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

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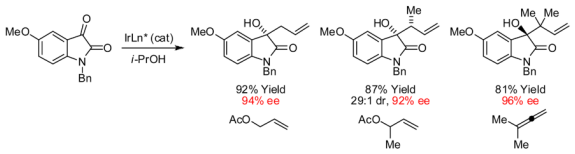
Oxindoles with a Twist

Transfer hydrogenation of substituted isatins in the presence of allyl acetate, α-methyl allyl acetate or 1,1,-dimethylallene employing an *ortho*-cyclometallated iridium catalyst modified by CTH-(*R*)-P-PHOS provides products of carbonyl allylation, crotylation and reverse prenylation, respectively, in highly enantiomerically enriched form. These studies represent the first use of activated ketones as electrophilic partners in asymmetric C-C bond forming transfer hydrogenation.



Keywords

Iridium; Allylation; Crotylation; Prenylation; Transfer Hydrogenation; Catalytic; Enantioselective

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] *While catalytic asymmetric additions to isatins are known,[2–6] highly enantioselective catalytic allylation, crotylation and reverse prenylation of isatins has remained elusive*. In the course developing hydrogen-mediated C-C couplings beyond hydroformylation,[7–15] chiral *ortho*-cyclometallated 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 that 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 prenylmetal 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

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reverse prenylation, constituting a convenient synthesis of optically enriched 3-substituted-3-hydroxy-oxindoles.

Our initial studies focused on the asymmetric allylation of *N*-benzyl isatin **1a**. Using the cyclometallated *C,O*-benzoate generated *in situ* from $[Ir(cod)Cl]_2$, BIPHEP and 4-chloro-3-nitrobenzoic acid,[14b] the coupling of allyl acetate (1000 mol%) to **1a** at 100 °C in THF (0.2 M) delivered the tertiary homoallyl alcohol **2a** in 42% isolated yield. Under otherwise identical conditions, but with a lower loading of allyl acetate (200 mol%) and optimization of reaction temperature, reaction time, and concentration, the isolated 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 homoallyl alcohol **2a** in 73% isolated yield and 91% enantiomeric excess using CTH-(*R*)-P-PHOS as ligand. Notably, under analogous conditions employing our initially disclosed iridium catalyst modified by 3-nitrobenzoic acid,[14a,b] **2a** is obtained in 61% isolated 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 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 isolated yield (65–92% yield) with uniformly high levels of optical enrichment (91–96% ee). The absolute stereochemical assignment of adducts **2a**–**2g** are based upon that determined for the 5-bromo-dervative **2b** *via* 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 isolated yield (64–87% yield) with moderate to excellent levels of optical enrichment (80–92% ee). In general, crotylation required longer reaction times (Table 2, entries 1, 2, 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-dervative **3b** *via* single crystal X-ray diffraction analysis using the anomalous dispersion method.

Finally, the reverse prenylation of substituted isatins **1a**–**1g** was attempted (Table 3). To our delight, adducts **4a**–**4g** were generated in uniformly high isolated yields (70–90% yield) and levels of optical enrichment (90–96 % ee) under mild conditions. Notably, this transformation enables creation of two contiguous quaternary carbon centers. The absolute stereochemical assignment of adducts **4a**–**4g** are based upon that determined for the 5-bromo-dervative **4b** *via* 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 1, left).14b,c Assuming isatin crotylation occurs through a chair-like transition structure and an (*E*)-σ-crotyl iridium intermediate, previously proposed absolute stereochemical models agrees with the observed π-facial selectivity with respect to the crotyl partner.[14c] The latter

observation suggests that isatin crotylation occurs by way of transition structure **A**, whereas isatin prenylation occurs by way of transition structures **B**. The basis of this partitioning may arise from non-bonded 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 non-bonded interactions of the axial methyl group with the electron-deficient rim of the arene (Scheme 1, right).

In summary, we report the first enantioselective allylations, crotylations and prenylations of isatin, which are achieved via isopropanol-mediated transfer hydrogenation. Unlike conventional allylation methodologies that employ stoichiometric quantities of allylmetal reagents, the present method exploits allyl acetate, α-methyl allyl acetate and 1,1-dimethylallene as precursors to transient allyl-, crotyl- and prenylmetal intermediates, respetively.[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 allylmetal reagents*. Future studies will focus on the development of related C-C bond forming transfer hydrogenations and synthetic applications of the methods reported herein.

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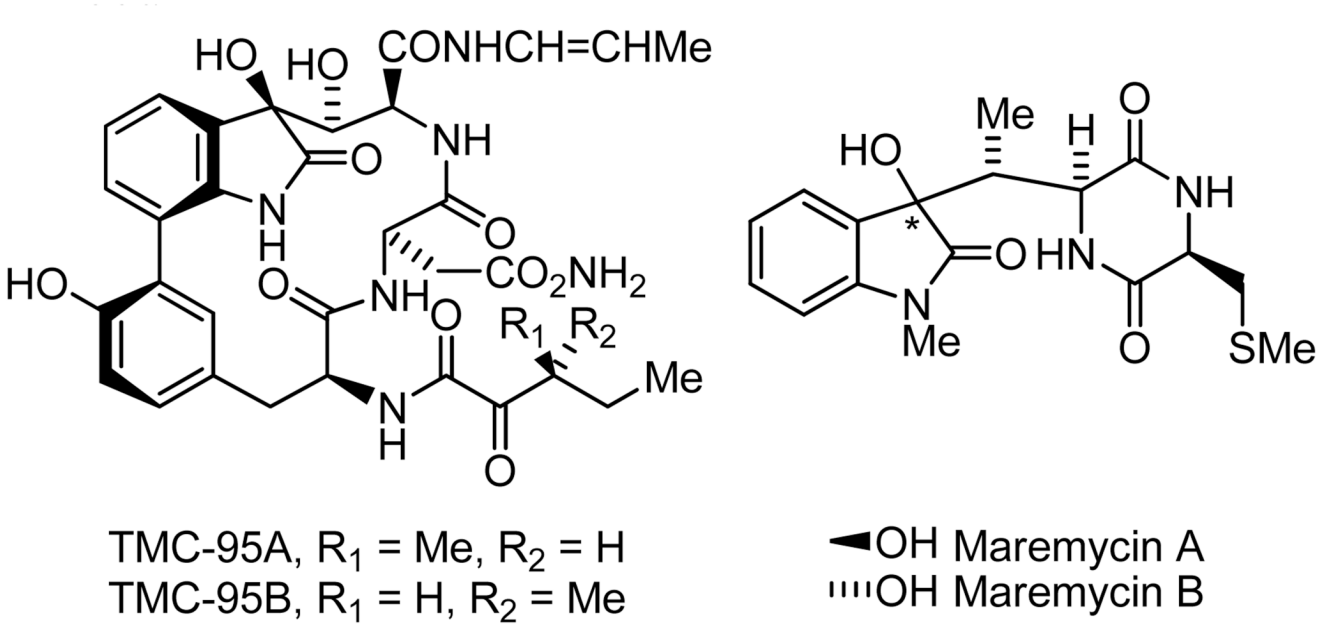
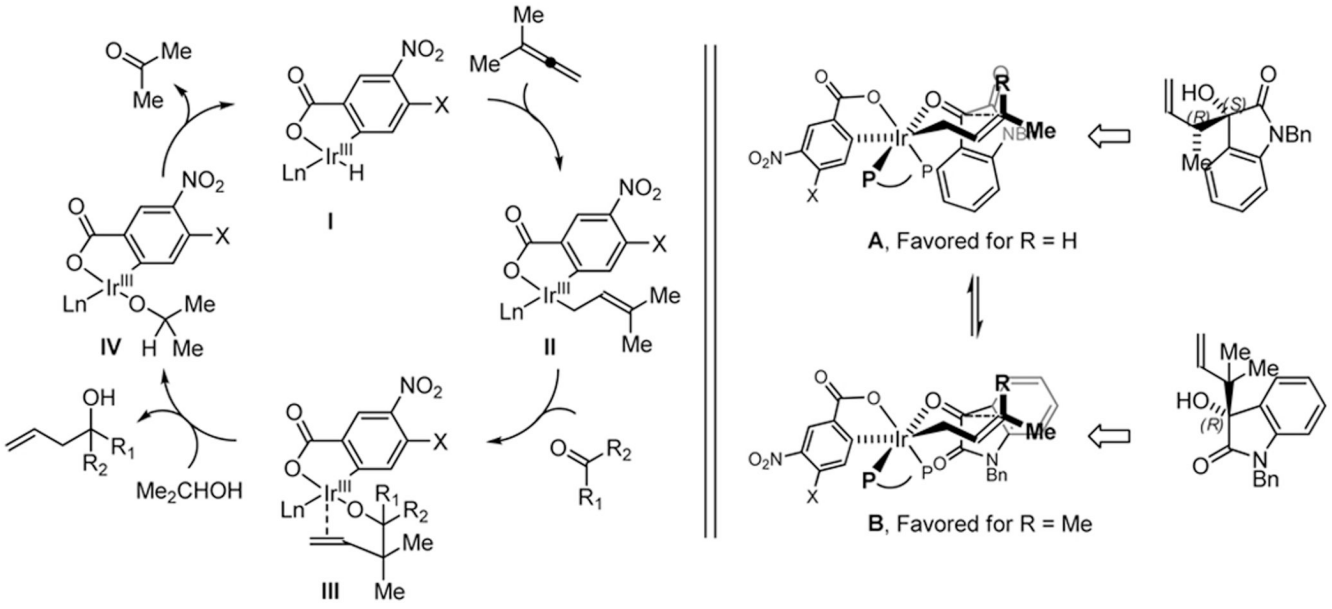


Figure 1.
Examples of naturally occurring 3-substituted-3-hydroxy-oxindoles.



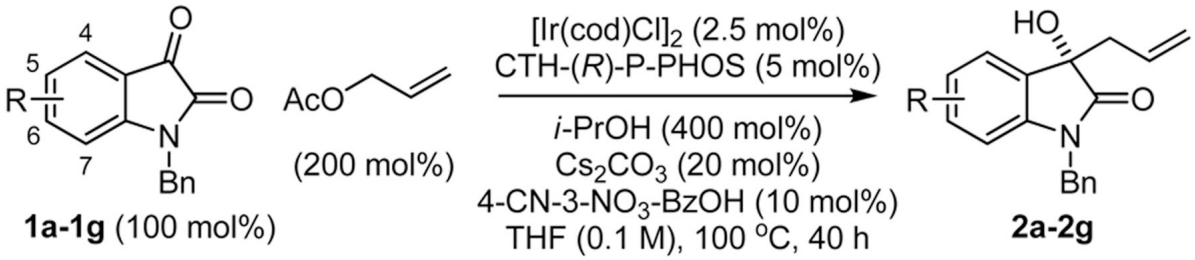
Scheme 1.

A simplified catalytic mechanism depicting isatin prenylation via transfer hydrogenation (left) and a plausible stereochemical model accounting for the observed inversion in absolute stereochemistry in the prenylation of isatins (right).a

[a]Ln = CTH-(*R*)-P-PHOS (omitted for clarity).

Table 1

Catalytic enantioselective allylation *N*-benzyl isatins **1a–1g** *via* iridium catalyzed C-C bond forming transfer hydrogenation.



Entry	Isatins 1a–1g	Products	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

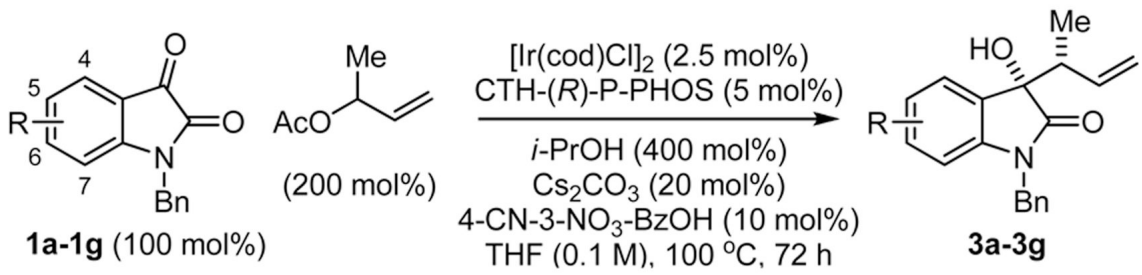
[a] All reactions were performed in 13 × 100 mm pressure tubes. Cited yields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See supporting information for further details.

[b] 10 mol% loading of Cs_2CO_3 was used and the reaction was conducted for 72 hours.

[c] 400 mol% loading of allyl acetate was used.

Table 2

Catalytic enantioselective crotylation of *N*-benzyl isatins **1a–1g** *via* iridium catalyzed C-C bond forming transfer hydrogenation.



Entry	Isatins 1a–1g	Products	Yield (%)	ee (%), dr
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 2 footnotes.

[b] 10 mol% loading of Cs_2CO_3 was used.

[c] 400 mol% loading of allyl acetate was used.

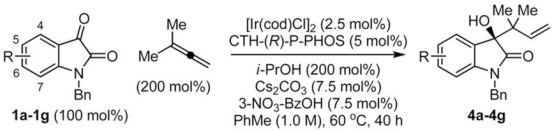
[d] Me-THF was used as solvent.

[e] The reaction was run for 40 hours.

[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.

Table 3

Catalytic enantioselective prenylation of *N*-benzyl isatins **1a–1g** *via* iridium catalyzed C-C bond forming transfer hydrogenation.



Entry	Isatins 1a–1g	Products	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 2 footnotes.

[b] The reaction was run for 72 hours.