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

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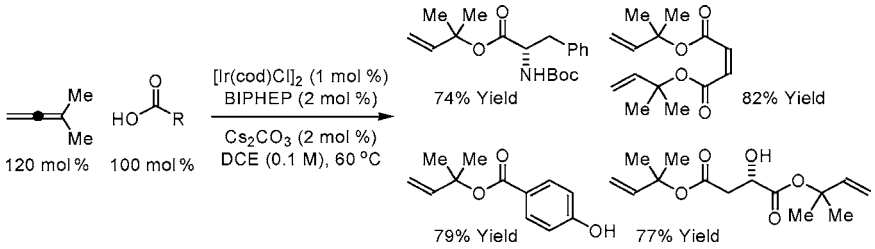
ABSTRACT



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 [Ir(cod)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 2-propanol 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 [Ir(cod)Cl]$_2$ and BIPHEP enables formation of the corresponding 1,1-dimethylallyl (reverse prenyl) esters. Excluding the results described herein, only a single example of metal-catalyzed allene hydrocarboxylation has been reported by Yamamoto under the conditions of palladium catalysis.[3−6] The palladium-catalyzed hydrocarboxylations are restricted to the use of arylallenes, as the putative allylpalladium 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

(1) For reviews on hydrogenative C−C coupling, see: (a) Ngai, M.-Y.; Kong, J. R.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (b) Iida, H.; Krische, M. J. *Top. Curr. Chem.* **2007**, *279*, 77. (c) Skucas, E.; Ngai, M.-Y.; Komanduri, V.; Krische, M. J. *Acc. Chem. Res.* **2007**, *40*, 1394.

(2) (a) Skucas, E.; Bower, J.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12678. (b) Bower, J.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134.

(3) Al-Masum, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 3809.

(4) For reviews, see: (a) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1998**, *28*, 199. (b) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067.

(5) A single example of palladium-catalyzed cyclohexadiene hydrocarboxylation has been reported; see: Utsunomiya, M.; Kawatsura, M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5865.

(6) For Brønsted acid catalyzed hydrocarboxylation of unactivated olefins, see: Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175.

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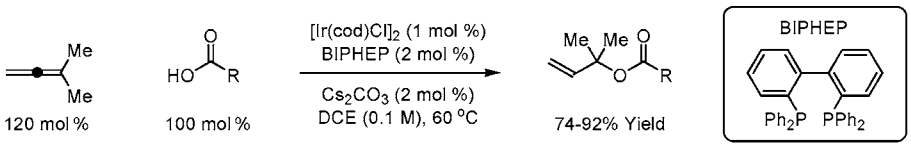
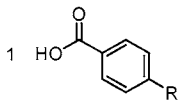
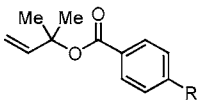
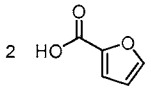
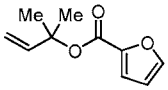
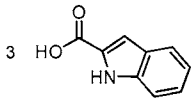
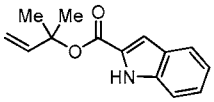
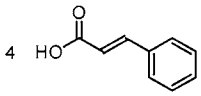
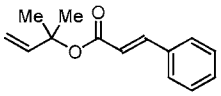
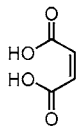
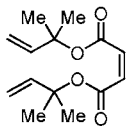
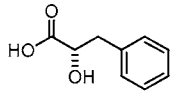
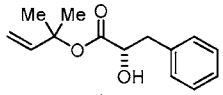
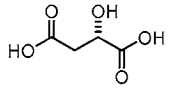
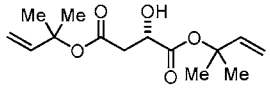
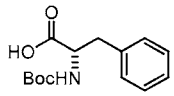
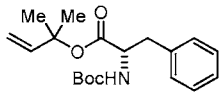
Table 1. Iridium-Catalyzed Hydrocarboxylation of 1,1-Dimethylallene To Furnish Reverse Prenyl Esters **1b**−**12b**[a,b]



entry	substrate	product	yield%
1			
	1a, R = H	1b	84
	2a, R = NO_2	2b	85
	3a, R = OMe	3b	91
	4a, R = Br	4b	82
	5a, R = OH	5b	79
2			
	6a	6b	81
3			
	7a	7b	92
4			
	8a	8b	82
5			
	9a	9b	82[c]
6			
	10a	10b	74
7			
	11a	11b	77[c]
8			
	12a	12b	74

[a] **Representative Procedure.** To an oven-dried flask under 1 atm of argon gas charged with carboxylic acid **1a** (36.6 mg, 0.3 mmol, 100 mol %), $[Ir(cod)Cl]_2$ (2.0 mg, 0.003 mmol, 1 mol %), BIPHEP (3.1 mg, 0.006 mmol, 2 mol %), and Cs_2CO_3 (1.95 mg, 0.006 mmol, 2 mol %) was added 1,2-dichloroethane (3 mL, 0.1 M) followed by 1,1-dimethylallene (24.5 mg, 0.360 mmol, 120 mol %). The reaction mixture was allowed to stir at 60 °C for a period of 24 h, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate/hexanes, 1:30) provides **1b** (48 mg, 0.252 mmol) as a clear oil in 84% yield. [b] Cited yields are of material isolated via silica gel column chromatography. [c] For diacids **9a** and **11a**, 240 mol % of 1,1-dimethylallene was used.

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.

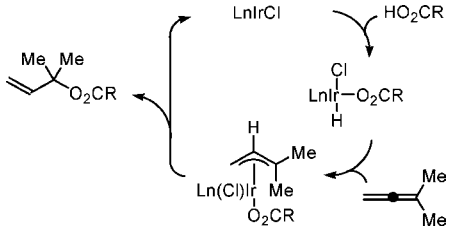
Preliminary studies focused on the coupling of 1,1-dimethylallene to benzoic acid **1a**. Eventually, it was found that the iridium catalyst prepared in situ from $[Ir(cod)Cl]_2$ and BIPHEP (2 mol %) efficiently converts benzoic acid **1a** to the corresponding reverse prenyl ester **1b** (84% yield) 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 *p*-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 $LnIr(H)(Cl)(O_2CR)$.[7] Hydrometalation of 1,1-dimethylallene generates an iridium allyl,[8] which upon C−O reductive elimination[9] from the more substituted *σ*-allyl haptomer delivers the reverse prenyl ester and releases LnIrCl to close the catalytic cycle (Scheme 1).

(7) For oxidative addition of carboxylic acid O−H bonds to iridium(I) complexes, see: (a) Smith, S. A.; Blake, D. M.; Kubota, M. *Inorg. Chem.* **1972**, *11*, 660. (b) Kong, P.-C.; Roundhill, D. M. *Inorg. Chem.* **1972**, *11*, 1437. (c) Ladipo, F. T.; Kooti, M.; Merola, J. S. *Inorg. Chem.* **1993**, *32*, 1681. (d) Ladipo, F. T.; Merola, J. S. *Inorg. Chem.* **1993**, *32*, 5201. (e) Yamagata, T.; Tadaoka, H.; Nagata, M.; Hirao, T.; Kataoka, Y.; Ratovelomanana-Vidal, V.; Genet, J. P.; Mashima, K. *Organometallics* **2006**, *25*, 2505.

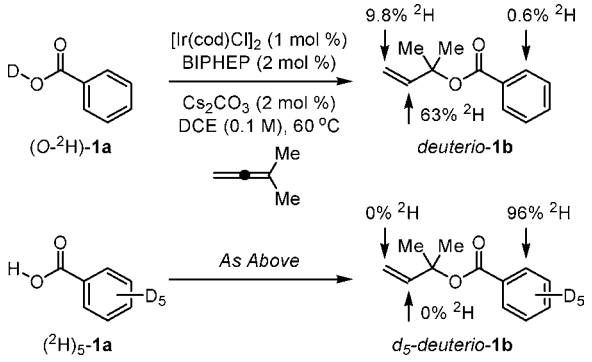
(8) For iridium-mediated allene hydrometalation to form iridium π-allyls, see: Osakada, K.; Kimura, M.; Choi, J.-C. *J. Organomet. Chem.* **2000**, *602*, 144.

Scheme 1. Proposed Catalytic Mechanism



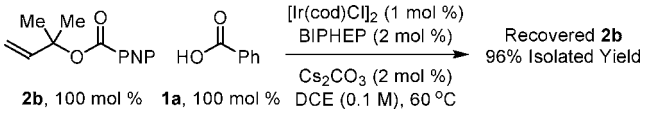
To gain further insight into the catalytic mechanism, 1,1-dimethylallene was coupled to deuteriobenzoic acid (*O*-^{2}H)-**1a**. The product *deuterio*-**1b** incorporates deuterium at both the interior vinylic position (63%) and exterior vinylic position (9.8%). Additionally, a small quantity of deuterium is incorporated at the ortho position of the benzoate (0.6%). Incomplete deuterium incorporation may be due to adventitious moisture or an exchange of ^{1}H—^{2}H between the iridium hydride intermediate and the *o*-hydrogens of BIPHEP.[10,11] 1,1-Dimethylallene also was coupled to benzoic acid-2,3,4,5,6-d$_5$ (^{2}H)$_5$-**1a**. The product, *d*$_5$-*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).

Scheme 2. Isotopic Labeling Experiments



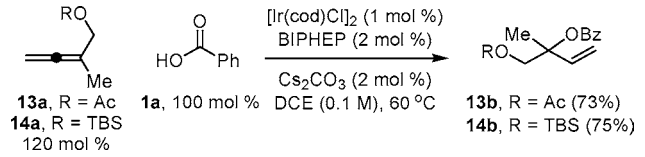
To establish whether the hydrocarboxylation is reversible, the reverse prenyl ester **2b** was exposed to benzoic acid **1a** under otherwise standard reaction conditions. The reverse prenyl ester **2b** was recovered in 96% isolated yield. The reverse prenyl ester **1b** was not detected. The absence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

Scheme 3. Negligible Carboxylate Exchange Suggests Irreversible Hydrocarboxylation



Owing to the ubiquity of the reverse prenyl moiety in diverse naturally occurring compounds, the present study focuses on the hydrocarboxylation of 1,1-dimethylallene. However, this process is not restricted to 1,1-dimethylallene. For example, exposure of allenes **13a** and **14a** to benzoic acid **1a** under the standard conditions cited in Table 1 delivers the tertiary allylic esters **13b** and **14b** in good yield and as single regioisomers. A more detailed investigation into the scope of the allene partner will be published in due course (Scheme 4).

Scheme 4. Hydrocarboxylation of Allenes **13a** and **14a**



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.

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

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(9) For selected examples of C—O reductive elimination from noble metal complexes, see: (a) Mann, G.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 13109. (b) Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787. (c) Han, R.; Hillhouse, G. L. *J. Am. Chem. Soc.* **1997**, *119*, 8135. (d) Widenhoefer, R. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6504. (e) Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224. (f) Williams, B. S.; Goldberg, K. I. *J. Am. Chem. Soc.* **2001**, *123*, 2576. (g) Dick, A. R.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 12790.

(10) For ortho-metalated iridium arylphosphine complexes, see: (a) Del Piero, G.; Perego, G.; Zazzetta, A.; Cesari, M. *Crys. Struct. Commun.* **1974**, *3*, 725. (b) Longato, B.; Morandini, F.; Bresadola, S. *J. Organomet. Chem.* **1975**, *88*, C7. (c) Crabtree, R. H.; Quirk, J. M.; Felkin, H.; Fillebeen-Khan, T.; Pascard, C. *J. Organomet. Chem.* **1980**, *187*, C32. (d) Brym, M.; Jones, C. *Trans. Metal Chem.* **2003**, *28*, 595. (e) Review: Mohr, F.; Priver, S. H.; Bhargava, S. K.; Bennett, M. A. *Coord. Chem. Rev.* **2006**, *250*, 1851.

(11) For H—D exchange employing elemental deuterium under the conditions of iridium catalysis, see: (a) Heys, R. *J. Chem. Soc., Chem. Commun.* **1992**, 680. (b) Skaddan, M. B.; Yung, C. M.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 11. (c) Ellames, G. J.; Gibson, J. S.; Herbert, J. M.; Kerr, W. J.; McNeill, A. H. *J. Labelled Compd. Radiopharm.* **2004**, *47*, 1.