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Coordination-Induced Stereocontrol over Carbocations: Asymmetric Reductive Deoxygenation of Racemic Tertiary Alcohols

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ABSTRACT

The inherent difficulty in eliciting facial control over carbocations has limited their utility as intermediates in asymmetric catalysis. We have now shown that a docking strategy involving the reversible coordination of a substrate to a chiral transition metal catalyst can be used to enable highly stereoselective nucleophilic attack on intermediate tertiary carbocations. This approach has been implemented to achieve the first example of enantioselective reductive deoxygenation of tertiary alcohols. This reduction occurs with high enantio- (up to 96% ee) and regioselectivity (up to >50:1 rr) by applying a novel Hantzsch ester analog as a convenient hydride source. In-depth mechanistic studies support the involvement of a tertiary carbocation which is coordinated to the iridium metal center via the key allene moiety.

INTRODUCTION

Carbocations have prompted the development of myriad chemical reactions since their independent discovery by Norris and by Kehrman and Wentzel in 1901.[1] Despite their ubiquity in organic chemistry, the role of carbocations as intermediates in asymmetric synthesis has lagged behind considerably.[2] This disparity lies in the intrinsic difficulty in biasing nucleophilic attack on one of the two prochiral faces of their planar structure (Scheme 1A, left). Accordingly, the two main strategies for stereocontrol over carbocations have involved diastereoselective substrate-control (Scheme 1A, center)[3] or the formation of ion pairs between chiral anions (i.e. *X⁻) and achiral carbocations (Scheme 1A, right).[4-7] These approaches have been most successfully applied to transformations proceeding through secondary carbocations, whereas their use in achieving enantiocontrol over tertiary species has been less fruitful.[8,9] A major breakthrough in this area was recently made by Jacobsen who exploited ion pair interactions involving chiral hydrogen bond-donor-acceptor complexes to achieve enantiocontrol over discrete tertiary carbocations.[10] Therein, enantioenriched quaternary carbons could be constructed via asymmetric allylation, while circumventing the need for dynamic substrate epimerization,[8a] or heteroatoms that assist in solvolysis and carbocation stabilization.[8b]

We recently reported the asymmetric alkylation of secondary allenyl carbonates (Scheme 1B).[11] Accompanying theoretical studies pointed to the involvement of an unusual intermediate that contains an electrophilic η^2-allene ligand with a highly delocalized positive charge (i.e. **A**).[12] The obvious parallels between this overall transformation and the S_N1 reaction manifold led us to hypothesize that this mode of reactivity could also be used to command stereocontrol of tertiary carbocations. In this approach, the chiral metal complex emulates the effect of an existing stereocenter via coordination to the substrate, while the ensuing ionization would generate a tertiary carbocation which is confined within the chiral coordination sphere (Scheme 1C).[13]

In 1982, Siehl and Mayr reported that cations of type **B** could be generated via the ionization of tertiary α-allenyl alcohols and spectroscopically characterized (Scheme 1D).[14-16] These studies provided insight into the nature of the charged intermediate and revealed that the positive charge was mostly localized at C_α and C_γ (i.e. **B1** or **B2**, respectively). On account of the orthogonality of the p-orbitals constituting the 1,2-diene motif, resonance stabilization is possible without loss of the C_γ–C_δ double bond. We have been interested in examining whether cations of type **B** could be generated after coordination of

tertiary α-allenyl alcohols to a chiral metal catalyst through the remaining double bond,[17] and, if so, whether a regio- and enantioselective S_N1-type reaction could be accomplished.
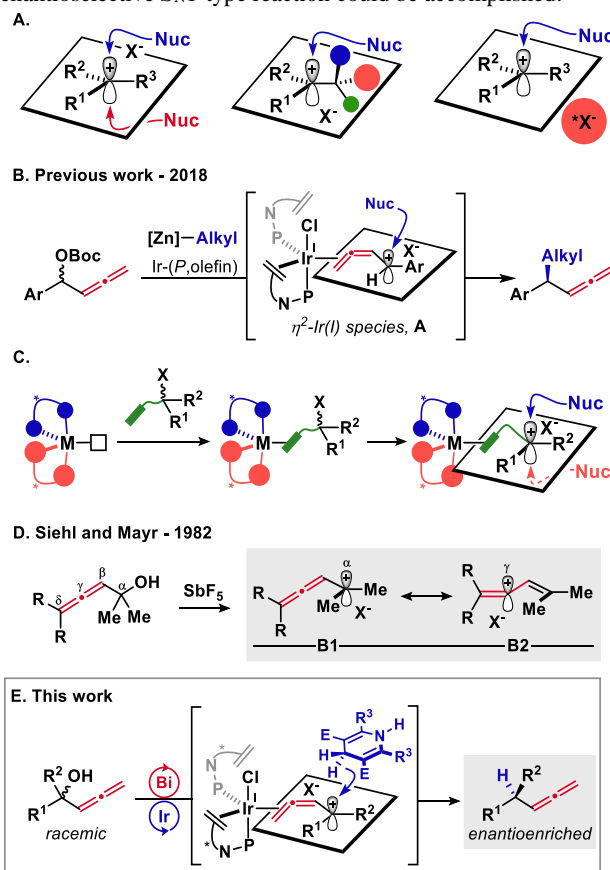
**Scheme 1. A.** (left) The innate challenge in stereocontrol with carbocations; (center) using substrate control; (right) using chiral ion pairing to elicit stereocontrol; **B.** Asymmetric Ir-catalyzed alkylation of allenyl carbonates involving an electrophilic η^2-bound butadienylium intermediate; **C.** Applying an anchoring strategy involving metal–substrate coordination as a means to gain enantiocontrol over tertiary carbocations; **D.** Generation of stable α-vinyl substituted vinyl cations. **E.** Coordination-induced stereocontrol of 3° carbocations in asymmetric reductive deoxygenation.

Herein, we outline the implementation of this strategy for stereocontrolled additions to tertiary carbocations as a design element in the first catalytic, asymmetric, reductive, deoxygenation reaction (Scheme 1E).[18-22]

It is important to note that metal-catalyzed allenylic substitutions have largely been reported for Pd and Ir complexes with activated secondary alcohol derivatives (Scheme 2A).[11,23,24] In general, asymmetric substitution reactions of tertiary allenylic leaving groups are, to the best of our knowledge, unknown.[25] The use of bismuth(III) triflate[26] and a chiral Ir(I)-bis(phosphoramidite,olefin) complex has now enabled the direct and stereoselective reductive deoxygenation of racemic tertiary α-allenyl alcohols. A collection of mechanistic studies has provided experimental evidence for the involvement of a coordinated tertiary carbocation as a key catalytic intermediate in this highly enantioconvergent transformation.[27]
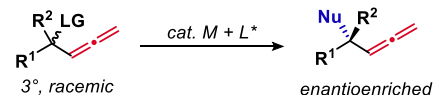
Scheme 2. Transition metal-catalyzed allenylic substitution.

Prior work
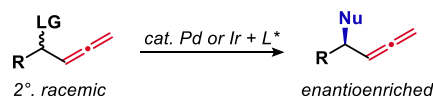
LG = OAc, OPO(OEt)$_2$, OBoc — Nu = malonates, HNR$_2$, [Zn]—Alkyl

Previously Unknown (This work; LG = OH, Nu = H)

RESULTS AND DISCUSSION

Reaction Optimization. Our studies were initiated using racemic α-allenyl alcohol (±)-**1a** which could be prepared in two steps from commercially available 2-acetonaphthone via a route involving Ma's modified Cu(I) catalyzed Crabbé homologation.[28] Hantzsch pyridines were chosen as the hydride source in this process due to their successful use in numerous catalytic asymmetric transformations including allylic reduction[29] and transfer hydrogenation.[30,31] Furthermore, their ease of preparation and their high degree of modularity greatly facilitates reaction optimization.

After evaluating a wide array of reaction parameters, a system comprising [Ir(cod)Cl]$_2$ (2 mol%) and chiral phosphorous–olefin ligand (S)-**L1** (8 mol%) and Bi(OTf)$_3$ (0.4 mol%) in combination with the novel bis-isopropyl Hantzsch dihydropyridine analog **HEH-1** (1.5 equiv) in CPME ([(±)-**1a**] = 0.2 M) at room temperature was found to be optimal. Under these conditions, allene (S)-**2a** was obtained in 91% yield with 92% ee and >20:1 regioselectivity over the corresponding achiral 1,3-diene (E)-**2a'** (Table 1, entry 1). Moreover, the formation of vinyl allene **5a** could be almost completely supressed under these conditions. The application of standard Hantzsch dihydropyridine **HEH-2** had no deleterious effect on yield; however, marked decreases in both regio- and enantioselectivity were observed (entry 2). Although larger groups at the 2- and 6-positons of the HEH motif impacted the overall selectivity profile of this reaction, larger *tert*-butyl esters at the 3- and 5-positions resulted in lower yield and enantioselectivity, albeit with no observed change in regioselectivity (entry 3). Furthermore, commonly employed *N*-benzyl dihydronicotinamide **3** was found to be an unsuitable hydride donor in this transformation (entry 4). Of note was the sensitivity of the enantioselectivity to the loading of the Bi(OTf)$_3$ co-catalyst.[26] When the loading was increased from 0.4 mol% to 1.0 mol%, the yield, regio- and enantioselectivity all decreased to 75%, 14:1 rr, and 86% ee, respectively (entry 5). This suggests that a higher co-catalyst loading may increase the rate of the non-Ir-catalyzed background reduction (*vide infra*).

Table 1. **Effect of Reaction Parameters.**[a]

entry	variation from the "standard" conditions	(S)-**2a** (%)[b,c]	rr[c] **2a:2a'**	ee (%)[d]
1	**None**	**91(81)**[e]	**>20:1**	**92**
2	**HEH-2** instead of **HEH-1**	91	11:1	84
3	**HEH-3** instead of **HEH-1**	18	>20:1	80
4	**3** instead of **HEH-1**	<2	–	–
5	1 mol% of Bi(OTf)$_3$	75	14:1	86
6[f]	no Bi(OTf)$_3$	<2	–	–
7[g]	**4** instead of Bi(OTf)$_3$	16	12:1	94
8[h]	4 °C instead of rt	53	>20:1	92
9	no [Ir]/(S)-**L1**	9	7:1	0
10	no [Ir]	8	6:1	0
11	no (S)-**L1**	6	2:1	0
12[i]	1:1 [Ir]:**L1**	23	15:1	74
13	(S)-**L2** used	6	3:1	39
14[j]	(S,S,S)-**L3** used	<2	–	–
15	[Rh(cod)Cl]$_2$ used	<2	–	–

[a] Reactions run on 0.5 mmol scale. ≤ 3% of vinyl allene **5a** was observed. [b] Combined yield of regioisomers. [c] Determined by ^{1}H NMR analysis of the unpurified reaction mixture. [d] Determined by GC using a chiral stationary phase. [e] Isolated yield of (S)-**2a**. [f] Starting material was recovered quantitatively. [g] Reaction was run using 5 mol% of **4**; 13% of vinyl allene **5a** was observed. [h] Reaction time = 50 h. [i] [Ir] = 4.0 mol% and (S)-**L1** = 4.0 mol%. [j] Catalyst pre-formed using ^{n}PrNH$_2$, see ref. 33. − = not determined; CPME = cyclopentolates methyl ether; cod = 1,5-cyclooctadiene; 2-Np = 2-naphthyl; OTf = trifluoromethanesulfonate.
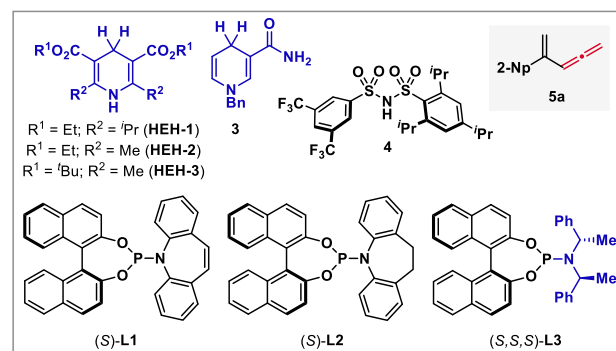
Conversely, no products are observed in the absence of Bi(OTf)$_3$, and only starting material is recovered (entry 6). Our group previously showed that sulfonamide **4** was an optimal Brønsted acid co-catalyst for asymmetric allyl-alkene couplings.[32] The use of 5 mol% of **4** in place of Bi(OTf)$_3$ resulted in decreased reaction efficiency (16% yield), albeit with slightly increased enantioselectivity (entry 7). Decreasing the reaction temperature to 4 °C in an effort to increase enantioselectivity rendered the reaction sluggish and had no positive effect on selectivity (entry 8).
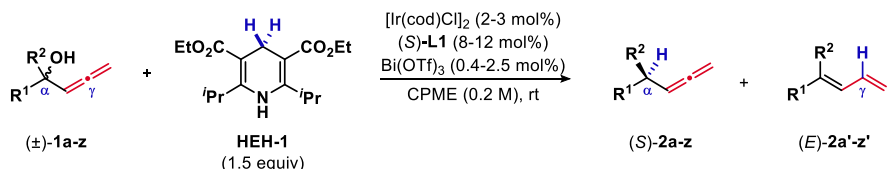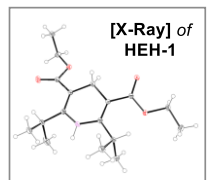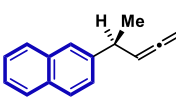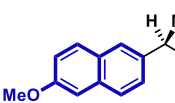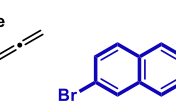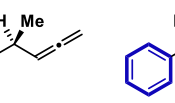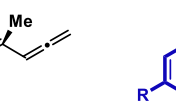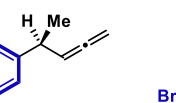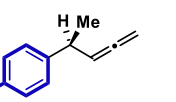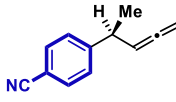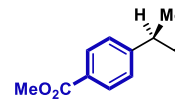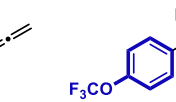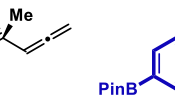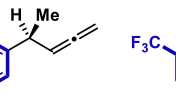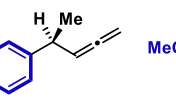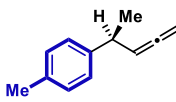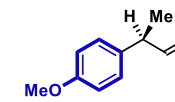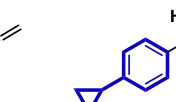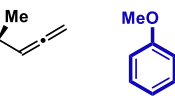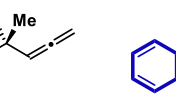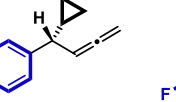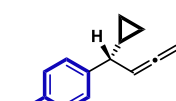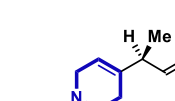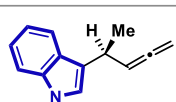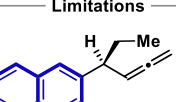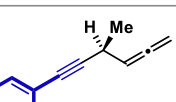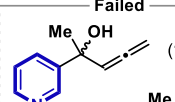
The highly activated nature of (±)-**1a** presumably increases its susceptibility to background reaction giving racemic product. In order to determine the extent to which these reactions occur, experiments were performed in the absence of the [Ir(cod)Cl]$_2$/(S)-**L1** catalyst combination or its other individual components (entries 9-11). Therein, products (S)-**2a** and (E)-**2a'** could be observed, albeit with low yield (6-9%) and regioselectivity (2:1 to 7:1). When the [Ir]:(S)-**L1** ratio was changed from 1:2 to 1:1, the yield, regio- and enantioselectivity all significantly decreased to 23%, 15:1 rr, and 74% ee, respectively (entry 12). In accord with our previously reported asymmetric alkylation of allenylic carbonates, these findings support the notion that a 1:2 Ir:(P,olefin) complex is operative

(*vide infra*).[11,18] Both structural and electronic permutations of **L1** led to less satisfactory reaction outcomes. The olefin motif of the ligand was found to be crucial for overall reaction efficiency and selectivity. When dihydro analog (*S*)-**L2** was employed, the product was obtained in only 6% yield with 3:1 rr and 39% ee (entry 13). In our previously allenylic alkylation, we observed that employing a catalyst system comprising (*S*,*S*,*S*)-**L3** leads to exclusive formation of the undesired 1,3-diene isomer.[11,33] However, neither reduction regioisomer was observed with the catalyst system employed as optimal in this study (entry 14). Recently, You and co-workers have shown that the combination of [Rh(cod)Cl]₂ and **L1** was an effective catalyst for the asymmetric allylic alkylation of racemic allylic alcohols.[34] When [Rh(cod)Cl]₂ was used in place of [Ir(cod)Cl]₂, no reaction occurred, and the starting material was recovered quantitatively (entry 15). Overall, this reaction is simple,

practical and can be performed using standard benchtop techniques, without the need to strictly avoid air and moisture.

Reaction Scope. Various racemic tertiary α-allenyl alcohols were found to undergo the desired transformation to afford products with high levels of enantiomeric excess (Table 2). 2-Naphthyl analogs containing electron-donating (**2b**) and -withdrawing (**2c**) substituents were tested, and the desired products could be obtained in 84% and 67% yield with 90% and 94% ee, respectively. Less reactive non-naphthyl-based substrates were also examined. Products containing a wide array of aryl analogs with *para* electron-withdrawing groups including halogens (**2e-2g**), a nitrile (**2h**), a methyl ester (**2i**), or an –OCF₃ (**2j**) group were furnished in 55-72% yield with 90-94% ee. The pinacolborane functionality was also retained under these conditions, and the corresponding product (**2k**) was obtained in 74% yield with 96% ee. Substrates incorporating *meta* substituents such as –CF₃ (**2l**)

Table 2. Scope of the asymmetric Ir-catalyzed reductive deoxygenation of racemic tertiary alcohols.[a]

[a] Reaction conditions: [Ir(cod)Cl]₂ = 3.0 mol%, (*S*)-**L1** = 12 mol%, (±)-**1** (0.5 mmol), **HEH-1** (1.5 equiv), CPME (c = 0.2 M), rt unless otherwise noted. Isolated yields shown. Enantiomeric excess values (ee) were determined by GC analysis using a chrial stationary phase. Regiochemical ratios (rr) were determined by ¹H NMR analysis of the unpurified reaction mixtures. [b] Reaction was run using [Ir] = 4.0 mol% and (*S*)-**L1** = 8 mol%. [c] 0.2 mol% of Bi(OTf)₃ was used. [d] Reaction was run in Et₂O. [e] 3.0 mol% of Bi(OTf)₃ was used. [f] 2.5 mol% of Bi(OTf)₃ was used. [g] 1.0 mol% of Bi(OTf)₃ was used. [h] 1.5 mol% of Bi(OTf)₃ was used. [i] 0.8 mol% of Bi(OTf)₃ was used.

or –OMe (**2m**) were also tolerated, and the corresponding products were obtained in 55% and 68% yield with 93% and 92% ee, respectively. Products containing electron-donating groups (**2n-2q**) such as –Me (**2n**), –OMe (**2o, 2q**), and cyclopropyl (**2p**) were also obtained in 61-88% yield with 71-

90% ee. Given the well-established stability of cyclopropyl carbinyl cations,[16,36] substrates containing cyclopropyl rings at the stereogenic carbon center were also examined. Subjecting the analogous cyclopropyl carbinols possessing 2-naphthyl (**2r**), *para*-fluoro (**2s**) or *para*-chloro (**2t**) aromatic groups to

the reaction conditions led to the formation of the desired cyclopropane-containing products in 72-79% yield with 93-96% ee.

The use of cyclopropyl-containing substrates led to several interesting observations. The corresponding products were obtained with the opposite absolute configuration with respect to the corresponding Me analogs, and neither the achiral diene regioisomer, nor products resulting from cyclopropane ring-opening were observed. The exclusive regioselectivity observed with these substrates is presumably a manifestation of the cyclopropanes ability to stabilize a significant proportion of the positive charge, generated upon ionization at the benzylic carbon. The scalability of this transformation was highlighted using substrate **1t** where the corresponding product could be obtained in 81% yield and with >50:1 rr and 93% ee when the experiment was conducted on a 1.2 gram scale. Tetrahydropyridine derivative containing an *N*-CBz group was also tolerated under the reaction conditions and the desired product **2u** was obtained in 57% yield with >20:1 rr and 99% ee. Some limitations of the methodology were encountered. For example, tosylated indole **2v** was obtained in 72% yield and with >20:1 rr, albeit with only 38% ee. Furthermore, use of a substrate containing an –Et group at the stereocenter led to both an attenuation in yield and selectivity and product **2w** was obtained in 44% yield with 17:1 rr and 50% ee. Finally, 1,4-ynallene product **2x** was obtained in 58% yield with >20:1 rr and 55% ee. This reaction proved to be intolerant of substrates containing highly Lewis basic functionalities (i.e. **1y**) or sterically large groups like *i*Pr at the stereocenter (i.e. **1z**). These effects likely arise from the poisoning of the Bi(OTf)₃ co-catalyst and a highly encumbered approach of **HEH-1** in the reduction step, respectively.

The general trend observed across this series of substrates is that electron-deficient ones typically lead to higher levels of enantioselectivity and attenuated levels of regioselectivity while the opposite is true for electron-rich substrates. The variation in regioselectivity across electron-rich and -poor substrates is in line with our proposed model of a coordinated carbocation wherein positive charge is mostly localized at the two carbons at which hydride transfer delivers the competing regioisomers (i.e. C_α in **B1** and C_γ in **B2**). The work of Mayr and co-workers concerning allyl cations indicates that electron-releasing substituents increase and decrease positive charge at the proximal and distal carbons, respectively, whereas the opposite is true for electron-accepting substituents.[36] In this regard, higher allene:diene regioselectivities in substrates containing electron-rich aryl groups or cyclopropyl substituents is likely the result of increased positive charge population at C_α in the coordinated carbocation.

Mechanistic Studies. We undertook in-depth experimental investigations to examine the underlying catalytic mechanism. A series of experiments were initially performed using isotopically labeled reagents and substrates (Scheme 3). The reductive deoxygenation was carried out using 4,4-*d₂*-**HEH-1** (>99% D) which led to the complete transfer of the deuterium label to the benzylic carbon of the substrate (Scheme 3A). This finding confirms the sole origin of the hydrogen at the stereogenic benzylic carbon to be the 4-position of the Hantzsch ester. Product (*S*)-**2a**-*d₁* was obtained in comparable yield (84%) and selectivity (>20:1 rr and 92% ee) as to when non-labeled **HEH-1** was employed. Vinyl allene **5a**, resulting from dehydration of the tertiary alcohol substrate, was observed as a side product in varying quantities during reaction optimization. Two sets of experiments were carried out to probe whether this species is an intermediate in the reaction mechanism. Substrate (±)-**1a**-*d₃* containing a perdeuterated methyl group (>98% D) was first subjected to

the standard conditions (Scheme 3B). It was found to undergo the desired transformation with nearly identical efficiency to non-deuterated (±)-**1a**, and without erosion of isotopic purity or scrambling of the label. Second, a cross-over experiment involving methoxynaphthyl substrate (±)-**1b** and vinyl allene **5a** led only to the formation of the asymmetric reductive deoxygenation product (*S*)-**2b** (Scheme 3C). Together, these results suggest that the tertiary alcohol substrate undergoes direct conversion to product by way of a mechanism which does not involve an initial dehydration step.[37]

Scheme 3. Deuterium labeling studies and cross-over experiments.
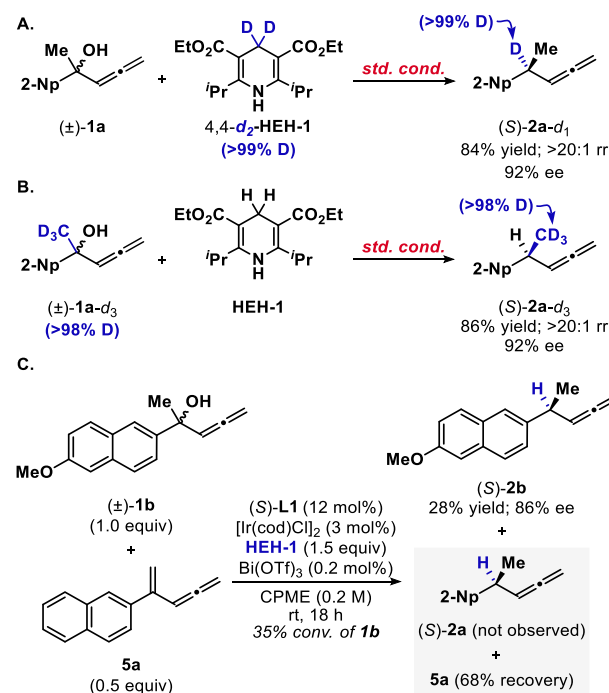
The proposed reductive deoxygenation resembles an S_N1-type reaction that is likely to proceed via a mechanism involving turnover-limiting ionization of the tertiary alcohol motif.[38] In line with this hypothesis, a series of kinetic isotope effect (KIE) studies were first conducted to determine if hydride transfer could be ruled out as the turnover-limiting step. As such, intermolecular primary KIE experiments (same vessel) were carried out on two different racemic tertiary alcohol substrates (±)-**1a** or (±)-**1g** in the presence of a mixture of **HEH-1** and 4,4-*d₂*-**HEH-1**. Therein, substrates (±)-**1a** and (±)-**1g** led to calculated k_H/k_D values of 2.90 and 2.33, respectively. (Scheme 4A). Since findings of this nature do not always provide sufficient evidence to conclude that C–H bond cleavage, here in the step of hydride attack, is turnover-limiting, parallel KIE experiments (separate vessels) were also conducted.[39]

During these parallel KIE studies, we determined that the minute quantities of Bi(OTf)₃ required under the standard conditions (0.4 mol%) precluded its usefulness for obtaining a high level of reproductivity between runs. This challenge was compounded by its low solubility in organic solvents which negated our ability to precisely administer this reagent from a stock solution. We hypothesized that if a well-defined hydride transfer pathway was operative, it would lead to the generation of a pyridinium species which possesses a counterion (i.e. ⁻OTf) derived from the Lewis acid promoter.[29b] Due to the acidity of this resulting pyridinium hydrotriflate, we hypothesized that it could also serve as an effective Brønsted

acid promoter for the reductive deoxygenation. Indeed, when as little as 0.3 mol% of **6·HOTf** was employed in place of Bi(OTf)$_3$, nearly identical yield, regioselectivity, enantioselectivity and intermolecular KIE values were obtained in comparison to the standard conditions (Table 3). Fortunately, **6·HOTf** is an easily-prepared, crystalline solid which displays high solubility in organic solvents such as methylene chloride and tetrahydrofuran. Given this data, **6·HOTf** was used in place of Bi(OTf)$_3$ during the parallel KIE studies.

Scheme 4. Kinetic isotope effect and reversibility experiments.

A. Intermolecular 1° KIE experiment (same vessel)

R =   2-Np: $k_H/k_D = 2.33$
4-Br-C$_6$H$_4$: $k_H/k_D = 2.90$
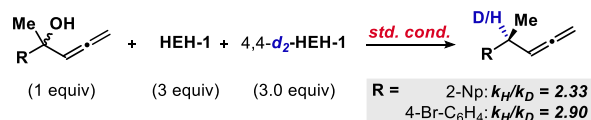
B. Parallel 1° KIE experiment (separate vessels)

(S)-**L1** (8 mol%)
[Ir(cod)Cl]$_2$ (2 mol%)
6·HOTf (0.4 mol%)
CPME (0.2 M), rt

R =   2-Np: $k_H/k_D = 1.13 \pm 0.09$
4-Br-C$_6$H$_4$: $k_H/k_D = 1.02 \pm 0.12$

C. Reversibility of C–H bond formation
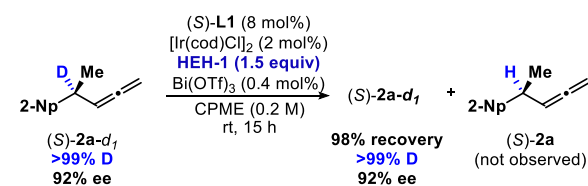
Accordingly, the initial rates observed for the reactions employing either **HEH-1** or 4,4-d_2-**HEH-1** in separate reaction vessels were carefully measured over triplicate runs and led to negligible isotope effects with average calculated k_H/k_D values of 1.13 ± 0.09 and 1.02 ± 0.12 for (±)-**1a** and (±)-**1g**, respectively (Scheme 4B). We also noted that the subjection of monodeuterated product (S)-**2a**-d_1 to the standard condition with **HEH-1** led to no observable H/D exchange (Scheme 4C) which suggests that the product-forming step of hydride attack is irreversible. Together, the set of data displayed in Scheme 3 is consistent with C–H bond cleavage of Hantzsch ester (product C–H bond-forming) in a step that is both irreversible and product-determining, but this step is not turnover-limiting.[39,40]

Table 3. Evaluating the competency of pyridinium triflate salt 6·HOTf as a Brønsted acid promoter.[a]

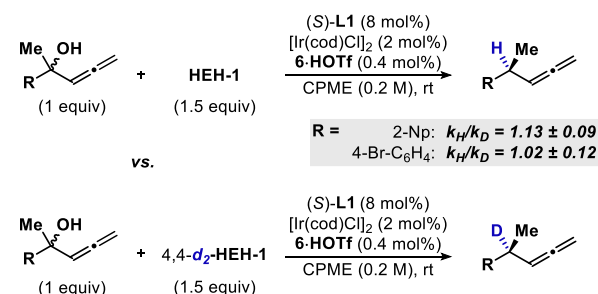| entry	6·HOTf (mol%)	(S)-2a (%)[b,c]	rr 2a:2a[b]	ee (%)[d]
1	1.2	80	>20:1	84
2	0.8	84	>20:1	87
3[e]	0.4	86	>20:1	91
4[f]	0.3	84	>20:1	92
5	0	0	–	–

[a] Reaction run on a 0.5 mmol scale. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture using 1,3,5,-trimethoxybenzene as an internal standard. [c] Combined yield of regioisomers. [d] Determined by GC using a chiral stationary phase. [e] Intermolecular KIE using **HEH-1** and 4,4-d_2-**HEH-1** remained unchanged. [f] Reaction was run for 18 hours. − = not determined.

The nature of the ionization step of the asymmetric reductive deoxygenation was then examined. A linear free-energy relationship (LFER) study was carried out, and a strong linear correlation with a moderately negative slope (ρ = -1.16, Scheme 5A) was obtained from the corresponding plot of the Hammett substituent constants (σ)[41] versus $\log(k_X/k_H)$ for a variety of *para*-substituted analogs.

Scheme 5. Linear free-energy relationship and 2° β-deuterium kinetic isotope effect studies.

A. LFER study: Hammett analysis

$y = -1.15x - 0.0444$
$R^2 = 0.997$
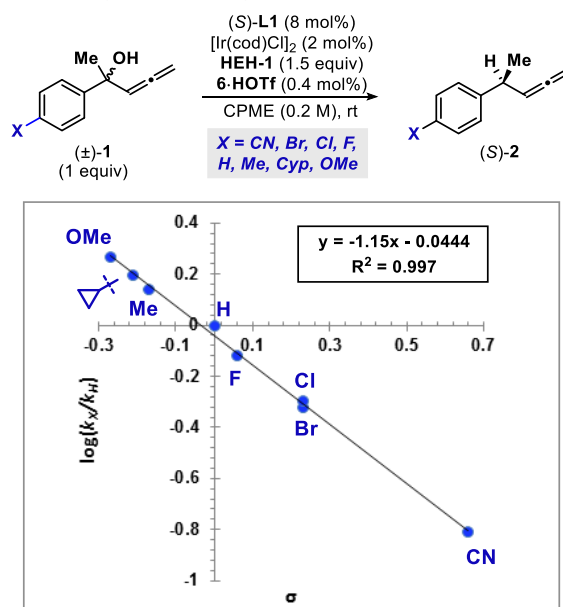
B. Intermolecular 2° KIE experiment (same vessel)

$k_H/k_D = 1.08 \pm 0.01$
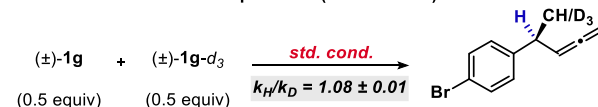
The observation of a linear free-energy dependence in this context provides strong evidence for positive charge accumulation in the turnover-limiting transition state, which is consistent with an S$_N$1-type ionization step. In order to further study the nature of the turnover-limiting step, a β secondary isotope effect study was conducted (Scheme 5B). Rate attenuation of carbonium ion-forming reactions in cases when β-hydrogen atoms are substituted for deuterium atoms is a well-established phenomenon when ionization/solvolysis is rate-limiting. In reactions which exhibit a secondary β-KIE effect, values of around 1.1-1.2 can typically be calulated.[38,42] We calculated a normal secondary KIE (k_H/k_D) of 1.08 ± 0.01 from the intermolecular competition experiment between (±)-**1g** and (±)-**1g**-d_3 across a triplicate series of runs. Although this experimentally obtained value is outside of the above-stated range, it is in line with our previous observations, and

suggests that the benzylic carbon may change hybridization from sp^3 to sp^2 during the turnover-limiting transition state.

The enantioconvergent nature of this reaction, whereby both starting material enantiomers are converted to a single product enantiomer,[27] led us to explore the nature of the interaction between the chiral catalyst and the racemic substrate. When the reaction involving (±)-**1a** was run to partial conversion, **1a** was recovered without enantioenrichment, whereas (*S*)-**2a** was obtained in 46% yield with 91% ee and >20:1 rr (Scheme 6A). This data evokes two significant conclusions: first, a kinetic resolution is not operative, meaning the catalyst processes both enantiomers of the racemic mixture with equivalent rates, and second, the enantiomeric excess of the product largely remains constant over the course of the reaction. To emphasize this point, scalemic substrate (–)-**1a** (87% ee) was subjected to the standard conditions using the individual enantiomers of **L1**, and the reactions were run to partial conversion (Scheme 6B). In both cases, recovered (–)-**1a** was observed to have slightly eroded enantiomeric excess (79% for (*S*)-**L1** and 80% ee for (*R*)-**L1** vs. 87% ee).

Scheme 6. Studies probing enantioconvergence and catalyst control of enantioselectivity.

A. Probing for a kinetic resolution
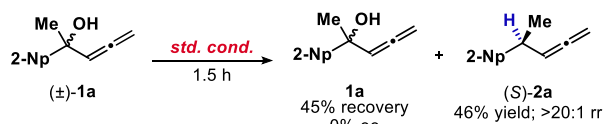
B. Enantioenriched α-allenyl alcohol
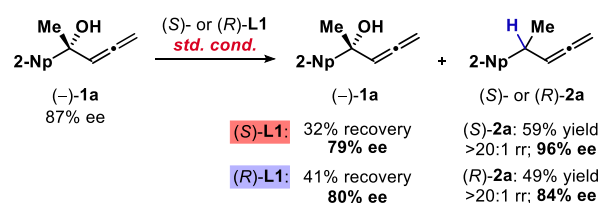
C. Proposed equilibration of diastereomeric complexes
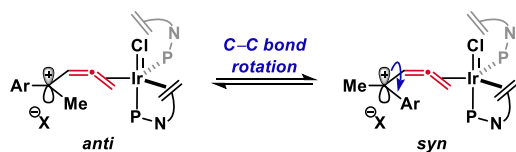
D. Allylic reduction
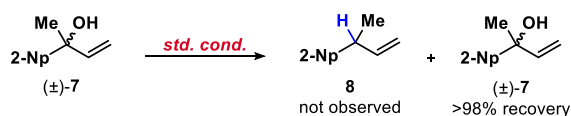
In separate experiments, product (*S*)-**2a** was obtained in 59% yield with 96% ee using (*S*)-**L1**, while (*R*)-**2a** was obtained in 49% yield with opposite absolute stereochemistry (-84% ee) when (*R*)-**L1** was used. These results suggest that the reaction is non-stereospecific, and enantioselectivity is under catalyst control. This rules out the possibility of a dynamic kinetic resolution wherein rapid substrate epimerization occurs while one enantiomer is processed selectively by the chiral Ir catalyst. Ionization of the two enantiomers of the η^2-coordinated α-allenyl alcohol would, in principle, lead to two diastereomeric complexes. In one of these, the aryl moiety finds itself in an *anti* relationship to the Ir center, while in the other the corresponding relationship is *syn* (Scheme 6C). The interconversion of these *syn* and *anti* diastereomers effectively

acts to erase the stereochemical information originating from the starting material. If attack of **HEH-1** is assumed to occur exclusively from the top face of the planar, cationic ligand (i.e. from the side nearest the axial Cl⁻ ligand),[11] the observed product enantiomeric ratio would reflect the selectivity of attack on the *syn* versus the *anti* complexes. The observation that scalemic substrate (–)-**1a** (87% ee, i.e. 93.5:6.5 er) leads to products possessing opposite, yet non-equal enantioselectivities (96% ee vs. -84% ee) in the presence of either (*S*)- or (*R*)-**L1** sheds light on this process. In the presence of (*S*)-**L1**, stereoretention is observed for the enantiomer of (–)-**1a** in excess (major). By contrast, the enantiomer in excess undergoes substitution with inversion of configuration when (*R*)-**L1** is employed. Therefore, since a higher proportion of the 'matched' starting material enantiomer is already present (and subsequently, the *anti* complex) when (*S*)-**L1** is employed, only a small quantity of the *syn* complex is left to convert to the *anti* complex. This leads to a *higher* product enantioselectivity compared to when (±)-**1a** is employed (94% ee vs. 92% ee). Conversely, since a higher proportion of the 'mismatched' starting material enantiomer is present when (*R*)-**L1** is employed, a large quantity of the resulting *syn* complex must convert to the *anti* complex which ultimately leads to the major enantiomer observed upon hydride attack. This leads to a *lower* product enantioselectivity compared to when (±)-**1a** is employed (-84% ee vs. 92% ee). These results reflect a mechanism in which ionization occurs after the substrate coordinates to the chiral Ir catalyst. Moreover, the observations are consistent with a rate of product-forming hydride attack which is competitive with the rate of *syn*-to-*anti* interconversion. As such, if ionization were to occur in the absence of Ir-coordination (i.e. off metal), the separate experiments employing (*R*)-**L1** or (*S*)-**L1** would be expected to give the identical absolute-value for enantiomeric excess.[43]

Given, the large body of work concerning allylic substitution with the present metal-ligand combination, it is reasonable to assume that the analogous *allylic* reduction would also proceed.[44] However, subjection of racemic tertiary allyl alcohol (±)-**7** to the standard conditions led to no observable quantities of the known 2-allyl naphthalene derivative **8** or its regioisomer, and starting material was recovered quantitatively (Scheme 6D). This finding indeed stresses the overall importance of the allene moiety in this reductive deoxygenation. As the sensitivity of this class Ir-phosphoramidite catalyst to increased steric effects at allylic stereocenters is well-established, we hypothesize that the three carbon allene functionality (versus two for olefins) provides an extra one carbon atom spacer which places the bulky Ir-catalyst further away from the tetrasubstituted carbon stereocenter upon η^2 coordination. As a result of the decreased substrate-catalyst steric clash in the case of tertiary α-allenyl alcohols, substitution can proceed under mild conditions.

The geometry of the proposed mode of substrate binding was supported experimentally. Complex (*S*,*S*)-**Ir-1** bearing an η^2-tertiary α-allenyl alcohol ligand could be prepared in 41% yield by combining [Ir(coe)Cl]₂ (0.5 equiv), (±)-**1r** (2.5 equiv) and (*S*)-**L1** (1.7 equiv) in CDCl₃ followed by trituration with pentane (Scheme 7). The off-white powder obtained via filtration was readily characterized by NMR spectroscopy (1D and 2D experiments). Furthermore, X-ray quality crystals of a single diastereomer could be obtained via vapor diffusion into an equimolar mixture of (*S*,*S*)-**Ir-1** and its enantiomer which was prepared using the enantiomeric ligand (*R*)-**L1**.[45,46] As in our previous studies,[11] this analysis unambiguously confirms that binding of the allene occurs via the terminal double bond, which results in the considerable bending of the allene ($\angle C_1$–C_2–C_3 = 147.6°). Furthermore, the terminal carbon of the

allene is further from the metal center than the central carbon (C$_1$–Ir = 2.167 Å vs. C$_2$–Ir = 2.095 Å).

**Scheme 7. Synthesis of an η^2-allene Ir(I) complex bearing a coordinated substrate molecule.**
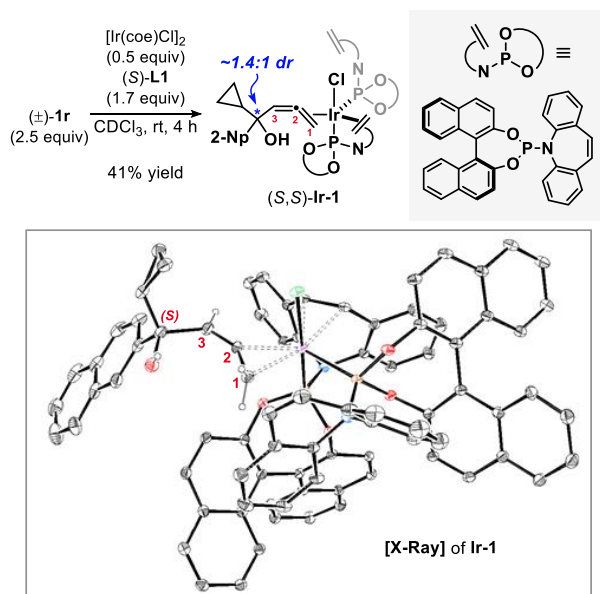
In order to examine the reversibility of allene binding which acts to facilitate catalyst turnover, known complex (*S*,*S*)-**Ir-2** bearing η^2-coordinated unfunctionalized allene **9** was prepared (Scheme 8A),[47] and shown to act as an effective pre-catalyst (4 mol%) for the asymmetric reductive deoxygenation of (±)-**1a** (Scheme 8B). This enabled product (*S*)-**2a** to be obtained in 81% yield with 92% ee and >20:1 rr. This experiment also provides additional support for a 1:2 Ir:(*P*,olefin) complex being operative in this transformation (cf. Table 1, entry 12).

Scheme 8. Preparation and use of an η^2-allene complex as a pre-catalyst for asymmetric reduction deoxygenation.
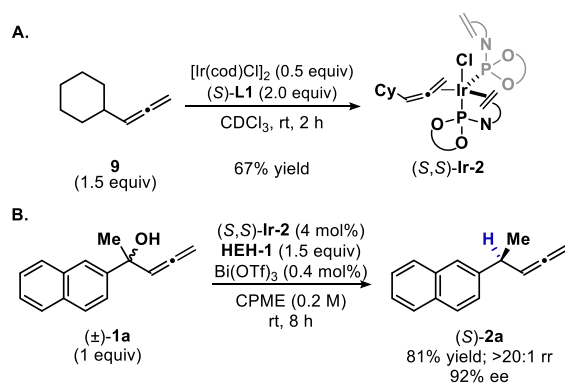
Proposed Mechanism. Based on the experimental data described herein, in addition to previously described theoretical evidence,[11] we propose the tentative mechanism for the present asymmetric reductive deoxygenation shown in Scheme 9. The catalyst precursor [Ir(cod)Cl]$_2$ coordinates to (*S*)-**L1** and the racemic α-allenyl alcohol substrate (i.e. (±)-**1d**) to generate complex **10**, wherein the substrate is bound to Ir via the terminal C=C bond of the allene in an η^2-fashion. In the presence of Bi(OTf)$_3$, the carbon–oxygen bond of the tertiary alcohol undergoes turnover-limiting, heterolytic cleavage resulting in the formation of intermediate **11** containing a planar, η^2-bound cationic ligand.

Scheme 9. Proposed mechanism for the asymmetric Ir catalyzed direct reductive deoxygenation (R = ^{i}Pr).
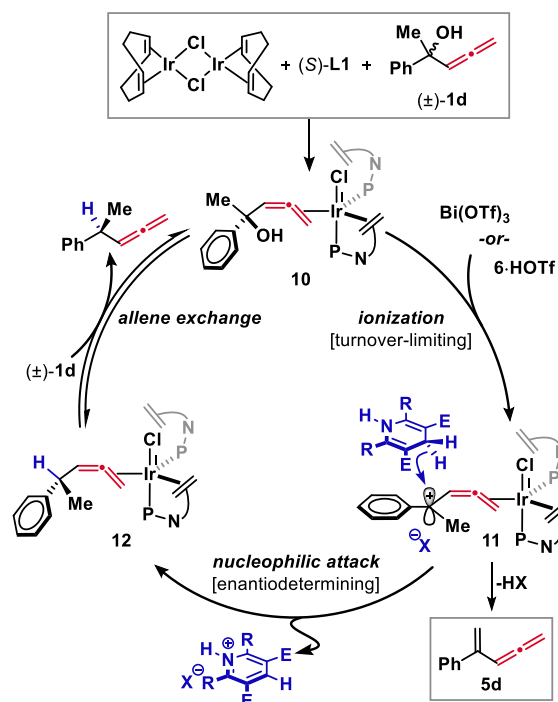
Although the generation of HOTf through hydrolysis of metal triflate salts is a known phenomenon, base-quenching experiments utilizing the hindered 2,6-di-tertbutyl-4-methyl pyridine as a Brønsted acid scavenger suggest that Bi(OTf)$_3$ is indeed acting primarily as a Lewis acid instead of as a precursor to HOTf (see Supporting Information for details).[48] Complex **11** can partition itself between two pathways. The first minor (<3%) pathway leads to the irreversible formation of a vinyl allene (i.e. **5d**) by loss of a proton. In the second (major) path, enantiodetermining hydride transfer from the 4-position of **HEH-1** to the benzylic carbocation results in product-bound Ir(I) complex **12**. Finally, allene exchange occurs to free the product and regenerate active Ir(I) complex **10**.

CONCLUSIONS

We have developed the first catalytic, enantioselective direct reductive deoxygenation of tertiary alcohols by employing a coordination-based strategy for stereocontrol over tertiary carbocations. Transition metal Lewis acid co-catalysis involving an Ir-bis(phosphoramidite,olefin) complex, Bi(OTf)$_3$ and a novel bis-isopropyl Hantzsch ester analog enables the highly enantioconvergent reduction of racemic tertiary α-allenyl alcohols. Using this method, allene-containing products are obtained in high enantiomeric excess (up to 96% ee) and with excellent regioselectivity (up to >50:1) over the corresponding achiral 1,3-dienes. This method also represents the first asymmetric substitution of tertiary alcohols using Ir catalysis to the best of our knowledge. A combination of Hammett analysis with crossover, isotope labeling and KIE experiments have provided insight into the mechanism of this transformation. The data obtained herein supports a turnover-limiting S$_N$1-type ionization event that generates a discrete allenyl cation coordinated to the Ir center. These studies also suggest that this intermediate undergoes irreversible hydride attack where the facial, and thus, enantioselectivity is controlled by the Ir center. This approach is expected to inspire the development of other new coordination-based methods for facial control of carbocations.

ASSOCIATED CONTENT

The information is available free of charge via the internet at http://pubs.acs.org.

Experimental details of synthetic procedures, X-ray data, and computational details (PDF).

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Notes

The authors declare no competing financial interests.

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TOC Graphic:

— deuterium labelling — KIE and Hammett analysis — cross-over studies —