

Carbonyl Allylation in the Absence of Preformed Allyl Metal Reagents: Reverse Prenylation via Iridium-Catalyzed Hydrogenative Coupling of Dimethylallene

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Nearly half a century ago, Mikhailov and Bubnov (1964) reported the first carbonyl allylation employing an isolable preformed allyl metal reagent, triallylborane.^{1a} Twelve years later, Hosomi and Sakurai (1976) reported that carbonyl compounds are subject to allylation upon exposure to allylsilanes in the presence of Lewis acids.^{1b,c} These studies set the stage for enantioselective carbonyl allylations employing chirally modified allyl metal reagents. The first reagent of this type, reported by Hoffmann (1978),^{2a,b} was an allylborane derived from camphor. Subsequently, a host of chirally modified allyl metal reagents for asymmetric carbonyl allylation were disclosed. These include reagents developed by Kumada (1982),^{2c} Brown (1983),^{2d} Roush (1985),^{2e} Reetz (1988),^{2f} Masamune (1989),^{2g} Corey (1989),^{2h} Seebach (1987),²ⁱ Duthaler (1989),^{2j} Panek (1991),^{2k} and Leighton (2002).^{2l,m} Catalytic enantioselective carbonyl allylations have been achieved using chirally modified Lewis acid catalysts, as described in seminal studies by Umani-Ronchi (1993)^{3a} and Keck (1993).^{3b} Additionally, enantioselective carbonyl allylation may be catalyzed using chirally modified Lewis bases, as revealed in elegant studies by Denmark (1994).^{3c,d} Other methods for catalytic carbonyl allylation involve the reduction of metallo- π -allyls derived from allylic alcohols and allylic carboxylates.⁴ Here, stoichiometric quantities of metal-based terminal reductants, for example SmI_2 , SnCl_2 , and Et_2Zn , are required for catalytic turnover.⁵ Finally, carbonyl-ene processes enable access to products of carbonyl allylation.^{6,7}

Clearly, enormous effort has been devoted to the development of carbonyl allylation methodologies.⁸ However, withstanding carbonyl-ene processes,^{6,7} the aforementioned protocols invariably employ stoichiometric quantities of preformed allyl metal reagents^{1–3} or metallic reductants,^{4,5} mandating stoichiometric generation of metallic byproducts.

Hydrogen-mediated reductive coupling offers a byproduct-free alternative to stoichiometrically preformed organometallic reagents in an ever increasing range of $\text{C}=\text{X}$ ($\text{X} = \text{O}, \text{NR}$) addition processes.⁹ It was postulated that the allyl metal species arising transiently upon allene hydrogenation¹⁰ may be subject to capture by exogenous carbonyl electrophiles to furnish products of carbonyl allylation. Precedent for such a transformation was rendered tenuous, as intermolecular allene-carbonyl reductive coupling under the conditions of nickel catalysis using silane as terminal reductant provides products of carbonyl vinylation via coupling to the central allenic carbon atom.¹¹ The regiochemistry required for homoallyl alcohol formation had only been observed in multi-component reaction of allenes and aldehydes with halo- or metallo-arenes.^{12,13} To date, simple catalytic reductive allene-carbonyl coupling to furnish homoallylic alcohols has not been achieved. Here, we report that iridium catalyzed hydrogenation¹⁴ of dimethylallene in the presence of carbonyl electrophiles delivers products of carbonyl allylation, specifically, products of reverse prenylation.

In our initial studies, a range of rhodium and iridium catalysts were assayed for their ability to catalyze the hydrogenative coupling of gaseous allene to various carbonyl electrophiles. Here, it was

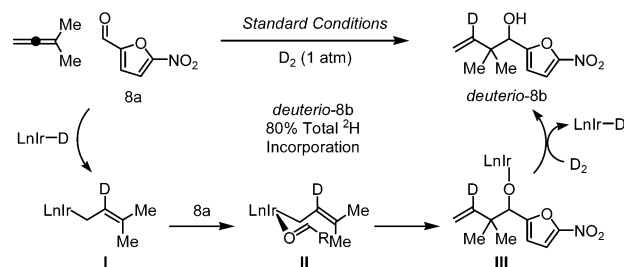


Figure 1. Iridium-catalyzed reductive coupling of dimethylallene to aldehyde **8a** under an atmosphere of deuterium.

found that catalysts derived from the cationic iridium complex $[\text{Ir}(\text{cod})_2]\text{BARF}$ ($\text{BARF} = \text{B}(3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3)_4$) and the chelating phosphine ligand BIPHEP promote the desired reaction. However, using the parent allene, the initially formed homoallylic alcohol is subject to over-reduction to furnish the product of carbonyl propylation. For this reason, dimethylallene was selected as the nucleophilic partner, as the anticipated product of carbonyl prenylation should be more resistant to over-reduction. To our delight, iridium-catalyzed hydrogenation of dimethylallene in the presence phenethyl glyoxalate **1a** delivers the product of *reverse prenylation* in good isolated yield with only partial over-reduction of the terminal alkene. An assay of various additives revealed that over-reduction is completely suppressed for reactions conducted in DCE-EtOAc (1:1) in the presence of the basic additive Li_2CO_3 . Alternate bases, for example KOAc, LiOH, Cs_2CO_3 , $i\text{-Pr}_3\text{NEt}$, were only slightly less effective at suppressing over-reduction. Under these conditions, diverse aldehydes undergo reverse prenylation in good to excellent yield. One limitation of this first generation catalytic system is that unactivated aliphatic aldehydes do not couple efficiently. However, as established by the formation of **12b**, for electronically activated systems even ketone addition is possible (Table 1).

A plausible general catalytic mechanism involves allene hydro-metallation to provide the primary σ -allyl iridium complex **I**, which engages the carbonyl partner in a closed six-centered transition state **II**. Carbonyl addition with allylic inversion accounts for the formation of reverse prenylated adducts. Hydrogenolytic cleavage of the resulting iridium alkoxide **III** delivers *deuterio-8b* with concomitant regeneration of $\text{Ir}(\text{H})(\text{Ln})$ to close the cycle. To corroborate the proposed mechanism, dimethylallene was coupled to aldehyde **8a** under an atmosphere of deuterium (Figure 1). As revealed by ^2H NMR analysis, the total amount of deuterium incorporated into *deuterio-8b* is 80%. It should be emphasized that mechanisms involving allene-aldehyde oxidative coupling are potentially operative and cannot be excluded on the basis of available data. Studies focused on uncovering the origins of incomplete deuterium incorporation are in progress. One possible explanation invokes β -hydride elimination from the tertiary σ -allyl haptomer of the iridium allyl to form isoprene.

Carbonyl allylation is employed extensively in organic synthesis.⁸ Yet, withstanding carbonyl-ene processes,^{6,7} prevailing protocols

Table 1. Reverse Prenylation via Iridium-Catalyzed Hydrogenative Coupling of Dimethylallene to Carbonyl Compounds^a

$ \begin{array}{c} \text{Me} \\ \diagup \\ \text{C}=\text{C} \\ \diagdown \\ \text{Me} \end{array} + \text{R}-\text{C}(=\text{O})-\text{H} \xrightarrow[\text{DCE-EtOAc (1:1), 60 }^\circ\text{C, H}_2 \text{ (1 atm)}]{[\text{Ir}(\text{BIPHEP})(\text{cod})]\text{BARF (5 mol\%)} \\ \text{Li}_2\text{CO}_3 \text{ (35 mol\%)}} \begin{array}{c} \text{OH} \\ \\ \text{Me}-\text{C}-\text{C}-\text{R} \\ \diagup \quad \diagdown \\ \text{Me} \quad \text{Me} \end{array} $			
Entry	Substrate	Product	Yield ^b
1			78
2			68 ^b 69 82
3			74
4			92
5			60 ^b 95
6			84 ^b
7			80
8			70
9			69 ^b

^a In all cases, cited yields are of isolated material. Standard conditions employ 1 equiv of aldehyde and 4 equiv of allene using 5 mol % loading of precatalyst. ^bFor substrates **2a**, **7a**, **9a**, and **12a**, 8 equiv allene and 10 mol % loading of precatalyst were used (see Supporting Information for detailed experimental procedures).

invariably employ stoichiometric quantities of preformed allyl metal reagents^{1–3} or metallic reductants.^{4,5} The preliminary studies reported herein reveal that carbonyl allylation, specifically reverse prenylation, may be achieved simply by hydrogenating dimethylallene in the presence of carbonyl electrophiles, representing a departure from the use of stoichiometric organometallic reagents in carbonyl allylation. Future studies will focus on the development of related hydrogenative protocols for carbonyl allylation and crotylation.

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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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