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Enantioselective Iridium-Catalyzed Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Using Allyl Acetate as an Allyl Metal Surrogate

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Abstract

A method for carbonyl allylation and crotylation from the alcohol oxidation state *via* allyl acetate-alcohol transfer hydrogenative C-C coupling is described. Exposure of allyl acetate to benzylic and allylic alcohols **1a-9a** in the presence of an iridium catalyst derived from $[\text{IrCl}(\text{cod})]_2$ and BIPHEP delivers products of C-allylation **1b-9b**. Similarly, 3-acetoxy-1-butene couples to allylic alcohols **1a-9a** to furnish crotylation products **1c-9c**. The ability of this allylation protocol to transcend the boundaries imposed by oxidation level are demonstrated by the coupling of allyl acetate to aldehydes **1d-3d** under standard conditions, but employing isopropanol as terminal reductant. The products of C-allylation **1b-3b** are obtained in isolated yields comparable to those obtained in the corresponding alcohol coupling reactions. These studies contribute to a paradigm shift in carbonyl addition chemistry that defines a departure from preformed organometallic reagents.

The allylation of carbonyl compounds has emerged as a core synthetic method and gateway to polyketide natural products.¹ Despite enormous effort devoted to the development of carbonyl allylation methodologies, the vast majority of protocols rely upon the use of preformed allyl metal reagents. Pursuant to the first carbonyl allylations mediated by isolable allylboranes (1964)^{2a} and allylsilanes (1976),^{2b,c} enantioselective carbonyl allylations employing chirally modified allyl metal reagents were established,³ as first reported by Hoffmann (1978).^{3a,b} An potentially more attractive approach to carbonyl allylation involves the use of allylic acetates, alcohols and halides as allyl donors.⁴⁻⁵⁻⁶⁻⁷ This approach requires reductive generation of allyl metal species and, to date, stoichiometric metal-based terminal reductants are required for catalytic turnover.⁵

Recently, we devised a novel class of carbonyl allylations employing allenes and dienes as allyl donors under hydrogenative conditions.⁸⁻⁹ We first observed that hydrogenation of 1,1-dimethylallene in the presence of carbonyl electrophiles delivers products of reverse

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Supporting information available: Experimental procedures and spectral data for new compounds. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

prenylation.^{8a} Later, we found that allene-mediated carbonyl allylation, crotylation and reverse prenylation could be achieved from the aldehyde or alcohol oxidation level under the conditions of iridium catalyzed transfer hydrogenation.^{8b,c} Finally, under the conditions of ruthenium catalyzed transfer hydrogenation, we found that acyclic 1,3-dienes (butadiene, isoprene and 2,3-dimethylbutadiene) may be used as allyl donors, enabling carbonyl allylation from the aldehyde or alcohol oxidation level.^{8d} Notably, these allylation protocols circumvent stoichiometric use of metallic reagents.¹⁰

Because allyl acetate is a more desirable allyl donor than gaseous allene from the standpoint of cost and operational simplicity, we sought to develop related carbonyl allylations based upon allyl acetate-alcohol transfer hydrogenation.^{8·9·11,12} Here, we report that upon exposure of allylic acetates to alcohols in the presence of an iridium catalyst derived from $[\text{IrCl}(\text{cod})]_2$ and BIPHEP, products of *C*-allylation are obtained in good to excellent yield. This finding is remarkable, as iridium catalyzed allylic substitution (*O*-allylation) employing alcohol nucleophiles is a well established mode of reactivity.^{13,14}

***O*-Allylation via Conventional Allylic Substitution**

***C*-Allylation via Transfer Hydrogenative Coupling**

Initial experiments focused on the iridium catalyzed coupling various allylic carbonates to benzylic alcohol **1a**, which resulted in exclusive *O*-allylation. In contrast, using allyl acetate as the allyl donor, the desired product of *C*-allylation **1b** was obtained. Optimal conditions involve the use of the commercially available iridium complex $[\text{IrCl}(\text{cod})]_2$ (2.5 mol%) in combination with BIPHEP (5 mol%) as ligand in THF solvent at 100 °C in a sealed tube, along with Cs_2CO_3 (20 mol%) and *m*- NO_2BzOH (10 mol%) as additives. Under these standard conditions, allyl acetate couples to a range of benzylic and allylic alcohols **1a-9a**, providing good to excellent yields of the *C*-allylation products. One limitation of the present catalytic system involves couplings to simple aliphatic alcohols, which occur in diminished yield.

The scope of the allyl donor was next explored. Whereas crotyl acetate does not couple under standard conditions, reactions performed using the isomeric allyl donor, 3-acetoxy-1-butene, proceed efficiently. Branch-selective coupling occurs to furnish products of *C*-crotylation **1c-9c** as single regioisomers in good to excellent yield from the same set of benzylic and allylic alcohols **1a-9a** with modest *anti*-diastereoselectivity. Thus, carbonyl allylation and crotylation is achieved from the alcohol oxidation level with acetic acid as the only stoichiometric byproduct. Attempted reverse prenylation employing 3-acetoxy-3-methyl-1-butene gave only trace quantities of adduct.

Carbonyl allylation directly from the alcohol oxidation level allows one to circumvent the redox manipulations so often required to convert alcohols to aldehydes. Nevertheless, it would be desirable to develop allylation protocols that transcend the boundaries imposed by oxidation level. Accordingly, the allylation of aldehydes **1d-3d** was explored employing isopropanol as terminal reductant. Remarkably, under otherwise standard reaction conditions, aldehydes **1d-3d** are converted to carbonyl allylation products **1b-3b** in isolated yields comparable to those obtained in the corresponding alcohol coupling reactions (Table 2). Thus, carbonyl allylation may be achieved from the alcohol or aldehyde oxidation level employing allyl acetate as a surrogate to preformed allyl metal reagents such as allyl stannanes, allyl silanes and allyl boranes.

The reversal of reactivity or “umpolung” of the purported allyl iridium intermediate is surprising, as closely related systems for iridium catalyzed allylic substitution (*O*-allylation) employing alcohol nucleophiles have been disclosed.¹³ In this aligned work, strongly π -acidic phosphoramidite ligands are employed, which likely enforces electrophilic behavior of the metal-bound allyl. In our own hands, such phosphoramidite complexes provide low yields of product that appear as mixtures of both *O*- and *C*-allylation.

To summarize, carbonyl allylation technology has had an enormous transformative impact on the field of organic synthesis. However, general protocols have relied uniformly on preformed allyl metal reagents, mandating stoichiometric generation of metallic byproducts. Here, we demonstrate that allyl acetate, an inexpensive commercial reagent, may serve as an effective allyl donor in carbonyl additions from the alcohol or aldehyde oxidation level. Our collective studies on hydrogenative and transfer hydrogenative C-C coupling contribute to a paradigm shift in carbonyl addition chemistry that defines a departure from preformed organometallic reagents.⁹ Having established these novel patterns of reactivity, future studies will be devoted to understanding the structural-interactional features of the catalytic system that govern stereoselectivity.

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Table 1

C-Allylation and crotylation of alcohols **1a-9a** via iridium catalyzed coupling to allylic acetates.^a

1a, R = *p*-NO₂Ph

2a, R = Ph

4a, R = *p*-(CO₂Me)Ph

5a, R = *p*-BrPh

7a, R = Piperonyl

8a, R = 2-(*N*-Me-Indo

80% Yield
1b

1a, R = *p*-NO₂Ph**4a, R = *p*-(CO₂Me)Ph****7a, R = Piperonyl**

88% Yield
4b**2a, R = Ph****5a, R = *p*-BrPh****8a, R = 2-(*N*-Me-Indo)** 85% Yield
5b

1a, R = *p*-NO₂Ph

4a, R = *p*-(CO₂Me)Ph

7a, R = Piperonyl

2a, R = Ph

5a, R = *p*-BrPh

8a, R = 2-(*N*-Me-Indo

81% Yield
7b

1a, R = *p*-NO₂Ph**4a**, R = *p*-(CO₂Me)Ph**7a**, R = Piperonyl**2a**, R = Ph**5a**, R = *p*-BrPh**8a**, R = 2-(*N*-Me-Indo)

78% Yield
2:1 dr, 1c

72% Yield
2:1 dr, 2c

1a, R = *p*-NO₂Ph**2a**, R = Ph**4a**, R = *p*-(CO₂Me)Ph**5a**, R = *p*-BrPh**7a**, R = Piperonyl**8a**, R = 2-(*N*-Me-Indo 85% Yield
2:1 dr, **4c**

1a, R = *p*-NO₂Ph
4a, R = *p*-(CO₂Me)Ph
7a, R = Piperonyl

74% Yield
2:1 dr, **7c**

2a, R = Ph
5a, R = *p*-BrPh
8a, R = 2-(*N*-Me-Indol-1-yl)

64% Yield
2:1 dr, **8c**

^a Cited yields are of isolated material. Standard conditions employ 1 equiv. of alcohol and 10 equivalents of the allylic acetate. See Supporting Information for detailed experimental procedures.

Table 2C-Allylation of aldehydes **1d-3d** via iridium catalyzed coupling to allyl acetate.^a

1d, R = <i>p</i> -NO ₂ Ph	2d, R = Ph

86% Yield	
1b

^aCited yields are of isolated material. Standard conditions employ 1 equiv. of aldehyde and 10 equivalents of allyl acetate. See Supporting Information for detailed experimental procedures.