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Enantioselective Carbonyl Reverse Prenylation from the Alcohol or Aldehyde Oxidation Level Employing 1,1-Dimethylallene as the Prenyl Donor

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Abstract

Enantioselective transfer hydrogenation of 1,1-dimethylallene **1a** in the presence of aromatic, α,β -unsaturated or aliphatic aldehydes **2a-2i** mediated by isopropanol and employing a cyclometallated iridium *C,O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid and (*S*)-SEGPHOS delivers products of reverse prenylation **4a-4i** in good to excellent isolated yields (65-96%) and enantioselectivities (87-93% ee). In the absence of isopropanol, enantioselective carbonyl reverse prenylation is achieved directly from the alcohol oxidation level to furnish an equivalent set of adducts **4a-4i** in good to excellent isolated yields (68-94%) and enantioselectivities (86-91% ee). Competition and isotopic labeling experiments suggest rapid alcohol-aldehyde redox equilibration in advance of carbonyl addition, and capture of the kinetically formed π -allyl complex at a rate faster than reversible β -hydride elimination-hydrometallation. This protocol represents an alternative to the use of allylboron reagents in enantioselective carbonyl reverse prenylation and represents the first use of allenes in enantioselective C-C bond forming transfer hydrogenation.

In the course of studies aimed at the development of C-C bond forming hydrogenations,¹⁻⁶ highly enantioselective carbonyl allylation^{3d,e} and crotylation^{3f} employing allyl acetate and α -methyl allyl acetate as allyl and crotyl donors, respectively, were achieved under the conditions of iridium catalyzed transfer hydrogenation. For such reductive couplings, isopropanol is exploited as the hydrogen donor. Remarkably, primary alcohols may serve dually as hydrogen donors and aldehyde precursors, enabling carbonyl allylation or crotylation directly from the alcohol oxidation level.

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Supporting information available: Experimental procedures, HPLC data, and spectral data for new compounds. Single crystal X-ray diffraction data for (*S*)-Ir-Complex **I**. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

With catalytic asymmetric methods for polyacetate and polypropionate construction in hand, an asymmetric prenylation protocol was sought. However, attempted use of allylic acetates as prenyl donors (2-methyl-3-butenyl acetate or 3-methyl-2-butenyl acetate) was unsuccessful. A potential solution to this problem resides in the use of 1,1-dimethylallene **1a** as prenyl donor. However, in earlier studies on the iridium catalyzed reductive coupling of 1,1-dimethylallene **1a** to aldehydes mediated by gaseous hydrogen, it was found that highly activated aldehydes were required and, despite an extensive assay of chiral phosphine ligands, only low levels of optical enrichment were observed.^{3a}

Here, exploiting an *ortho*-cyclometallated iridium *C,O*-benzoate catalyst recently developed in our laboratory,^{3e} we report an efficient protocol for enantioselective catalytic carbonyl reverse prenylation employing 1,1-dimethylallene **1a** as the prenyl donor under transfer hydrogenation conditions.⁷ Unlike the related process employing elemental hydrogen,^{3a} unactivated aldehydes couple efficiently. Additionally, the transfer hydrogenative protocol enables asymmetric carbonyl prenylation from the alcohol or aldehyde oxidation level, as demonstrated by the formation of identical sets of optically enriched adducts. This process constitutes an alternative to the use of stoichiometric metallic reagents in enantioselective carbonyl reverse prenylation⁸⁻¹² and represents the first use of allenes in enantioselective C-C bond forming transfer hydrogenation.

Initial studies focused on the coupling of 1,1-dimethylallene **1a** to aldehyde **2a**. After extensive study, which involved a nearly exhaustive assay of commercial chelating chiral phosphine ligands, optical results (**4a**, 94% yield, 89% ee, Table 1) were achieved upon exposure of a toluene solution of **1a** and **2a** to the cyclometallated iridium *C,O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid and (*S*)-SEGPHOS¹³ (eqn. 1), designated “(*S*)-Ir-Complex **I**,” in the presence of isopropanol (200 mol%). In contrast to related allyl acetate mediated allylations and crotylations, 1,1-dimethylallene **1a** couples at relatively low temperature in the absence of basic additives.

To explore the scope of this process, 1,1-dimethylallene **1a** was coupled to a structurally diverse set of aldehydes **2a-2i** (Table 1). Aromatic aldehydes **2a-2c**, α,β -unsaturated aldehydes **2d** and **2e**, and aliphatic aldehydes **2f-2i** are subject to reverse prenylation to furnish adducts **4a-4i** in good to excellent isolated yields (65-96%) and enantioselectivities (87-93% ee). In the absence of isopropanol, enantioselective carbonyl reverse prenylation occurs directly from the alcohol oxidation level to furnish an identical set of adducts **4a-4i**, once again with good to excellent isolated yields (68-94%) and enantioselectivities (86-91% ee). Especially noteworthy is the conversion of terpene **3e** to sesquiterpene **4e** in the absence of any conventional preactivation of the reactants.

To gain further mechanistic insight, a crossover experiment was performed at 50 °C in the absence of isopropanol using the achiral cyclometallated iridium *C,O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid and BIPHEP. Exposure of 1,1-dimethylallene **1a** to equimolar quantities of **2a** and **3b** under the aforementioned conditions provides **4a** and **4b** in

87% combined yield in a 1:1.2 ratio, respectively (eqn. 2, Scheme 1). Exposure of 1,1-dimethylallene **1a** to equimolar quantities of **3a** and **2b** under otherwise identical conditions provides **4a** and **4b** in 95% yield in a 1:1.6 ratio, respectively (eqn. 3, Scheme 1). These experiments suggest rapid alcohol-aldehyde redox equilibration in advance of carbonyl addition.

Isotopic labeling experiments also were performed at 50 °C using the achiral cyclometallated iridium *C,O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid and BIPHEP. Using *d*₈-isopropanol as terminal reductant, aldehyde **2a** is transformed to *deuterio-4a*, which incorporates deuterium at the interior vinylic position (97% ²H) and the terminal vinylic position (3% ²H) (eqn. 4, Scheme 1). Use of *deuterio-3a* in the absence of isopropanol delivers *deuterio-4a*, which incorporates deuterium at the interior vinylic position (95% ²H) and at the carbinol methine (>99% ²H) (eqn. 5, Scheme 1). High fidelity incorporation of deuterium suggests that capture of the kinetically formed π -allyl complex is faster than reversible β -hydride elimination-hydrometallation.

In summary, we report the first use of allenes in enantioselective C-C bond forming transfer hydrogenation, as demonstrated by the development of an effective protocol for carbonyl reverse prenylation from the alcohol or aldehyde oxidation level. Future studies will focus on related alcohol-unsaturate C-C couplings, including diastereo- and enantioselective carbonyl crotylations employing 1,3-butadiene.

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Scheme 1. Isotopic labeling and competition experiments.^a

^aYields are of material isolated by silica gel chromatography. See Supporting Information for detailed experimental procedures.

Table 1Enantioselective carbonyl reverse prenylation from the aldehyde oxidation level.^a

2a, R = Ph
2d, R = CH=CHPh
2g, R = (CH₂)₂OBn

94% Yield (48 hrs)
89% ee (40 °C), **4a**

2a, R = Ph
2d, R = CH=CHPh
2g, R = (CH₂)₂OBn

81% Yield (48 hrs)
93% ee (40 °C), **4d**

85%
93%

2a, R = Ph
2d, R = CH=CHPh
2g, R = (CH₂)₂OBn

65% Yield (72 hrs)
89% ee (60 °C), 4g^b

^aYields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. Absolute stereochemistry was assigned by correlation of **4a**, **4d** and **4i** to known compounds. See Supporting Information for details.

^bPhCl was used as solvent.

Table 2Enantioselective carbonyl reverse prenylation from the alcohol oxidation level.^a

3a, R = Ph
3d, R = CH=CHPh
3g, R = (CH₂)₂OBn

85% Yield (15 hrs)
86% ee (40 °C), 4a

80
90

3a, R = Ph
3d, R = CH=CHPh
3g, R = (CH₂)₂OBn

84% Yield (28 hrs)
87% ee (30 °C), **4d**

3a, R = Ph
3d, R = CH=CHPh
3g, R = (CH₂)₂OBn

68% Yield (72 hrs)
88% ee (50 °C), 4g^b

^aYields are of material isolated by silica gel chromatography. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. Absolute stereochemistry was assigned by correlation of **4a**, **4d** and **4i** to known compounds. See Supporting Information for details.

^bPhCl was used as solvent.