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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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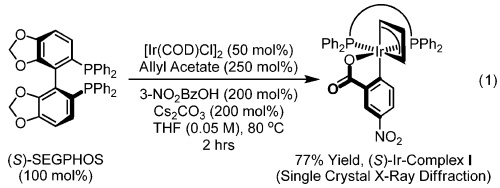
In the course of studies aimed at the development of C−C bond-forming hydrogenations,[1−6] highly enantioselective carbonyl allylation[3d,e] and crotylation[3f] employing allyl acetate and α-methyl allyl acetate as allyl and crotyl donors, respectively, were achieved under the conditions of iridium-catalyzed transfer hydrogenation. For such reductive couplings, 2-propanol was 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.

With catalytic asymmetric methods for polyacetate and polypropionate construction in hand, an asymmetric prenylation protocol was sought. However, attempted use of allylic acetates (2-methyl-3-butenyl acetate or 3-methyl-2-butenyl acetate) as prenyl donors was unsuccessful. A potential solution to this problem resides in the use of 1,1-dimethylallene **1a** as a prenyl donor. However, in earlier studies on the iridium-catalyzed reductive coupling of **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 enantiomeric enrichment were observed.[3a]

Here, exploiting an ortho-cyclometalated iridium *C*,*O*-benzoate catalyst recently developed in our laboratory,[3e] we report an efficient protocol for enantioselective catalytic carbonyl reverse prenylation employing **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 enantiomerically enriched adducts. *This process constitutes an alternative to the use of stoichiometric metallic reagents in enantioselective carbonyl reverse prenylation*[8−12] *and represents the first use of allenes in enantioselective C−C bond-forming transfer hydrogenation.*

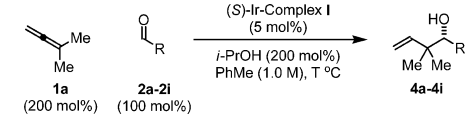
Initial studies focused on the coupling of **1a** to benzaldehyde (**2a**). After extensive study involving a nearly exhaustive assay of commercial chelating chiral phosphine ligands, optimal results (**4a**, 94% yield, 89% ee, Table 1) were achieved upon exposure of a toluene solution of **1a** and **2a** to the cyclometalated iridium *C*,*O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid, and (*S*)-SEGPHOS,[13] designated "(*S*)-Ir-Complex **I**" (eq 1), in the



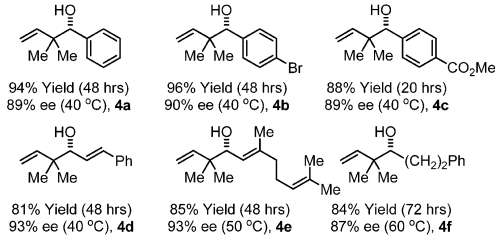
(1)

presence of 2-propanol (200 mol %). In contrast to related allyl acetate-mediated allylations and crotylations, **1a** couples at relatively low temperature in the absence of basic additives.

Table 1. Enantioselective Carbonyl Reverse Prenylation from the Aldehyde Oxidation Level[a]



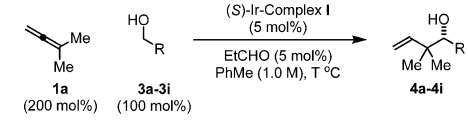
2a, R = Ph	**2b**, R = *p*-BrPh	**2c**, R = *p*-(CO_2Me)Ph
2d, R = CH=CHPh	**2e**, R = Geranyl	**2f**, R = $(CH_2)_2$Ph
2g, R = $(CH_2)_2$OBn	**2h**, R = $(CH_2)_3$OBn	**2i**, R = $(CH_2)_7$Me



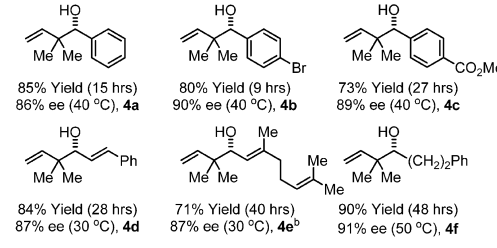
94% Yield (48 hrs), 89% ee (40 °C), **4a**
96% Yield (48 hrs), 90% ee (40 °C), **4b**
88% Yield (20 hrs), 89% ee (40 °C), **4c**
81% Yield (48 hrs), 93% ee (40 °C), **4d**
85% Yield (48 hrs), 93% ee (50 °C), **4e**
84% Yield (72 hrs), 87% ee (60 °C), **4f**
65% Yield (72 hrs), 89% ee (60 °C), **4g**[b]
86% Yield (48 hrs), 93% ee (50 °C), **4h**
71% Yield (48 hrs), 92% ee (50 °C), **4i**[b]

[a] Yields 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** with known compounds. See the Supporting Information for details. [b] PhCl was used as the solvent.

Table 2. Enantioselective Carbonyl Reverse Prenylation from the Alcohol Oxidation Level[a]



3a, R = Ph	**3b**, R = *p*-BrPh	**3c**, R = *p*-(CO_2Me)Ph
3d, R = CH=CHPh	**3e**, R = Geranyl	**3f**, R = $(CH_2)_2$Ph
3g, R = $(CH_2)_2$OBn	**3h**, R = $(CH_2)_3$OBn	**3i**, R = $(CH_2)_7$Me



85% Yield (15 hrs), 86% ee (40 °C), **4a**
80% Yield (9 hrs), 90% ee (40 °C), **4b**
73% Yield (27 hrs), 89% ee (40 °C), **4c**
84% Yield (28 hrs), 87% ee (30 °C), **4d**
71% Yield (40 hrs), 87% ee (30 °C), **4e**[b]
90% Yield (48 hrs), 91% ee (50 °C), **4f**
68% Yield (72 hrs), 88% ee (50 °C), **4g**[b]
87% Yield (48 hrs), 91% ee (50 °C), **4h**
94% Yield (48 hrs), 90% ee (50 °C), **4i**

[a] See footnote [a] of Table 1. [b] PhCl was used as the solvent.

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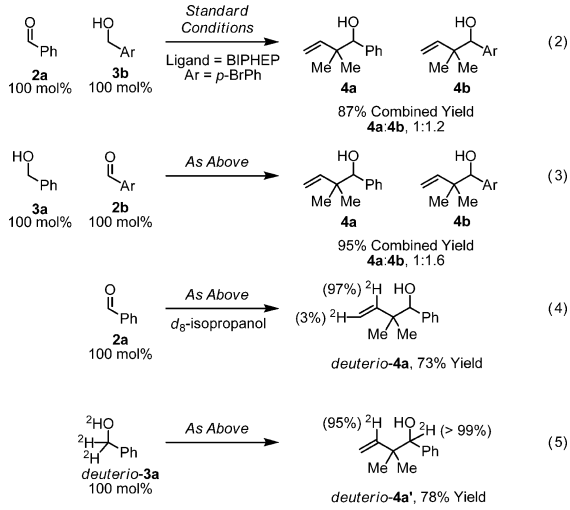
To explore the scope of this process, **1a** was coupled to a structurally diverse set of aldehydes **2a**−**i** (Table 1). Aromatic aldehydes **2a**−**c**, α,β-unsaturated aldehydes **2d** and **2e**, and aliphatic aldehydes **2f**−**i** were subject to reverse prenylation to furnish adducts **4a**−**i** in good to excellent isolated yields (65−96%) and enantioselectivities (87−93% ee). In the absence of 2-propanol, enantioselective carbonyl reverse prenylation occurred directly from the alcohol oxidation level to furnish an identical set of adducts **4a**−**i**, once again with good to excellent isolated yields (68−94%) and enantioselectivities (86−91% ee) (Table 2). Especially noteworthy is the conversion of terpene **3e** to sequiterpere **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 2-propanol using the achiral cyclometalated iridium *C*,*O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid, and BIPHEP. Exposure of **1a** to equimolar quantities of **2a** and **3b** under the aforementioned conditions provided **4a** and **4b**, respectively, in 87% combined yield in a 1:1.2 ratio (eq 2 in Scheme 1). Exposure of **1a** to equimolar quantities

Scheme 1. Isotopic Labeling and Competition Experiments[a]



[a] Yields are of material isolated by silica gel chromatography. See the Supporting Information for detailed experimental procedures.

of **3a** and **2b** under otherwise identical conditions provided **4a** and **4b**, respectively, in 95% yield in a 1:1.6 ratio (eq 3 in 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 cyclometalated iridium *C*,*O*-benzoate derived from allyl acetate, *m*-nitrobenzoic acid, and BIPHEP. When 2-propanol-d_8 was used as the terminal reductant, aldehyde **2a** was transformed to *deuterio*-**4a**, which incorporates deuterium at the interior vinylic position (97% ^{2}H) and the terminal vinylic position (3% ^{2}H) (eq 4 in Scheme 1). Use of *deuterio*-**3a** in the absence of 2-propanol delivered *deuterio*-**4a′**, which incorporates deuterium at the interior vinylic position (95% ^{2}H) and the carbinol methine (>99% ^{2}H) (eq 5 in Scheme 1). High-fidelity incorporation of deuterium suggests that capture of the kinetically formed π-allyl complex is faster than reversible β-hydride elimination−hydrometalation.

In summary, we have reported 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−unsaturated C−C couplings, including diastereo- and enantioselective carbonyl crotylations employing 1,3-butadiene.

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

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