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Hydroamination *versus* Allylic Amination in Iridium Catalyzed Reactions of Allylic Acetates with Amines: 1,3-Aminoalcohols *via* Ester-Directed Regioselectivity

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Abstract

In the presence of a neutral dppf-modified iridium catalyst and Cs₂CO₃, linear allylic acetates react with primary amines to form products of hydroamination with complete 1,3-regioselectivity. The collective data, including deuterium labeling studies, corroborate a catalytic mechanism involving rapid, reversible acetate-directed aminoiridation with inner-sphere/outer-sphere crossover followed by turn-over limiting protodemetalation mediated by amine.

Graphical Abstract

The importance of nitrogen-containing compounds in pharmaceutical and agrochemical research continues to inspire efforts toward the development of metal catalysts for alkene hydroamination.^{1,2} Among late transition metal catalysts,^{1g} those based on rhodium^{3,4} and iridium^{5,6} have shown great promise, however, despite decades of research, significant challenges remain. Many hydroaminations are limited to intramolecular processes.^{4,6} Intermolecular variants often require highly activated alkenes,^{3b,5a-d} are accompanied by

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oxidative amination side-products^{3c-i,5f} or exploit specialized directing groups to control regioselectivity.^{3j,k} Further, the mechanisms of these processes are obfuscated by the fact that simple Brønsted acids – even ammonium salts^{7b,f} – catalyze hydroamination with levels of efficiency equal to or greater than the corresponding metal catalyzed reactions.^{7,8} *Here, we report the first hydroaminations of allylic acetates.* Specifically, using a neutral dppe-modified iridium catalyst in the presence of Cs₂CO₃, linear allylic acetates react with primary amines to form products of hydroamination with complete 1,3-regioselectivity. These results are remarkable, as iridium complexes are well-known to catalyze the substitution of allylic acetates with amines to form products of allylic amination (Figure 1).⁹

Recently, in a collaborative endeavor, we reported that commercially available π -allyliridium *C,O*-benzoates catalyze highly enantioselective substitutions of branched allylic acetates with primary amines.¹⁰ In the course of developing this process, significant quantities (30-40% yield) of hydroamination product were formed as single regioisomers in attempted substitutions of linear allylic acetates. Both iridium *C,O*-benzoates and non-cyclometallated phosphine-modified iridium complexes derived *in situ* from [Ir(cod)Cl]₂ displayed roughly equivalent efficiencies. In both cases, chiral ligands did not induce asymmetry, so the simpler non-cyclometallated complexes were chosen for further optimization. From a survey of achiral phosphine ligands, the phosphine ligand dppe, 1,1'-bis(diphenylphosphino)ferrocene, was found to be most effective. Hydroamination products were not observed in the absence of metal, phosphine ligand or upon use of monophosphine ligands.

At this point, the effect of base was systematically investigated (Table 1, entries 1-5). In the presence of [Ir(cod)Cl]₂ (2.5 mol%), dppe (5 mol%) and Cs₂CO₃ (200 mol%) at 90 °C in THF (1 M), cinnamyl acetate **1a** (100 mol%) and benzyl amine **2a** (200 mol%) were converted to the hydroamination products **3a** and the deacetylated compound **3a'** in a 2:1 ratio and a combined 66% yield along with trace amounts of cinnamyl alcohol. In an attempt to minimize formation of **3a'**, lower loadings of Cs₂CO₃ were explored (Table 1, entries 1-3), however, although the reaction is heterogeneous, the combined yield of hydroamination products **3a** and **3a'** declined.¹¹ Other bases were explored (Table 1, entries 4, 5), but Cs₂CO₃ provided superior results. The use of cinnamic esters less prone to saponification were explored (Table 1, entries 6-10), but this also led to a decrease in the combined yield of hydroamination products **3a** and **3a'**. In all experiments, products of acyl transfer to benzyl amine were not observed.

Acute sensitivity to the steric features of the cinnamic ester (cf. Table 1, entries 1 and 7) along with the regioselectivity of hydroamination suggested chelation of iridium by the acetate carbonyl and olefin moieties might play an integral role in the mechanism. To perhaps favor chelation of iridium and minimize formation of **3a'** the stoichiometry of cinnamyl acetate **1a** and benzyl amine **2a** was altered (Table 1, entries 11-13). Using cinnamyl acetate **1a** (300 mol%) and benzyl amine **2a** (100 mol%), the hydroamination product **3a** was obtained in 76% yield accompanied by only trace quantities of the **3a'** (Table 1, entry 13). To mitigate solvent evaporation, a number of higher boiling solvents were evaluated and it was found that 1,2-dimethoxyethane (DME), provided **3a** with equivalent efficiencies (Table 1, entry 14). Finally, although this effect was not pronounced

in reactions of cinnamyl acetate **1a**, it was also found that in certain cases milled Cs_2CO_3 led to higher and more reproducible yields.¹¹

To illustrate scope, optimal conditions for hydroamination were applied across a diverse set of reactants (Table 2). As demonstrated by the formation of hydroamination products **3a-3g**, primary benzylic amines are effective partners for hydroamination. Saturated primary amines provide moderate yields of hydroamination product (**3h**). A range of aryl-substituted linear allylic acetates also were evaluated (**3i-3p**). These experiments, which were all conducted using benzyl amine, reveal that both electron rich and electron deficient aryl groups, as well as heteroaryl groups, are tolerated. The formation of adduct **3p**, derived from AZD-9496 (a non-steroidal oral estrogen receptor inhibitor),¹² which incorporates an unprotected indole moiety, highlights the functional group tolerance of the present hydroamination method. As illustrated by formation of **3q** and **3r**, alkyl-substituted allylic acetates provide modest yields of hydroamination product as single regioisomers. *The regioselective formation 3r is noteworthy, as it provides strong evidence of the directing influence of the acetate moiety.* Indeed, as cinnamyl methyl ether, *trans*- β -methyl styrene and 1-octene do not engage in hydroamination under these conditions, it would appear that the acetate moiety not only directs regioselectivity, but is actually required for hydroamination to occur. Under the present conditions, secondary amines and anilines only provide trace quantities of hydroamination product, and the parent unsubstituted allyl acetate, $\text{H}_2\text{C}=\text{CHCH}_2\text{OAc}$, provides mixtures of hydroamination and allylic substitution products.

To gain insight into the reaction mechanism, *mono*- and *di*-deuterated cinnamyl acetates *d*₁-**1a** and *d*₂-**1a** were exposed to standard hydroamination conditions (Scheme 1). To facilitate assignment of relative stereochemistry, the reaction products were converted to the cyclic carbamates *d*₁-**3a** and *d*₂-**3a**. Axial disposition of the phenyl moiety was corroborated by nOe experiments and is presumably due to nonbonded interactions with the *N*-benzyl moiety. As determined by ¹H NMR, ²H NMR and HRMS, both compounds *d*₁-**3a** and *d*₂-**3a**, completely retain deuterium and were each generated as 1.7:1 mixtures of diastereomers. Guided by the results of deuterium labeling, a general catalytic mechanism for iridium catalyzed hydroamination of linear allylic acetates was proposed (Scheme 2). Base-induced formation of amidoiridium species **I** enables entry into the catalytic cycle.¹¹ Association of *d*₁-**1a** provides the chelated olefin complex **II**, which undergoes rapid and reversible inner- or outer-sphere alkene aminoiridation to form the σ -alkyliridium species *cis*-**III** and *trans*-**III**, respectively. Equilibration between *cis*-**III** and *trans*-**III** occurs in advance of turn-over limiting proto-demetalation mediated by benzyl amine to release the product *d*₁-**3a** and regenerate amidoiridium species **I** to close the catalytic cycle. Consistent with this mechanistic interpretation, in particular, interconversion between *cis*-**III** and *trans*-**III**, diverse chiral iridium complexes did not deliver enantiomerically enriched hydroamination product. Using *cis*-cinnamyl acetate, low conversion to hydroamination product is observed (15% yield) and recovered cinnamyl acetate is partially isomerized to the *trans*-isomer (8:1, *cis:trans*). These data suggest the small quantity of hydroamination product observed in reactions of *cis*-cinnamyl acetate are likely formed by way of the *trans*-isomer and, for *cis*-cinnamyl acetate, allylic strain may prevent acetate-mediated chelation of the olefin by

iridium. On the basis of these data, mechanisms involving alkene isomerization appear less plausible.

To summarize, allylic acetates are well-known to undergo Tsuji-Trost amination upon exposure to amines in the presence of iridium catalysts with cationic character. Here, using *neutral* iridium catalysts under basic conditions, we report the first examples of allylic acetate hydroamination. The collective data, including deuterium labeling studies, corroborate a catalytic mechanism involving rapid, reversible acetate-directed aminoiridation with inner sphere/outer-sphere crossover in advance of turn-over limiting amine-mediated proto-demetalation. The present studies establish a new mechanistic pathway for alkene hydroamination under basic conditions, broadening access to 1,3-aminoalcohols and related *N*-containing compounds.¹³ More broadly, this study and prior collaborative work from the present authors¹⁰ demonstrate the effectiveness of academic-industrial cooperation for the discovery of useful and robust methods for chemical synthesis. Future studies will be aimed at developed related metal catalyzed C-N bond forming processes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cationic vs neutral iridium catalysts promote Tsuji-Trost allylic amination and hydroamination, respectively.

Scheme 1.

Deuterium labelling experiments.

^aReactants and products characterized by ¹H NMR, ²H NMR and HRMS. See Supporting Information for further experimental details.

Scheme 2.

General catalytic mechanism for iridium catalyzed hydroamination of linear allylic acetates, as corroborated by deuterium labeling.

Table 1.

Selected optimization experiments in the reaction of cinnamyl acetate **1a** with benzyl amine **2a** to form hydroamination product **3a**.^a

Entry	1a/2a (mol %)	R	Base (mol%)	Solvent	3a/3a' Yield (%)
1	100 / 200	Me	Cs₂CO₃ (200 mol%)	THF	45 / 21
2	100 / 200	Me	Cs₂CO₃ (50 mol%)	THF	15 / 6
3	100 / 200	Me	Cs₂CO₃, (20 mol%)	THF	trace
4	100 / 200	Me	K₂CO₃ (200 mol%)	THF	trace
5	100 / 200	Me	K₃PO₄ (200 mol%)	THF	22 / 8
6	100 / 200	Et	Cs ₂ CO ₃ (200 mol%)	THF	28 / 9
7	100 / 200	<i>i</i>Pr	Cs ₂ CO ₃ (200 mol%)	THF	12 / trace
8	100 / 200	<i>t</i>Bu	Cs ₂ CO ₃ (200 mol%)	THF	NR
9	100 / 200	OMe	Cs ₂ CO ₃ (200 mol%)	THF	NR
10	100 / 200	NMe₂	Cs ₂ CO ₃ (200 mol%)	THF	NR
11	100 / 100	Me	Cs ₂ CO ₃ (200 mol%)	THF	36 / trace
12	200 / 100	Me	Cs ₂ CO ₃ (200 mol%)	THF	65 / trace
13	300 / 100	Me	Cs ₂ CO ₃ (200 mol%)	THF	76 / trace
14	300 / 100	Me	Cs ₂ CO ₃ (200 mol%)	DME	77 / trace

^a All reactions were performed on 0.2 mmol scale. All yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.

Table 2.

Regioselective iridium-catalyzed hydroamination of linear allylic acetates.^a

3a, 77% Yield >20:1 rr	3b, 63% Yield >20:1 rr	3c, 65% Yield >20:1 rr	3d, 74% Yield >20:1 rr	3e, 68% Yield >20:1 rr	3f, 71% Yield >20:1 rr

3g, 67% Yield >20:1 rr	3h, 54% Yield >20:1 rr	3i, 64% Yield >20:1 rr	3j, 67% Yield >20:1 rr	3k, 78% Yield >20:1 rr	3l, 52% Yield >20:1 rr

3m, 81% Yield >20:1 rr	3n, 71% Yield >20:1 rr	3o, 52% Yield ^b >20:1 rr	3p, 53% Yield ^b 1:1 dr, >20:1 rr	3q, 30% Yield >20:1 rr	3r, 53% Yield ^b >20:1 rr

^aYields of material isolated by silica gel chromatography. Standard conditions: Ir(cod)Cl]₂ (2.5 mol%), dppe (5 mol%), Cs₂CO₃ (200 mol%), amine (100 mol%), DME (1 M), 90 °C. All yields are of material isolated by silica gel chromatography.

^bCs₂CO₃ (300 mol%). See Supporting Information for further experimental details.