

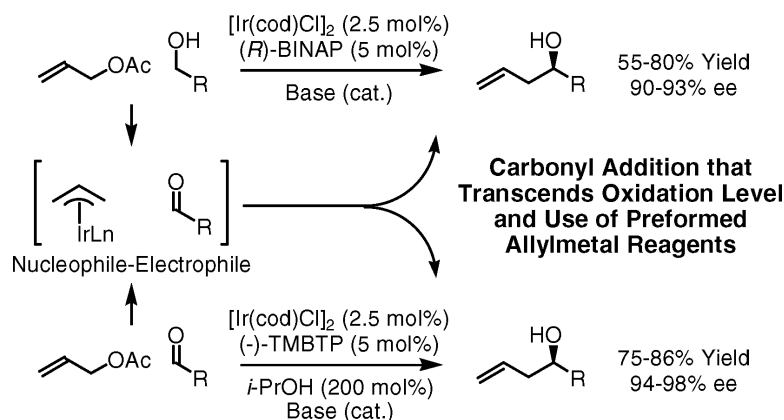
Communication

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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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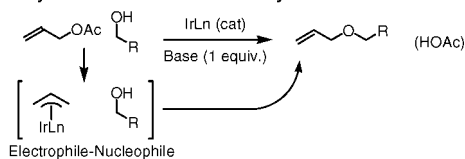
Carbonyl allylation is a core synthetic method and gateway to polyketide natural products.¹ The vast majority of allylation protocols employ preformed allyl metal reagents. Pursuant to the first carbonyl allylations mediated by isolable allylboranes (1964)^{2a} and allylsilanes (1976),^{2b,c} enantioselective carbonyl allylations employing chirally modified allyl metal reagents were achieved,³ as first reported by Hoffmann (1978).^{3a,b} A more attractive approach to carbonyl allylation involves the use of allyl acetates, allyl alcohols, and allyl halides as allyl donors.^{4–7} This approach requires reductive generation of the allyl metal species, and, to date, stoichiometric amounts of metal-based terminal reductants are required for catalytic turnover.⁵

Recently, we devised carbonyl allylations employing allenes and dienes as allyl donors under hydrogenative conditions.^{8,9} First, it was observed that hydrogenation of 1,1-dimethylallene in the presence of carbonyl electrophiles delivers products of reverse prenylation.^{8a} Later, allene-mediated carbonyl allylation, crotylation, and reverse prenylation were achieved from the aldehyde or alcohol oxidation level under transfer hydrogenation conditions employing iridium catalysts.^{8b,c} Finally, under the conditions of ruthenium catalyzed transfer hydrogenation, it was found that acyclic 1,3-dienes serve as allyl donors, enabling carbonyl allylation from the aldehyde or alcohol oxidation level.^{8d} Notably, these allylation protocols circumvent the stoichiometric use of metallic reagents.¹⁰

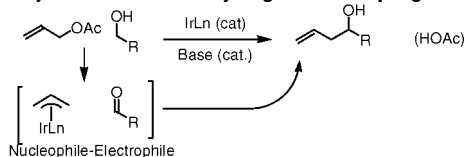
Allyl acetate is a desirable allyl donor from the standpoint of cost and tractability. Accordingly, carbonyl allylations based upon allyl acetate-alcohol transfer hydrogenative coupling were sought.^{8,9,11,12}

Here, we report that upon exposure of allyl acetate to alcohols in the presence of an iridium catalyst derived from [Ir(cod)Cl]₂ and (*R*)-BINAP, products of *C*-allylation are generated in good yield with exceptional enantioselectivity. Further, enantioselective carbonyl allylation is achieved from the aldehyde oxidation level under nearly identical conditions employing isopropanol as the terminal reductant and (–)-TMBTP as the ligand. These findings are remarkable, as iridium catalyzed allylic substitution (*O*-allylation) of alcohol nucleophiles is a well-known mode of reactivity.^{13,14}

O-Allylation via Conventional Allylic Substitution



C-Allylation via Transfer Hydrogenative Coupling



Initial experiments focused on coupling allylic carbonates to benzylic alcohol **1a** using a catalyst derived from [Ir(cod)Cl]₂ and BIPHEP, resulting in exclusive *O*-allylation. Remarkably, using allyl

Table 1. Carbonyl Allylation from the Alcohol Oxidation Level via Iridium-Catalyzed Coupling of Allyl Acetate to Alcohols **1a–i**^a

1a , R = <i>p</i> -NO ₂ Ph 1d , R = <i>p</i> -(CO ₂ Me)Ph 1g , R = Piperonyl	1b , R = Ph 1e , R = <i>p</i> -BrPh 1h , R = <i>o</i> -MeOPh	1c , R = <i>p</i> -MeOPh 1f , R = 3,5-Cl ₂ Ph 1i , R = 2-(<i>N</i> -Me-indolyl)
 72% Yield 91% ee, 2a	 62% Yield 93% ee, 2b	 73% Yield 93% ee, 2c
 77% Yield 93% ee, 2d	 74% Yield 93% ee, 2e	 61% Yield 92% ee, 2f
 76% Yield 91% ee, 2g	 80% Yield 92% ee, 2h	 55% Yield 90% ee, 2i

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

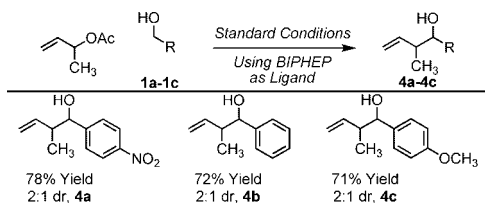
Table 2. Carbonyl Allylation from the Aldehyde Oxidation Level via Iridium-Catalyzed Coupling of Allyl Acetate to Aldehydes **3a–i**^a

3a , R = <i>p</i> -NO ₂ Ph 3d , R = <i>p</i> -(CO ₂ Me)Ph 3g , R = Piperonyl	3b , R = Ph 3e , R = <i>p</i> -BrPh 3h , R = <i>o</i> -MeOPh	3c , R = <i>p</i> -MeOPh 3f , R = 3,5-Cl ₂ Ph 3i , R = 2-(<i>N</i> -Me-indolyl)
 78% Yield 97% ee, 2a	 76% Yield 96% ee, 2b	 75% Yield 94% ee, 2c
 85% Yield 97% ee, 2d	 77% Yield 97% ee, 2e	 76% Yield 98% ee, 2f
 83% Yield 94% ee, 2g	 86% Yield 95% ee, 2h	 82% Yield 94% ee, 2i

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

acetate as the allyl donor, the desired product of *C*-allylation **2a** was obtained. Under optimal conditions, which employ the commercially available iridium complex [Ir(cod)Cl]₂ (2.5 mol %) in combination with BIPHEP (5 mol %) as ligand in THF at 100 °C in a sealed tube, along with Cs₂CO₃ (20 mol %) and *m*-NO₂BzOH

Table 3. Carbonyl Crotylation from the Alcohol Oxidation Level via Iridium-Catalyzed Coupling of 3-Acetoxy-1-butene to Alcohols **1a–c**^a



^a Cited yields are of isolated material. Standard conditions employ 1 equiv of alcohol and 10 equiv of the 3-acetoxy-1-butene. See Supporting Information for detailed experimental procedures.

(10 mol %) as additives, racemic **2a** is obtained in 80% isolated yield. Using (*R*)-BINAP as ligand under otherwise identical conditions, **1a** is converted to **2a** in 72% isolated yield and 91% enantiomeric excess. Under these standard conditions, allyl acetate couples to a range of benzylic alcohols **1a–i** to furnish products of *C*-allylation **2a–i** in good yield and with excellent levels of enantioselectivity (Table 1). Couplings to aliphatic and allylic alcohols are presently underway and a full account of the scope of this allylation protocol will be published in due course.

Inspired by the prospect of developing carbonyl allylation protocols that transcend the boundaries imposed by oxidation level, the allylation of aldehydes **3a–i** was explored using isopropanol as the terminal reductant and (–)-TMBTP as ligand. Under otherwise standard reaction conditions, aldehydes **3a–i** are converted to the identical carbonyl allylation products **2a–i** in good to excellent isolated yields and again with exceptional levels of enantioselectivity (Table 2). *Enantioselective carbonyl allylation may be achieved from the alcohol or aldehyde oxidation level using 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 intermediate allyl iridium is surprising, as closely related systems for iridium-catalyzed allylic substitution (*O*-allylation) employing alcohol nucleophiles are known.¹³ In this aligned work, π -acidic phosphoramidite ligands are used, which may enforce electrophilic behavior. Additionally, the oxidation state of iridium may play a decisive role in partitioning electrophilic and nucleophilic behavior: high-valent iridium(III) allyls bound to π -acidic phosphoramidites should display electrophilic behavior, whereas low-valent iridium(I) allyls possessing less π -acidic triarylphosphine ligands should display nucleophilic behavior. Known conditions for iridium catalyzed *O*-allylation have not been applied to the substrate combinations reported herein. However, in the course of optimization, phosphoramidite complexes were examined under otherwise standard conditions cited in Table 1, which led to mixtures of both *O*- and *C*-allylation products in low yield. From the standpoint of mechanism, it is also noteworthy that crotyl acetate does not couple under standard conditions, yet isomeric 3-acetoxy-1-butene couples efficiently to alcohols **1a–c** to provide products of crotylation **4a–c** (Table 3).

Our studies on transfer hydrogenative C–C coupling define a departure from preformed organometallic reagents in carbonyl additions that transcend the boundaries of oxidation level.⁹ Mechanistic studies on these and related processes are underway.

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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>.

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