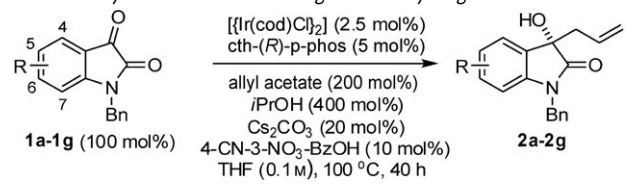
Table 1: Catalytic enantioselective allylation of *N*-benzyl isatins **1a–1g** by iridium-catalyzed C–C bond-forming transfer hydrogenation.[a]

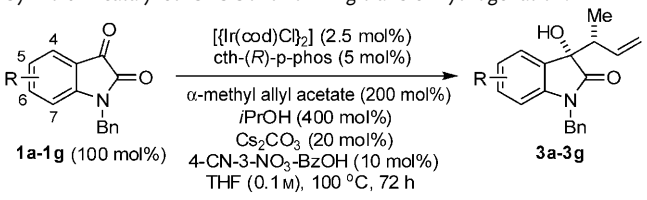


Entry	Isatin	Product	Yield [%]	*ee* [%]
1	**1a**: *N*-benzyl isatin	**2a**	73	91
2[b]	**1b**: 5-bromo-*N*-benzyl isatin	**2b**	83	94
3	**1c**: 5-methyl-*N*-benzyl isatin	**2c**	89	92
4	**1d**: 5-methoxy-*N*-benzyl isatin	**2d**	92	94
5	**1e**: 6-chloro-*N*-benzyl isatin	**2e**	73	96
6[b]	**1f**: 6-bromo-*N*-benzyl isatin	**2f**	80	94
7[c]	**1g**: 7-fluoro-*N*-benzyl isatin	**2g**	65	93

[a] All reactions were performed in 13×100 mm pressure tubes. Cited yields are of material isolated after silica gel chromatography. Enantiomeric excess was determined by chiral stationary-phase HPLC analysis. See the Supporting Information for further details. [b] 10 mol% loading of Cs_2CO_3 was used and the reaction was conducted for 72 h. [c] 400 mol% loading of allyl acetate was used.

87%) with moderate to excellent levels of optical enrichment (80–92% *ee*). In general, crotylation required longer reaction times (Table 2, entries 1, 2, and 5–7). Additionally, it was found that lower loadings of Cs_2CO_3 increased conversion in certain cases. The absolute stereochemical assignment of adducts **3a–3g** are based upon that determined for the 5-bromo derivative **3b** by single-crystal X-ray diffraction analysis using the anomalous dispersion method.

Table 2: Catalytic enantioselective crotylation of *N*-benzyl isatins **1a–1g** by iridium-catalyzed C–C bond-forming transfer hydrogenation.[a]

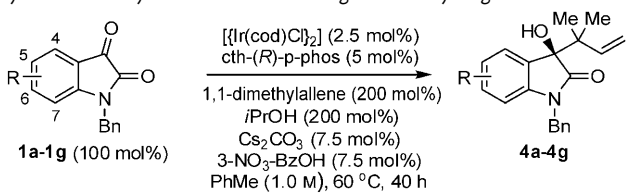


Entry	Isatin	Product	Yield [%]	*ee* [%], d.r.
1[b]	**1a**: *N*-benzyl isatin	**3a**	83	80, 13:1
2[f]	**1b**: 5-bromo-*N*-benzyl isatin	**3b**	72	86, 16:1
3[d,e]	**1c**: 5-methyl-*N*-benzyl isatin	**3c**	81	89, 18:1
4[d,e]	**1d**: 5-methoxy-*N*-benzyl isatin	**3d**	87	92, 29:1
5[b]	**1e**, 6-chloro-*N*-benzyl isatin	**3e**	70	91, 19:1
6[f]	**1f**: 6-bromo-*N*-benzyl isatin	**3f**	81	89, 15:1
7[b,c]	**1g**: 7-fluoro-*N*-benzyl isatin	**3g**	64	85, 19:1

[a] As described in Table 1 footnotes. [b] Used 10 mol% loading of Cs_2CO_3. [c] Used 400 mol% loading of allyl acetate. [d] Me-THF was used as the solvent. [e] The reaction was run for 40 h. [f] 5 mol% loading of [{Ir(cod)Cl}$_2$], 10 mol% loading of cth-(*R*)-p-phos, and 20 mol% loading of 4-CN-3-NO_2-BzOH were used.

Finally, the reverse prenylation of substituted isatins **1a–1g** was attempted (Table 3). To our delight, adducts **4a–4g** were generated in uniformly high yields (70–90%) and high

Table 3: Catalytic enantioselective prenylation of *N*-benzyl isatins **1a–1g** by iridium-catalyzed C–C bond-forming transfer hydrogenation.[a]



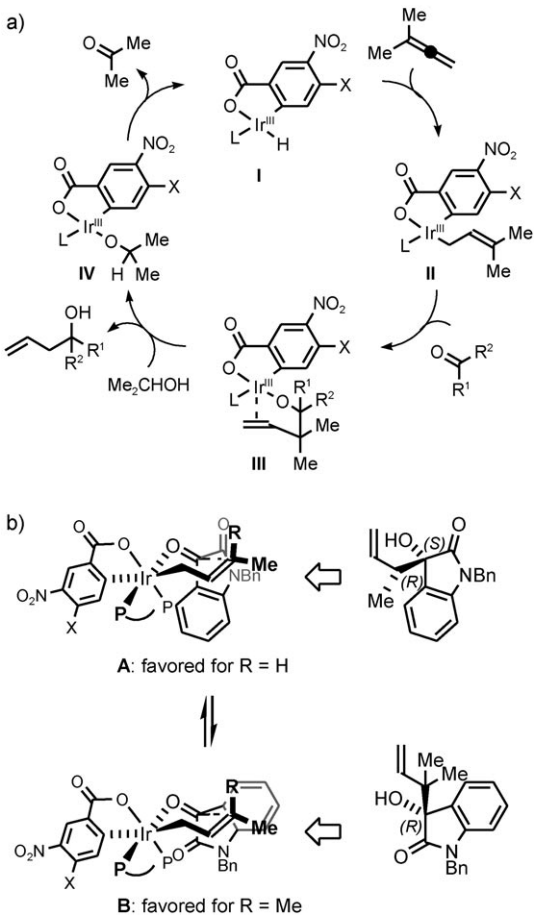
Entry	Isatin	Product	Yield [%]	*ee* [%]
1	**1a**: *N*-benzyl isatin	**4a**	90	96
2	**1b**: 5-bromo-*N*-benzyl isatin	**4b**	86	90
3	**1c**: 5-methyl-*N*-benzyl isatin	**4c**	79	93
4	**1d**: 5-methoxy-*N*-benzyl isatin	**4d**	81	96
5	**1e**: 6-chloro-*N*-benzyl isatin	**4e**	80	93
6[b]	**1f**: 6-bromo-*N*-benzyl isatin	**4f**	70	93
7[b]	**1g**: 7-fluoro-*N*-benzyl isatin	**4g**	79	94

[a] As described in Table 1 footnotes. [b] The reaction was run for 72 h.

levels of optical enrichment (90–96% *ee*) under mild reaction conditions. Notably, this transformation enables the creation of two contiguous quaternary carbon centers. The absolute stereochemical assignment of adducts **4a–4g** are based upon that determined for the 5-bromo derivative **4b** by single-crystal X-ray diffraction analysis using the anomalous dispersion method. Here, the enantiofacial selectivity of carbonyl addition is opposite to that observed in the case of allylation and crotylation.

The inversion in absolute stereochemistry observed in isatin reverse prenylation merits further explanation. The catalytic mechanism for carbonyl prenylation employing 1,1-dimethylallene is analogous to that previously reported for corresponding allylations and crotylations (Scheme 1a).[14b,c] Assuming isatin crotylation occurs through a chairlike transition structure and an (*E*)-σ-crotyl iridium intermediate, previously proposed absolute stereochemical models agree with the observed π-facial selectivity with respect to the crotyl partner.[14c] The latter observation suggests that isatin crotylation occurs by way of the transition structure **A**, whereas isatin prenylation occurs by way of the transition structure **B**. The basis of this partitioning may arise from nonbonded interactions of the axial methyl group of the σ-prenyl iridium intermediate with the amide π bond of isatin, which is presumably more destabilizing than nonbonded interactions of the axial methyl group with the electron-deficient rim of the arene (Scheme 1b).

In summary, we report the first enantioselective allylations, crotylations, and prenylations of isatin, which are achieved by isopropanol-mediated transfer hydrogenation. Unlike conventional allylation methodologies which employ stoichiometric quantities of allyl–metal reagents, the present method exploits allyl acetate, α-methyl allyl acetate, and 1,1-dimethylallene as precursors to transient allyl–, crotyl–, and prenyl–metal intermediates, respectively.[12,14a–c] To our knowledge, these studies represent the first examples of catalytic enantioselective ketone allylation, crotylation, and prenylation in the absence of stoichiometric amounts of allylmetal reagents. Future studies will focus on the develop-



Scheme 1. a) A simplified catalytic mechanism depicting isatin prenylation by transfer hydrogenation. b) A plausible stereochemical model accounting for the observed inversion in absolute stereochemistry in the prenylation of isatins. L = cth-(*R*)-p-phos (omitted for clarity).

ment of related C–C bond-forming transfer hydrogenations and synthetic applications of the methods reported herein.

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