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Iridium Catalyzed Hydrocarboxylation of 1,1-Dimethylallene: Byproduct-Free Reverse Prenylation of Carboxylic Acids

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Abstract

Exposure of carboxylic acids 1a–12a to commercially available 1,1-dimethylallene in the presence of substoichiometric quantities of an iridium catalyst prepared *in situ* from $[\text{Ir}(\text{cod})\text{Cl}]_2$ and BIPHEP provides the corresponding 1,1-dimethylallyl (reverse prenyl) esters 1b–12b in 74–92% isolated yield. This protocol represents the first branch-regioselective allene hydrocarboxylation. Stoichiometric byproducts are not generated in this process and protecting groups are not required for alcohols, phenols and indolic amines.

As part of a broad program aimed at the development of C–C bond forming hydrogenations,¹ we recently demonstrated that byproduct-free reverse prenylation of carbonyl compounds could be achieved under the conditions of iridium catalyzed hydrogenative C–C coupling using 1,1-dimethylallene as an allyl metal equivalent.² Later, it was found that carbonyl reverse prenylation, crotylation and allylation could be achieved under the conditions of transfer hydrogenation employing isopropanol as terminal reductant.^{2b} Finally, it was shown that carbonyl reverse prenylation, crotylation and allylation could be achieved *from alcohol oxidation level* by simply using the alcohol as both terminal reductant and aldehyde precursor.^{2b}

In the course of these studies, it was found that exposure of carboxylic acids to 1,1-dimethylallene in the presence of an iridium catalyst prepared *in situ* from $[\text{Ir}(\text{cod})\text{Cl}]_2$ and BIPHEP enables formation of the corresponding 1,1-dimethylallyl (reverse prenyl) esters. Withstanding the results described herein, only a single example of metal catalyzed allene hydrocarboxylation has been reported by Yamamoto under the conditions of palladium catalysis.^{3,4,5,6} The palladium catalyzed hydrocarboxylations are restricted to the use of aryl

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Supporting Information Available. Spectral data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS). This material is available free of charge *via* the internet at <http://pubs.acs.org>.

allenes, as the putative allyl palladium intermediates are prone to β -hydride elimination to furnish dienes.

Additionally, under the conditions of palladium catalysis, hydrocarboxylation occurs at the less substituted allene terminus to furnish linear allylic esters. The complementary regiochemistry encountered in our initial observations of the iridium catalyzed allene hydrocarboxylations, along with the commercial availability of 1,1-dimethylallene, prompted us to examine the scope of this byproduct-free reverse prenylation protocol.

Preliminary studies focused on the coupling of 1,1-dimethylallene to benzoic acid **1a**. Eventually it was found that the iridium catalyst prepared *in situ* from $[\text{Ir}(\text{cod})\text{Cl}]_2$ and BIPHEP (2 mol%) efficiently converts benzoic acid **1a** to the corresponding reverse prenyl ester **1b** (84% yield) using only a modest excess of 1,1-dimethylallene (120 mol%). These optimized conditions were applied to *para*-substituted benzoic acids **2a–5a**. The corresponding reverse prenyl esters **2b–5b** were isolated in excellent yields (Table 1, entry 1). Notably, the conversion of *para*-hydroxy benzoic acid **5a** to reverse prenyl ester **5b** does not require protection of the phenolic hydroxyl moiety. As demonstrated by the formation of **6b** and **7b**, heterocyclic aromatic carboxylic acids participate in the coupling (Table 1, entries 2 and 3). In the case of **7a**, protection of the indolic amine is not required. α,β -Unsaturated carboxylic acids **8a** and **9a** are efficiently transformed to the reverse prenyl esters **8b** and **9b**, respectively (Table 1, entries 4 and 5). Notably, the stereochemical integrity of the *cis*-configured olefin of the maleic diester **9b** is maintained. As demonstrated by the formation of adducts **10b** and **11b**, α -hydroxy acids undergo reverse prenylation in the absence of hydroxyl protecting groups (Table 1, entries 6 and 7). Finally, the applicability of this reverse prenylation protocol to α -amino acids is demonstrated by the formation **12b** (Table 1, entry 8).

A plausible catalytic mechanism is as follows. Protonation of the metal by the carboxylic acid, which is equivalent to O-H oxidative addition, delivers $\text{LnIr}(\text{H})(\text{Cl})(\text{O}_2\text{CR})$.⁷ Hydrometallation of 1,1-dimethylallene generates an iridium allyl,⁸ which upon C-O reductive elimination⁹ from the more substituted σ -allyl haptomer delivers the reverse prenyl ester and releases LnIrCl to close the catalytic cycle (Scheme 1).

To gain further insight into the catalytic mechanism, 1,1-dimethylallene was coupled to deuterio-benzoic acid (*O*-²H)-**1a**. The product *deuterio*-**1b** incorporates deuterium at both the interior vinylic position (63%) and exterior vinylic position (9.8%). Additionally, a small quantity of deuterium is incorporated at the *ortho*-position of the benzoate (0.6%). Incomplete deuterium incorporation may be due to adventitious moisture or an exchange of ¹H-²H between the iridium hydride intermediate and the *ortho*-hydrogens of BIPHEP.^{10, 11} 1,1-Dimethylallene also was coupled to benzoic acid-2,3,4,5,6-d₅ (²H)₅-**1a**. The product, d₅-*deuterio*-**1b**, does not incorporate deuterium in the reverse prenyl moiety, a small loss of deuterium at the *ortho*-position of the benzoate was observed (96%) (Scheme 2).

To establish whether the hydrocarboxylation is reversible, the reverse prenyl ester **2b** was exposed to benzoic acid **1a** under otherwise standard reaction conditions. The reverse prenyl ester **2b** was recovered in 96% isolated yield. The reverse prenyl ester **1b** was not detected. The absence of carboxylate exchange suggests irreversible hydrocarboxylation (Scheme 3).

In summary, we report an efficient byproduct-free conversion of carboxylic acids to reverse prenyl esters through the branch-regioselective hydrocarboxylation of 1,1-dimethylallene under the conditions of iridium catalysis. Future studies will focus on the development of related protocols for the enantioselective hydrocarboxylation and hydroamination of nonsymmetric 1,1-disubstituted allenes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Scheme 1.
Proposed catalytic mechanism.

Scheme 2.
Isotopic labeling experiments.

Scheme 3.

Negligible carboxylate exchange suggests irreversible hydrocarboxylation.

Table 1

Substrate	Product	Yield %
9a	9b	82 ^c

Substrate	Product	Yield%
10b	74

Substrate	Product	Yield%
<p>11a</p>	<p>11b</p>	77c

Substrate	Product	Yield%
12b	74

^c For diacids **9a** and **11a**, 240 mol% of 1,1-dimethylallene was used.