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Direct Conversion of Primary Alcohols to 1,2-Amino Alcohols: Enantioselective Iridium-Catalyzed Carbonyl Reductive Coupling of Phthalimido-Allene *via* Hydrogen Auto-Transfer

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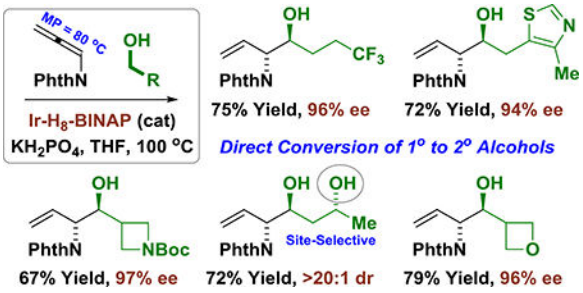
Abstract

The first catalytic enantioselective carbonyl (*α*-amino)allylations are described. Phthalimido-allene **1** and primary alcohols **2a-2z, 2a'−2c'** engage in hydrogen auto-transfer-mediated carbonyl reductive coupling by way of (*α*-amino)allyliridium-aldehyde pairs to form vicinal amino alcohols **3a-3z, 3a'−3c'** with high levels of regio-, *anti*-diastereo and enantioselectivity. Reaction progress kinetic analysis and KIE studies corroborate a catalytic cycle involving turn-over limiting alcohol dehydrogenation followed by rapid allene hydrometalation.

Graphical Abstract



Asymmetric carbonyl addition ranks foremost among methods used for the convergent construction of enantiomerically enriched alcohols.[1] Data mining of patents from the pharmaceutical industry reveals that carbonyl addition (alongside Suzuki coupling) remains one of the most frequently utilized methods for C-C bond formation.[2] The vast majority of carbonyl addition reactions rely on the use of preformed carbanions, which can be moisture sensitive, unsafe, and often require multi-step preparation and cryogenic conditions. Metal-catalyzed carbonyl reductive coupling of π-unsaturated pronucleophiles has emerged as an alternative to the use of stoichiometric carbanions.[3] However, many of the terminal reductants utilized in such processes (e.g. Mn, Zn, Et_3B, Et_2Zn) are as problematic as the

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Supporting Information Available: Experimental procedures and spectral data. X-Ray diffraction data for compounds **3a**, **3v** and the (*R*)-H_8-BINAP-modified iridium complex Ir-**VI**. This material is available free of charge *via* the internet at http://pubs.acs.org.

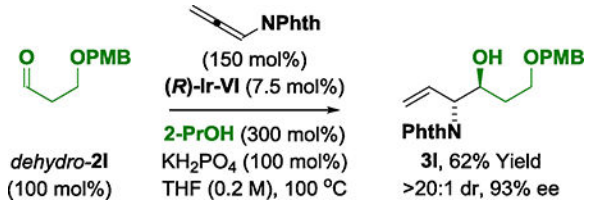
premetalated reagents they replace. Carbonyl reductive coupling via hydrogen auto-transfer does not require an exogenous reductant, as alcohol reactants serve dually as reductant and carbonyl proelectrophile.[4]

Based on this concept and motivated by the prevalence (>40%) of chiral amines (including vicinal amino alcohols) in FDA approved drugs,[5a,b] a catalytic enantioselective carbonyl (α-amino)allylation was sought.[6,7,8] In 1993, Barrett reported a boron reagent for asymmetric carbonyl (α-amino)allylation.[7] Remarkably, after more than 25 years, corresponding catalytic enantioselective processes have remained elusive, and the only related catalytic transformation to have appeared is the 2-azadiene-ketone reductive coupling reported by Malcolmson.[9] Here, we disclose that phthalimido-allene **1**, a tractable crystalline solid (M.P. = 79–81 °C), participates in catalytic enantioselective carbonyl reductive coupling via hydrogen auto-transfer to deliver vicinal amino alcohols with high levels of regio-, *anti*-diastereo- and enantiocontrol (Figure 1). This work represents a rare example of the use of allene pronucleophiles in enantioselective carbonyl reductive coupling.[10]

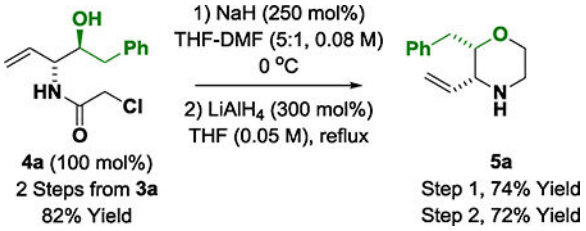
Phthalimido allene **1** is readily prepared through base-catalyzed isomerization of commercially available *N*-propargyl phthalimide.[11] Guided by seminal findings from our laboratory,[12] it was posited that hydrogen transfer from primary alcohols to allenimide **1** would generate transient (phthalimido)allyliridium-aldehyde pairs that combine by way of closed six-centered transition structures to furnish *anti*-vicinal amino alcohols. The feasibility of this transformation was rendered uncertain by competing conventional transfer hydrogenation of allene **1** in response to the steric demand of the phthalimide moiety, which may retard the rate of aldehyde addition. An assay of diverse chiral ruthenium and iridium complexes was undertaken and a promising result was obtained using the cyclometallated π-allyliridium complex modified by 3-nitrobenzoic acid and (*R*)-SEGPHOS, Ir-**I**, which delivered the desired amino alcohol **3a** in 10% yield and 40% ee with >20:1 *anti*-diastereoselectivity (Table 1). Enantioselectivity improved using the more Lewis acidic 4-cyano-3-nitro-*C*,*O*-benzoate, Ir-**II**, but the isolated yield of **3a** remained modest due to low conversion. Similar trends were observed with the corresponding catalysts based on (*R*)-BINAP, Ir-**III** and Ir-**IV**, but with a small increase in enantioselectivity. A pronounced improvement in both conversion and enantioselectivity was observed upon use of Ir-**V**, which incorporates (*R*)-H_8-BINAP.[13] Use of the (*R*)-H_8-BINAP iridium complex bound by 3,4-dinitro-*C*,*O*-benzoic acid, Ir-**VI**, provided still higher levels of enantioselectivity. Finally, introduction of mono-basic potassium phosphate led to higher conversion, allowing **3a** to be formed in 80% yield, 96% ee with complete *anti*-diastereoselectivity (Table 1). As borne out by single crystal X-ray diffraction analysis of Ir-**VI** (see Supporting Information), the dihedral angle between the tetralin rings of (*R*)-H_8-BINAP (ca. 86°) is significantly larger than the dihedral angle between the naphthalene rings of BINAP (ca. 75°) or SEGPHOS (ca. 72°),[14] which may better accommodate the sterically demanding phthalimide moiety to facilitate alkoxide exchange at the metal center.

Reaction scope was evaluated by applying optimal conditions identified for the (α-amino)allylation of 2-phenylethanol **2a** to diverse alcohols **2b-2z**, **2a′**−**2c′** (Table 2). All vicinal amino alcohols **3a-3z**, **3a′**−**3c′** were formed in good yield with excellent levels of diastereo- and enantioselectivity. The (α-amino)allylations of *N*-Boc-ethanolamine **2j**, *N*-

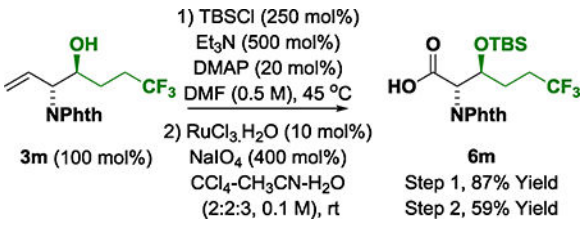
Boc-propanolamine **2k** and trifluorobutanol **2m**, which are commercially available, are significant as the corresponding aldehydes are not available for purchase and are relatively unstable. Modification of the heteroaryl-containing alcohols **2c**-**2i**, **2t** and **2u**, which includes perphenazine **2g**, an FDA approved drug, establishes the feasibility of utilizing this method for late-stage functionalization.[15] Due to a pronounced kinetic bias for primary alcohol dehydrogenation,[16] free secondary hydroxyl groups are tolerated, as illustrated in the site-selective formation of (*R*)-butane diol adducts **3b′** and **3c′**, which occur with complete levels of catalyst-directed diastereoselectivity. Using this first generation catalytic system, benzylic alcohols are converted to the amino alcohols in high yield but lower enantioselectivities are observed. As demonstrated by the conversion of *dehydro*-**2l** to amino alcohol **3l**, the reactions can also be conducted from the aldehyde oxidation level using 2-propanol as terminal reductant (eq. 1). Given the frequent appearance of morpholines as substructures in pharmaceutical ingredients,[17] compound **3a** was converted to the morpholine **5a** (eq. 2).[18] To further demonstrate utility of amino alcohols **3a**-**3z**, **3a′**−**3c′**, adduct **3m** was subjected to alkene oxidative cleavage to provide the non-proteinogenic amino acid derivative **6m** (eq. 3).[19]



(eq. 1)



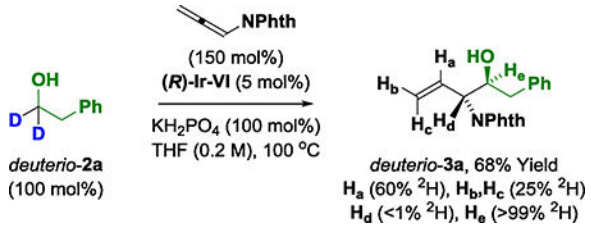
(eq. 2)



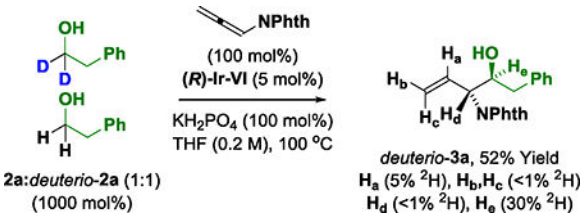
(eq. 3)

Reaction progress kinetic analysis (RPKA) using the “different excess” protocol was used to gain mechanistic insight (Figure 2).[20] The kinetic order of reactants varied over time; therefore, general trends were evaluated. Doubling the initial concentration of allene **1** slightly decreases the rate of product formation. This data suggests allene hydrometalation is rapid, allene **1** is not involved in the turnover-limiting step and, at higher concentrations, allene **1** inhibits the rate of product formation (Figure 2, left). Doubling the initial concentration of alcohol **2a** results in a slight increase in the rate of product formation, signifying a positive order in alcohol **2a** (Figure 2, middle). Increasing the loading of iridium catalyst, (*R*)-Ir-**VI**, results in a dramatic increase in the rate of product formation, demonstrating the reaction is positive order in catalyst (Figure 2, right). Separate experiments using the “same excess” protocol reveal significant catalyst deactivation that is contributed to by product inhibition.[21] Additionally, introduction of aldehyde *dehydro*-**2a** (10 mol%) inhibits product formation, suggesting carbonyl addition may not be turn-over limiting.[21]

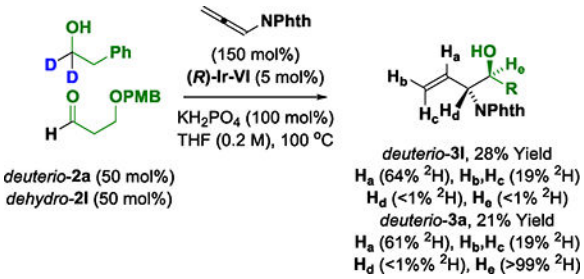
Deuterium labeling studies provide additional information on the reaction mechanism (eq. 4–6).[22] Exposure of allene **1** to *deuterio*-**2a** under standard reaction conditions delivers *deuterio*-**3a** (eq. 4). Deuterium is completely retained at the carbinol position, suggesting *deuterio*-**3a** is inert with respect to dehydrogenation. Incorporation of deuterium at both the internal and terminal vinylic positions corroborates reversible allene hydrometalation with incomplete regioselectivity. In a competition kinetics experiment, allene **1** was exposed to equimolar quantities of alcohol **2a** and *deuterio*-**2a** (eq. 5). The observed levels of deuterium incorporation at the carbinol position of *deuterio*-**3a** are consistent with a normal primary kinetic isotope effect ($k_H/k_D \approx 2.3$). Evaluation of the initial rates for the reaction of both **2a** and *deuterio*-**2a** also reveals a primary kinetic isotope effect ($k_H/k_D \approx 1.5$) (Figure 3). Along with the reaction orders suggested from the RKPA experiments, this KIE data was consistent with two scenarios: (1) reversible alcohol dehydrogenation followed by rate-determining carbonyl addition, or (2) rate-determining alcohol dehydrogenation.[22] To determine which of these processes is operative an additional experiment was undertaken (eq. 6). When pthalimido-allene **1** is exposed to equimolar quantities of *deuterio*-**2a** and *dehydro*-**2l** under standard conditions, hydrogen-deuterium exchange is not observed at the carbinol position of *deuterio*-**3a** and *dehydro*-**3l**, suggesting alcohol-aldehyde redox equilibration does not occur in advance of carbonyl addition. Hence, the collective data implicate turnover-limiting alcohol dehydrogenation followed by rapid allene hydrometalation.



(eq. 4)



(eq. 5)



(eq. 6)

Based on the kinetic and isotopic labeling studies, the indicated catalytic mechanism is proposed (Scheme 1). Entry into the catalytic cycle occurs through protonolysis of the allyliridium complex (*R*)-Ir-**VI** by the reactant alcohol. The resulting iridium alkoxide **I** undergoes irreversible dehydrogenation to form the iridium hydride **II**, which is rapidly consumed by reversible allene hydrometalation. Due to the steric demand of the phthalimide moiety, the (*Z*)-σ-(amino)allyliridium complex **IIIa** is anticipated to be the kinetic product of allene hydrometalation. Isomerization to the thermodynamically preferred (*E*)-σ-allyliridium complex **IIIb**, is followed by aldehyde coordination and carbonyl addition through a closed chair-like transition structure to form iridium(III) alkoxide **IV**. Exchange with the primary alcohol reactant releases product and regenerates iridium alkoxide **I** to close the catalytic cycle.

In summary, we report a catalytic method for the direct conversion of primary alcohols to vicinal amino alcohols that occurs with high levels of regio-, *anti*-diastereo- and enantioselectivity. This hydrogen auto-transfer process exploits the tractable, crystalline phthalimido-allene **1** as pronucleophile and represents the first protocol for catalytic enantioselective carbonyl (α-amino)allylation. More broadly, this work contributes to an evolution from use of traditional carbonyl addition methods that exploit preformed carbanions to byproduct-free catalytic carbonyl reductive couplings, where alcohol proelectrophiles and π-unsaturated pronucleophiles combine by way of *transient* organometallics.[4]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(20). For a review on reaction progress kinetic analysis, see: Blackmond DG Reaction Progress Kinetic Analysis: A Powerful Methodology for Mechanistic Studies of Complex Catalytic Reactions. Angew. Chem., Int. Ed 2005, 44, 4302.

(21). This experiment is described in the Supporting Information.

(22). An authoritative treatment of the execution and interpretation of kinetic isotope effect experiments in reactions involving C-H bond cleavage is reported. Our catalytic mechanism appears consistent with reaction coordinate 1, Figure 1: Simmons, E. M.; Hartwig, J. F. On the Interpretation of Deuterium Kinetic Isotope Effects in C-H Bond Functionalizations by Transition-Metal Complexes. Angew. Chem. Int. Ed 2012, 51, 3066.

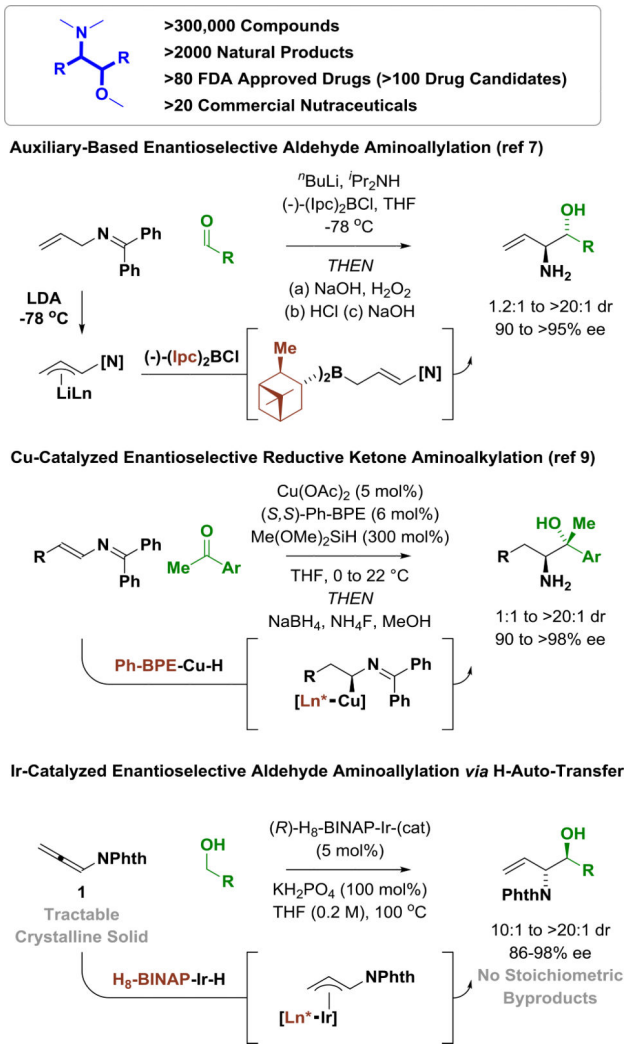


Figure 1.

Selected enantioselective methods for convergent construction of vicinal amino alcohols *via* classical and metal-catalyzed carbonyl addition.

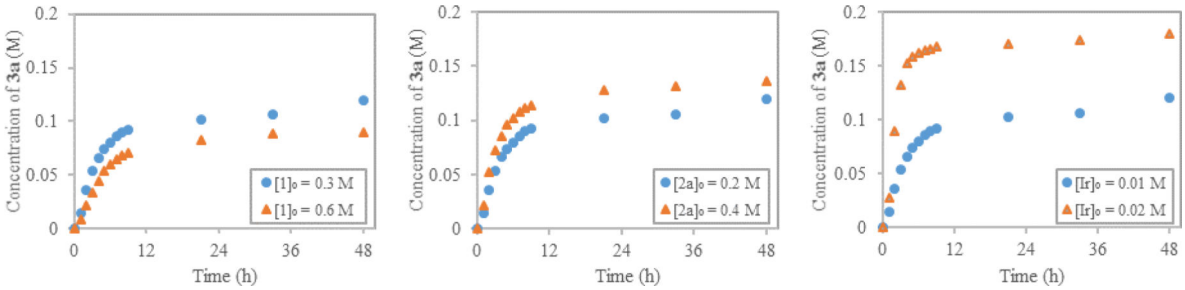


Figure 2.

Product formation as monitored by ^{1}H NMR analysis in reactions conducted using the "different excess" protocol: [Ir] = 0.01 M; [KH_2PO_4] = 0.2 M. (left) [**2a**]$_0$ = 0.2 M, [**1**]$_0$ = as noted; (middle) [**1**]$_0$ = 0.3 M, [**2a**]$_0$ = as noted. (right) Product formation varying catalyst loading reactions as monitored by NMR analysis: [**1**] = 0.3 M; [**2a**] = 0.2 M; [KH_2PO_4] = 0.2 M; [cat] = as noted.

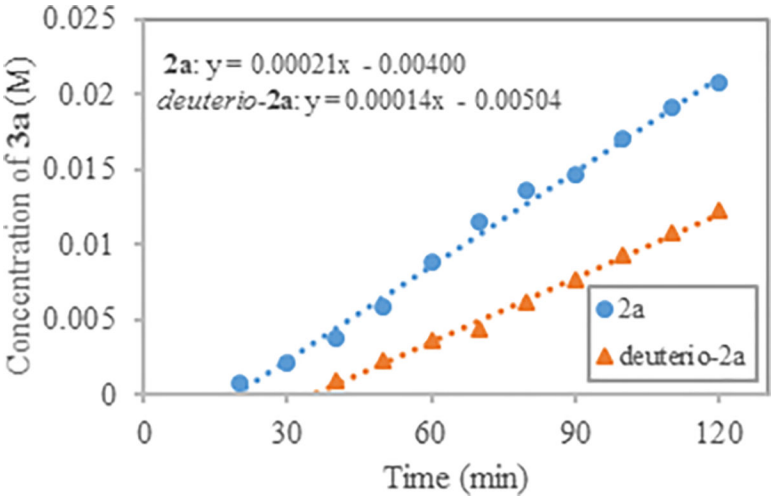
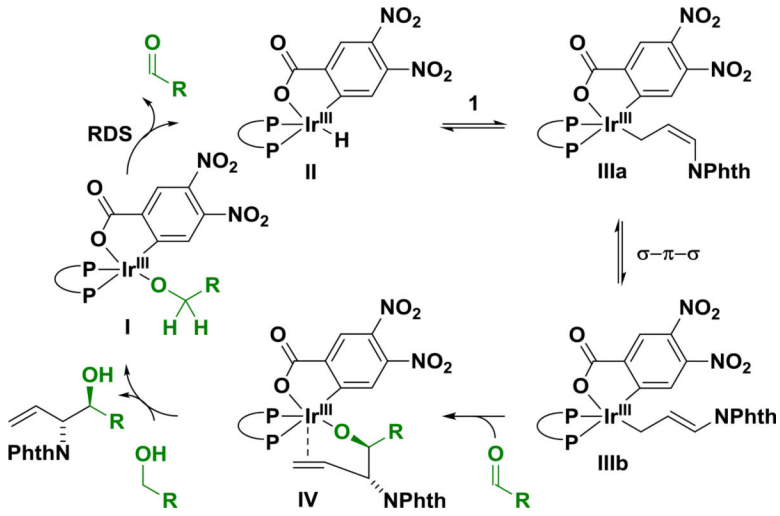


Figure 3.
Initial rates study: $[\mathbf{1}]_0$ = 0.3 M; $[\mathbf{2a}]_0$ or $[\textit{deuterio}\text{-}\mathbf{2a}]_0$ = 0.2 M; [cat] = 0.01 M.

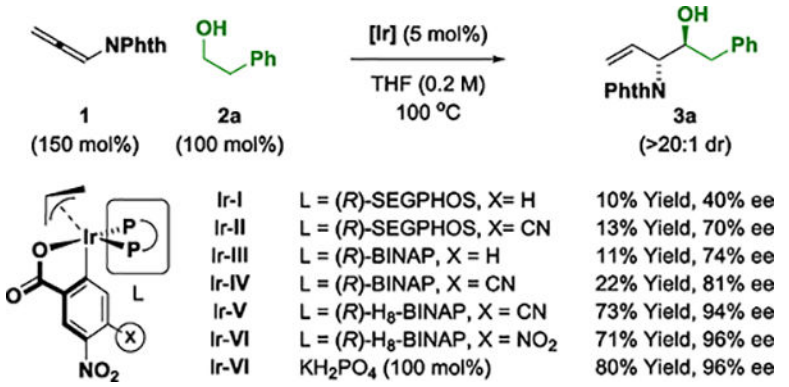


Scheme 1.

General catalytic mechanism as corroborated by kinetic and isotopic labeling studies.

Table 1.

Selected optimization experiments in the enantioselective iridium-catalyzed (α-amino)allylation of phthalimido-allene **1** with alcohol **2a**.[a]

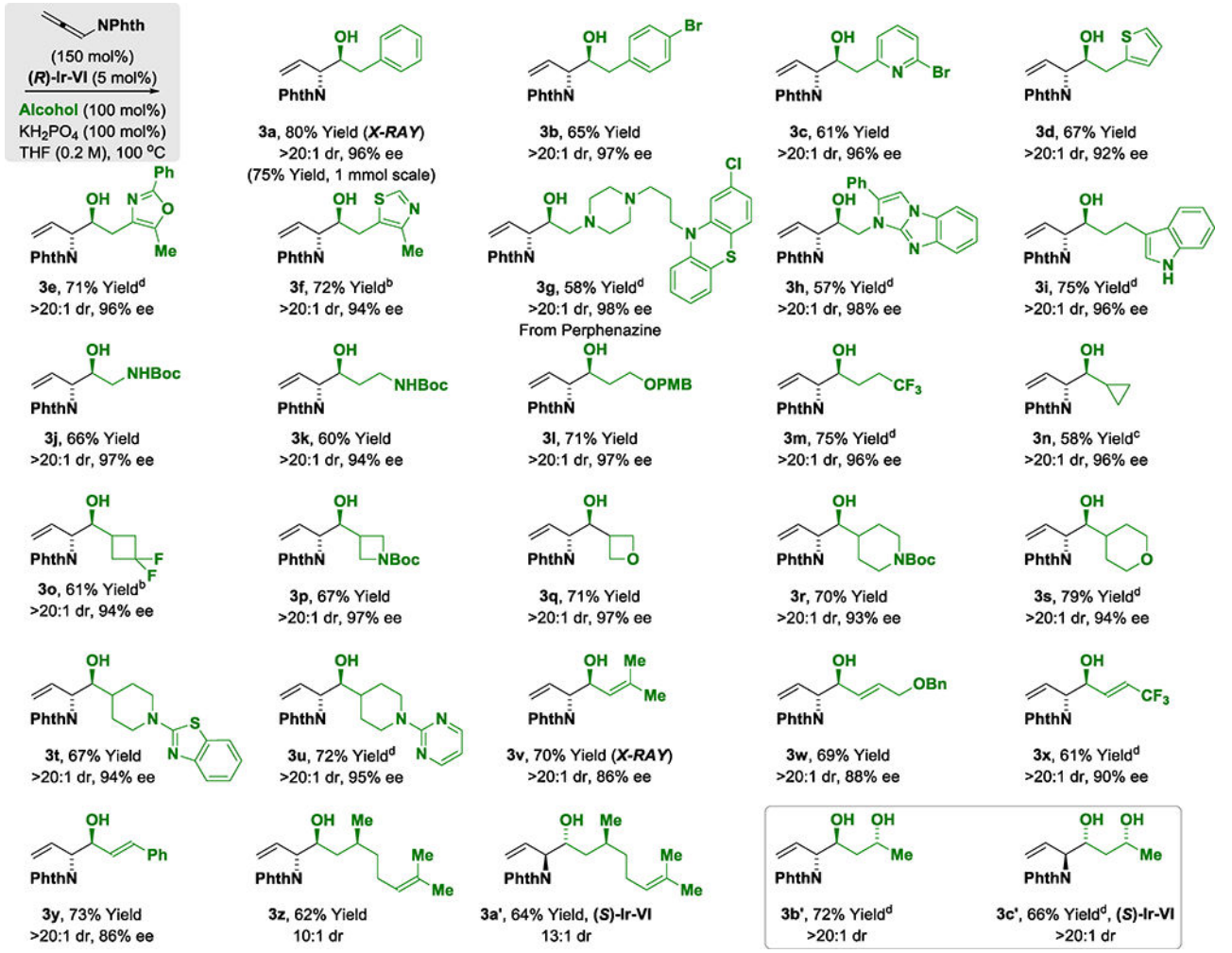


Ir-I	L = (*R*)-SEGPHOS, X= H	10% Yield, 40% ee
Ir-II	L = (*R*)-SEGPHOS, X= CN	13% Yield, 70% ee
Ir-III	L = (*R*)-BINAP, X = H	11% Yield, 74% ee
Ir-IV	L = (*R*)-BINAP, X = CN	22% Yield, 81% ee
Ir-V	L = (*R*)-H_8-BINAP, X = CN	73% Yield, 94% ee
Ir-VI	L = (*R*)-H_8-BINAP, X = NO_2	71% Yield, 96% ee
Ir-VI	KH_2PO_4 (100 mol%)	80% Yield, 96% ee

[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for experimental details.

Table 2.

Diastereo- and enantioselective iridium-catalyzed hydrohydroxyalkylation of phthalimido-allene **1** with alcohols **2a-2z**, **2a′−2c′** to form 1,2-amino alcohols **3a-3z**, **3a′−3c′**.[a]



[a]Yields are of material isolated by silica gel chromatography. Diastereoselectivities were determined by ^{1}H NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. Standard conditions: 0.2 mmol scale, 48 h. See Supporting Information for experimental details. [b]72 h, [c]Ir-**V**, [d]Ir-**VI** (7.5 mol%).