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Regio- and Enantioselective Iridium-Catalyzed Amination of Racemic Branched Alkyl-Substituted Allylic Acetates with Primary and Secondary Aromatic and Heteroaromatic Amines

Seung Wook Kim[†], Leyah A. Schwartz[†], Jason R. Zbieg[§], Craig E. Stivala[§], and Michael J. Krische[†]

[§]Discovery Chemistry, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, United States

[†]University of Texas at Austin, Department of Chemistry, Austin, TX 78712, USA

Abstract

The air and water stable π -allyliridium *C,O*-benzoate modified by (*S*)-tol-BINAP, (*S*)-Ir-**II**, catalyzes highly regio- and enantioselective Tsuji-Trost type aminations of racemic branched alkyl-substituted allylic acetates using primary or secondary (hetero)aromatic amines. Specifically, in the presence of (*S*)-Ir-**II** (5 mol%) in DME solvent at 60–70 °C, α -methyl allyl acetate **1a** (100 mol%) reacts with primary (hetero)aromatic amines **2a–2l** (200 mol%) or secondary (hetero)aromatic amines **3a–3l** (200 mol%) to form the branched products of allylic amination **4a–4l** and **5a–5l**, respectively, as single regioisomers in good to excellent yield with uniformly high levels of enantioselectivity. As illustrated by the conversion of heteroaromatic amine **3m** to adducts **6a–6g**, excellent levels of regio- and enantioselectivity are retained across diverse branched allylic acetates bearing normal alkyl or secondary alkyl substituents. For reactants **3n–3p**, which incorporate both primary and secondary aryl amine moieties, regio- and enantioselective amination occurs with complete site-selectivity to furnish adducts **7a–7c**. Mechanistic studies involving amination of the enantiomerically enriched deuterium labelled acetate **1h** corroborate C–N bond formation *via* outer-sphere addition.

Graphical Abstract

Correspondence to: Jason R. Zbieg; Craig E. Stivala; Michael J. Krische.

Supporting Information. Experimental procedures and spectroscopic data for all new compounds (¹H NMR, ¹³C NMR, IR, HRMS), including images of NMR spectra and HPLC traces for racemic and enantiomerically enriched compounds. Single crystal X-ray diffraction data for compound **7b**. This material is available free of charge *via* the internet at <http://pubs.acs.org>

Notes.

The authors declare no competing financial interest.

Introduction

Cyclometallated π -allyliridium *C,O*-benzoate complexes have been shown to catalyze diverse alcohol-mediated carbonyl allylations using allyl carboxylates as pronucleophiles.¹ In these unpoled allylations,² the *C,O*-benzoate moiety assists in maintaining neutrality and, hence, nucleophilicity of the π -allyliridium intermediate. Neutral iridium complexes that are not cyclometallated also display nucleophilic properties.³ In contrast, as illustrated by enantioselective Tsuji-Trost-type allylic aminations developed by Takeuchi,^{4,5} Helmchen,^{6,7} Hartwig,^{8,9} Carreira¹⁰ and You,^{11,12} cationic π -allyliridium species invariably serve as electrophiles. In this latter context, two distinct classes of iridium catalysts have emerged. Type I catalysts are used under basic conditions in combination with linear allyl proelectrophiles (as branched allyl proelectrophiles react stereospecifically).¹³ Type II catalysts are used under acidic conditions in combination with branched allyl proelectrophiles, which react in a non-stereospecific fashion, perhaps due to displacement of the π -bond of ($\sigma+\pi$)-allyl (enyl) iridium intermediates by the tethered olefin of the phosphoramidite ligand (Figure 1).¹⁴

The present authors recently found that neutral π -allyliridium *C,O*-benzoate complexes, which behave as nucleophilic allyl donors,¹ can also act as electrophiles, representing the first examples of amphiphilic reactivity in the context of transition metal catalysis.¹⁵ In the initial communication of these findings, enantioselective allylic aminations of branched allylic acetates bearing linear alkyl groups with primary aliphatic amines were disclosed.¹⁵ These aminations proceed with complete branched regioselectivity, overcoming a significant limitation associated with Type I and II catalysts, which display incomplete regioselectivity for π -allyl precursors bearing linear alkyl groups.^{16,17} With regard to the amine nucleophile, the Type III SEGPHOS-modified π -allyliridium complexes used in our initial study enforced high enantioselectivities in reactions of primary aliphatic amines (Figure 1). Here, we show that the corresponding tol-BINAP-modified iridium catalyst avail a significant expansion in scope, enabling highly enantioselective aminations of branched alkyl-substituted allylic acetates with electronically diverse primary and secondary aryl amines, including site-selective reactions of bis(amine) nucleophiles. Additionally, we report deuterium labelling studies that corroborate C-N bond formation through an outer-sphere mechanism.

Research Design and Methods

To develop highly regio- and enantioselective allylic aminations mediated by aryl amines, a series of π -allyliridium *C,O*-benzoate complexes were evaluated in reactions of α -methyl allyl acetate (100 mol%) and aniline (200 mol%) under conditions previously optimized for primary aliphatic amines.¹⁵ The iridium catalyst modified by tol-BINAP, (*S*)-**Ir-II**, delivered the product of allylic amination **4a** with significantly higher levels of enantioselectivity than the corresponding SEGPHOS-modified catalyst, (*S*)-**Ir-I**, but a lower isolated yield of **4a** was observed (eq. 1). Changing the solvent from THF to DME improved the isolated yield of **4a**, and by decreasing the reaction temperature from 80 °C to 70 °C **4a** could be formed in 82% yield and 89% enantiomeric excess (eq. 1).

Deviation from these reaction parameters did not avail further improvement, and given the low cost of tol-BINAP these conditions were adopted to explore the scope of primary aromatic and heteroaromatic amine nucleophiles **2a-21** in aminations of α -methyl allyl acetate (Table 1). Amine nucleophiles containing a diverse array of functional groups were examined to mirror challenges faced in medicinal chemistry. In each case, the targeted products of allylic amination **4a-4l** were formed with complete branched regioselectivity and uniformly high levels of enantioselectivity. As illustrated in the formation of **4d**, which incorporates a pinacol boronate moiety, the reaction conditions tolerate rather sensitive functional groups. The tolerance of *Ortho*-substituted anilines, as demonstrated by the formation of **4e**, is also noteworthy. Perhaps the most striking feature, however, is the compatibility of the catalyst with electronically diverse aryl amine partners and the tolerance of Lewis basic *N*-heterocycles, as illustrated by the formation **4k** and **4l**. The absolute stereochemical assignment of adducts **4b-4l** is made in analogy to that determined for

compound **4a**, which has been prepared in enantiomerically enriched form in two separate reports.^{8d,18}

In a further exploration of scope, optimized conditions were applied to the amination of α -methyl allyl acetate using secondary aromatic and heteroaromatic amine nucleophiles **3a-3l** (Table 2). Indoline **3a**, 6- and 7-aza-indolines **3b** and **3c** and the 3,3'-spirocyclic indoline **3d** each underwent asymmetric allylation with complete branched regioselectivity and high levels of enantioselectivity. Pronounced match-mismatched effects were observed in the conversion of chiral nonracemic (*S*)- and (*R*)-2-methyl indolines **3e** and **3f** to adducts **5e** and **5f**, respectively, suggesting the potential for kinetic resolution. The amination of **1a** using *N*-methyl aniline **3g** and related compounds **3h** and **3i** bearing electron withdrawing and donating groups at the *Para*-position proceeded smoothly to form adducts **5g-5i**, respectively. Among these three *N*-methyl aniline derivatives (**3g-3i**), amination using the more electron rich *N*-methyl-*Para*-anisidine **3i** occurred with notably higher levels of enantioselectivity. As illustrated by the formation of **5j** and **5k**, *N*-methyl anilines containing bromide (**3j**) and chloride (**3k**) functional groups are tolerated. Finally, amination of **1a** using *N*-Methyl-2-(methylamino)benzimidazole **3l** is remarkably efficient, providing adduct **5l** in 94% yield with complete selectivity for allylation of the extranuclear 2-(methylamino) moiety.

To assess how structural variation of the π -allyliridium intermediate impacts reactivity, regio- and stereoselectivity, a set of branched allylic acetates **1a-1g** were explored in amination mediated by 2-(methylamino)benzoxazole **3m** (Table 3). In addition to α -methyl allyl acetate **1a**, linear alkyl-substituted allylic acetates **1b** and **1c** smoothly underwent amination to form adducts **6a-6c** as single regioisomers with high levels of enantiomeric enrichment. Allylic acetates **1d-1f**, which incorporate cycloalkyl-substituents, delivered adducts **6d-6f** as single regioisomers, although an erosion in enantioselectivity is observed using the larger cyclopentyl-substituted allyl acetate **1f**. Finally, using the enantiomeric iridium catalysts (*S*)-Ir-**II** and (*R*)-Ir-**II**, the (*S*)-citronellol-derived allylic acetate **1g** reacts with **3m** to form **6g** and *iso*-**6g**, respectively, with good levels of catalyst-directed diastereoselectivity. Under these conditions, aryl-substituted allyl acetates gave low yields (<10%) of allylic amination product and linear allylic acetates provided mixtures of allylic amination and hydroamination product in low isolated yield.¹⁹

Having established the ability to functionalize both primary and secondary aromatic amines, the site-selective modification of reactants **3n-3p**, which incorporate both primary and secondary aromatic amines, was attempted using the branched allylic acetate **1a** (eq. 2-4). Upon exposure to standard conditions, 5-aminoindole **3n** undergoes completely chemoselective functionalization at the primary amine to form adduct **7a** as a single constitutional isomer with excellent levels of enantioselectivity (eq. 2). Similarly, in the conversion of **3o** to adduct **7b**, complete control of regio- and site-selectivity is accompanied by high levels of enantioselectivity (eq. 3). The structure of adduct **7b** was verified by single crystal X-ray diffraction analysis, further corroborating the absolute stereochemical assignment of adducts **4a-4l**, **5a-5l** and **6a-6g**. Finally, *N*-cyclohexyl-1,2-diaminobenzene **3p** reacts with **1a** to deliver adduct **7c**, which is modified exclusively at the primary amine (eq.

4). The ability to engage diamines in site-selective regio- and enantioselective amination enhances step economy by avoiding manipulations devoted to *N*-protection-deprotection.

(eq. 2)

(eq. 3)

(eq. 4)

Finally, to better understand the nature of the C-N bond forming event, asymmetric amination of the enantiomerically enriched (*Z*)-deuterated allylic acetate **1h** was conducted under standard conditions using (0*S*)-**Ir-II** (Scheme 1, eq. 5).²⁰ Compound **8a** is formed with complete alkene (*Z*)-stereoselectivity, as determined by ¹H NMR. Assuming formation of the π -allyliridium occurs with inversion of stereochemistry, as established in analogous iridium phosphoramidite catalyzed processes,⁴⁻¹² the stereochemistry of the amination product **8a** is consistent with outer-sphere addition of the nitrogen nucleophile. To corroborate the veracity of this experiment, the amination of allylic acetate **1h** was conducted using the enantiomeric iridium catalyst, (*R*)-**Ir-II** (Scheme 1, eq. 6). The amination product **8b** is formed with complete alkene (*E*)-stereoselectivity, as determined by ¹H NMR. The stereochemistry of **8a** is again consistent with outer-sphere C-N bond formation.

Based on the collective data, a general catalytic mechanism and stereochemical model were proposed (Scheme 2). The π -allyliridium(I) complex **I** is subject to outer-sphere amine addition to form the C-N bond and the zwitterionic iridium(I) olefin complex **II**. Deprotonation of ammonium moiety of complex **II** mediated by cesium carbonate generates the anionic iridium(I) species **III**. Alkene exchange with the allylic acetate releases the product of allylic amination and forms the olefin complex **IV**. Loss of acetate ion regenerates the π -allyliridium(I) complex **I** to close the catalytic cycle. The indicated stereochemical model accounts for the observed sense of absolute stereoselection for outer sphere addition of a nucleophile to the neutral iridium π -allyl complex **I**. This model is based upon the coordination mode revealed in closely related crystal structures.²¹ Orientation of the π -allyl is controlled through alleviation of steric clashes between the naphthyl and tolyl substituents of the phosphine ligand with the R-group of the resulting π -allyl, as illustrated in the disfavored mode of addition (Scheme 2).

Conclusions

Previously reported enantioselective allylic aminations are largely restricted to chiral iridium-phosphoramidite catalysts.⁴⁻¹² In the initial communication of our work,¹⁵ we have shown that the air and water stable π -allyliridium *C,O*-benzoate modified by SEGPFIOS, which is well-known for its ability to catalyze nucleophilic carbonyl allylation,^{1,2} also promotes highly regio- and enantioselective electrophilic allylation of primary aliphatic amines. As demonstrated here, the corresponding tol-BINAP-modified complex is a significantly more effective catalyst for allylic amination, which has enabled use of primary and secondary aromatic or heteroaromatic amine nucleophiles. These π -allyliridium *C,O*-benzoate catalyzed processes overcome a longstanding limitation associated with all known catalytic systems for asymmetric allylic amination - the ability to promote enantioselective aminations of racemic branched allylic acetates bearing *n*-alkyl groups with complete levels of regioselectivity.^{4-12,16} Another notable feature of these catalysts involves the ability to promote site-selective *N*-allylations of reactants that incorporate both primary and secondary aromatic amines. As demonstrated by mechanistic studies involving amination of the enantiomerically enriched deuterated allylic acetate **1h**, an outer-sphere mechanism for C-N bond formation is operative. This work, along with our prior studies,¹⁵ significantly expands

the scope of catalytic asymmetric allylic amination methodology, broadening access to diverse chiral α -stereogenic amines. Future work under the aegis of this academic-industrial collaboration will focus on expanding the range of amine nucleophiles for π -allyliridium *C,O*-benzoate catalyzed allylic amination, in particular, the use of secondary aliphatic amines and amide, and the development of related methods for asymmetric C-N bond formation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cationic vs neutral chiral iridium complexes for regio- and enantioselective allylic amination.

Scheme 1.

Iridium-catalyzed amination of enantiomerically enriched deuterated allylic acetate **1h** with the enantiomeric catalysts $(S)\text{-Ir-II}$ and $(R)\text{-Ir-II}$.^a

^a Yields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

Scheme 2.

General catalytic mechanism and stereochemical model for enantioselective iridium-catalyzed allylic amination.

Table 1.

Iridium-catalyzed amination of α -methyl allyl acetate **1a** with primary aromatic and heteroaromatic amines **2a-2l** to form enantiomerically enriched allylic amines **4a-4l**.^a

1a (100 mol%)	2a-2l (200 mol%)	4a-4l
2a , Ar = Ph	2b , Ar = 6-(benzodioxane)	2c , Ar = 4-F-Ph
2d , Ar = 3-Me-4-B(pin)-Ph	2e , Ar = 2-F-4-OMe-Ph	2f , Ar = 4-NMe ₂ -Ph
2g , Ar = 6-(<i>N</i> -Me-Indazole)	2h , Ar = 5-(2-morph-pym)	2i , Ar = 7-(benzothiazole)
2j , Ar = 3-SO ₂ Me-Ph	2k , Ar = 2-(pyridine)	2l , R = 3-(pyridine)
4a , 82% Yield, >99:1 rr 89% ee, [α] _D = -3.9 (c = 0.2, CHCl ₃)	4b , 85% Yield, >99:1 rr 90% ee	4c , 83% Yield, >99:1 rr 90% ee
4d , 78% Yield, >99:1 rr 89% ee	4e , 79% Yield, >99:1 rr 88% ee	4f , 89% Yield, >99:1 rr 90% ee
4g , 81% Yield, >99:1 rr 87% ee	4h , 82% Yield, >99:1 rr 89% ee	4i , 61% Yield, >99:1 rr 90% ee
4j , 76% Yield, >99:1 rr 91% ee	4k , 74% Yield, >99:1 rr 91% ee	4l , 87% Yield, >99:1 rr 91% ee

^aYields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

Table 2.

Iridium-catalyzed amination of α -methyl allyl acetate **1a** with secondary aromatic and heteroaromatic amines **3a-3l** to form enantiomerically enriched allylic amines **5a-5l**.^a

^aYields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

Table 3.

Iridium-catalyzed amination of α -substituted allyl acetates **1a-1g** with secondary heteroaromatic amine **3m** to form enantiomerically enriched allylic amines **6a-6g**.^a

^aYields of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.