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

Mayuko Isomura,[§] David A. Petrone,[§] and Erick M. Carreira*

ETH Zürich, Vladimir-Prelog-Weg 3, HCI, 8093 Zürich, Switzerland.

ABSTRACT

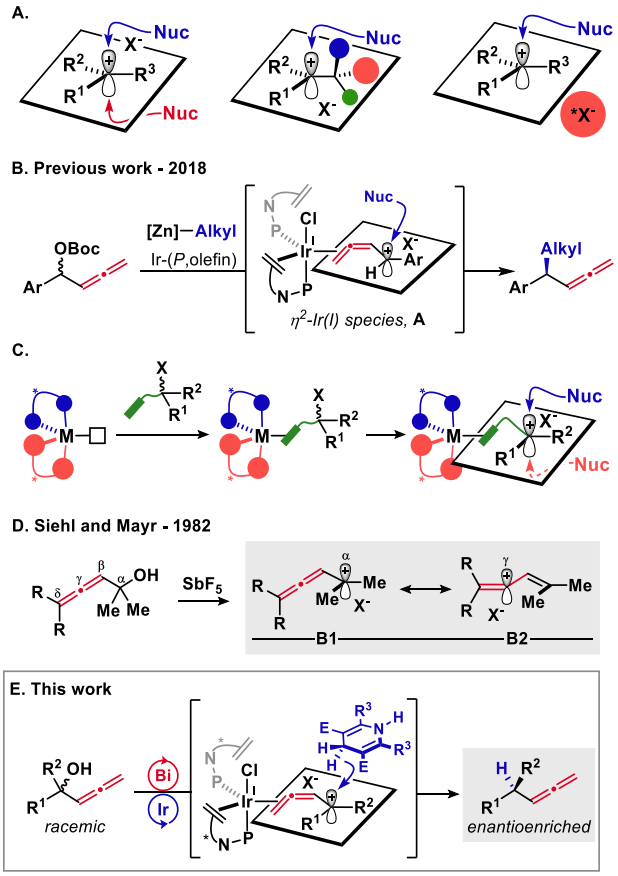
The inherent difficulty in eliciting facial control over carbocations has limited their utility as intermediates in asymmetric catalysis. We have now shown that a docking strategy involving the reversible coordination of a substrate to a chiral transition metal catalyst can be used to enable highly stereoselective 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.

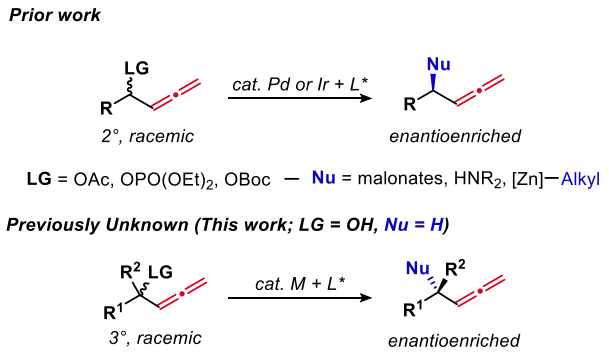


Scheme 1. A. (left) The innate challenge in stereocontrol with carbocations; (center) using substrate control; (right) using chiral ion pairing to elicit stereocontrol; **B.** Asymmetric Ir-catalyzed alkylation of allenyl carbonates involving an electrophilic η^2-bound butadienylium intermediate; **C.** 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.

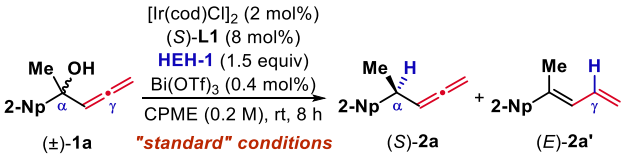


RESULTS AND DISCUSSION

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.

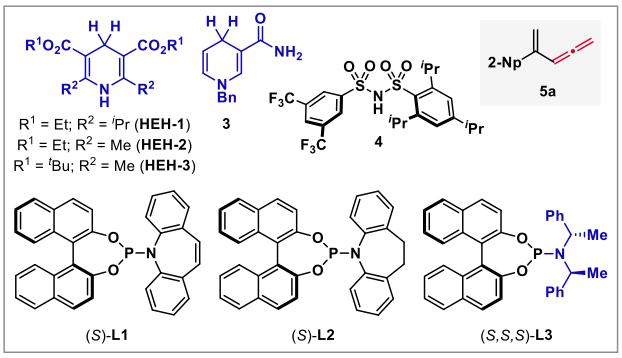
After evaluating a wide array of reaction parameters, a system comprising $[Ir(cod)Cl]_2$ (2 mol%) and chiral phosphorous–olefin ligand (*S*)-**L1** (8 mol%) and $Bi(OTf)_3$ (0.4 mol%) in combination with the novel bis-isopropyl Hantzsch dihydropyridine analog **HEH-1** (1.5 equiv) in CPME ([(±)-**1a**] = 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 ^1H 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 $^nPrNH_2$, see ref. 33. – = not determined; CPME = cyclopentolates methyl ether; cod = 1,5-cyclooctadiene; 2-Np = 2-naphthyl; OTf = trifluoromethanesulfonate.



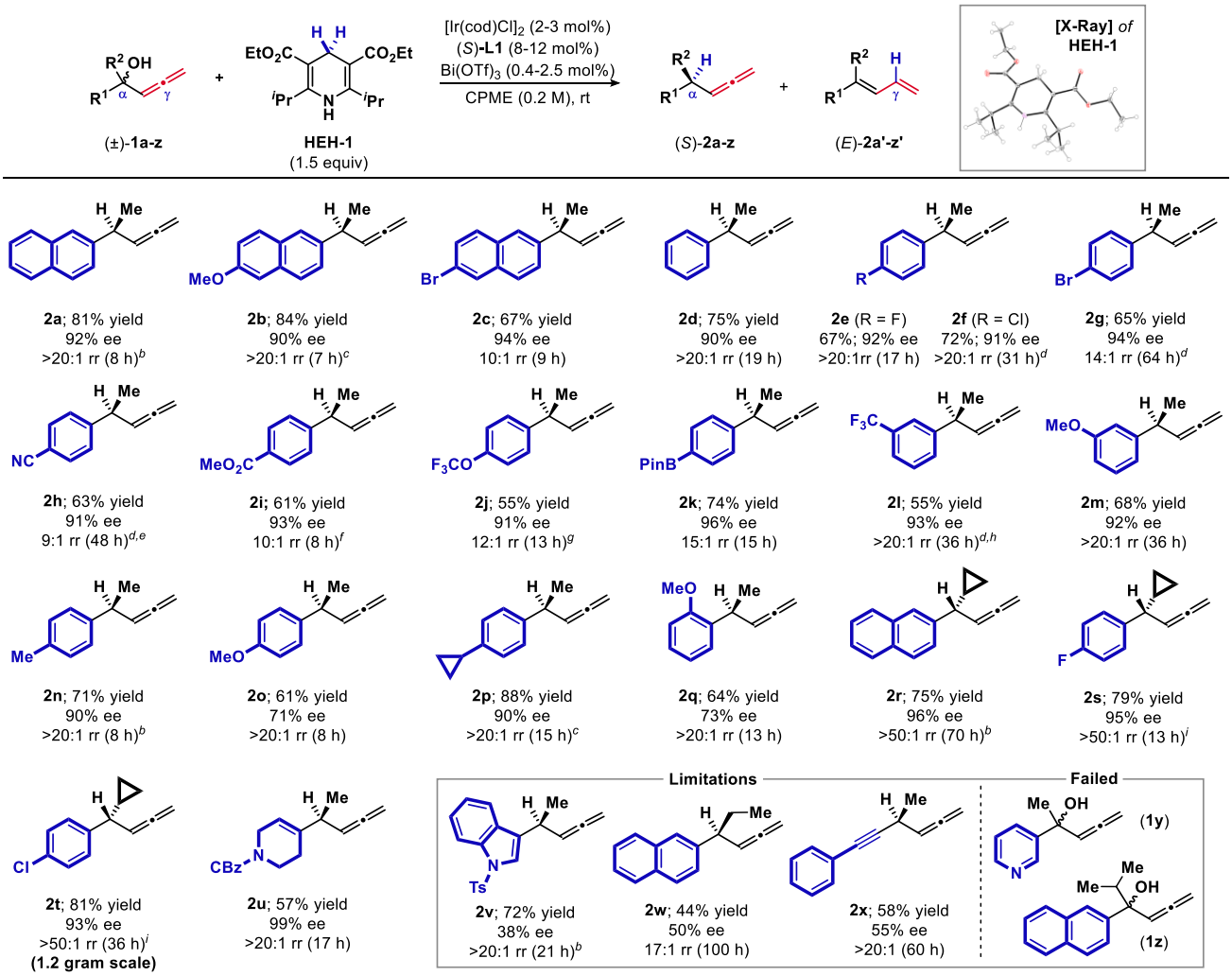
Conversely, no products are observed in the absence of $Bi(OTf)_3$, and only starting material is recovered (entry 6). Our group previously showed that sulfonamide **4** was an optimal Brønsted acid co-catalyst for asymmetric allyl-alkene couplings.[32] The use of 5 mol% of **4** in place of $Bi(OTf)_3$ 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 $–OCF_3$ (**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 $–CF_3$ (**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 Et_2O. [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

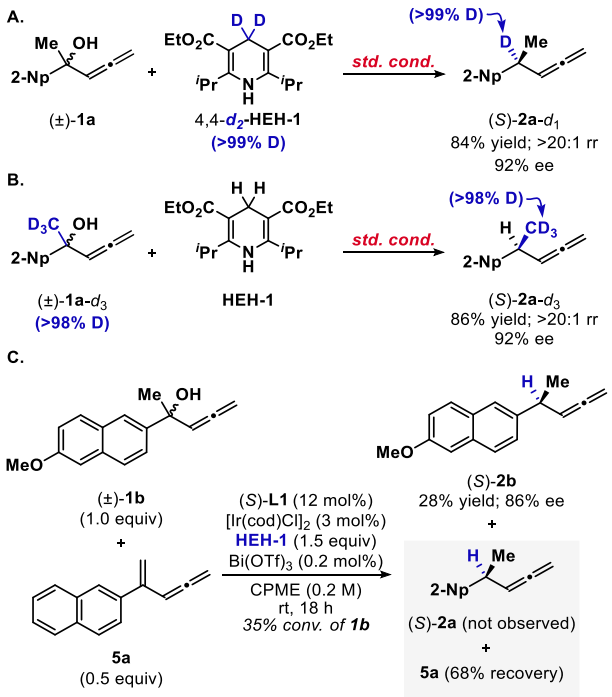
the reaction conditions led to the formation of the desired cyclopropane-containing products in 72-79% yield with 93-96% ee.

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-d_2-**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**-d_1 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**-d_3 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.

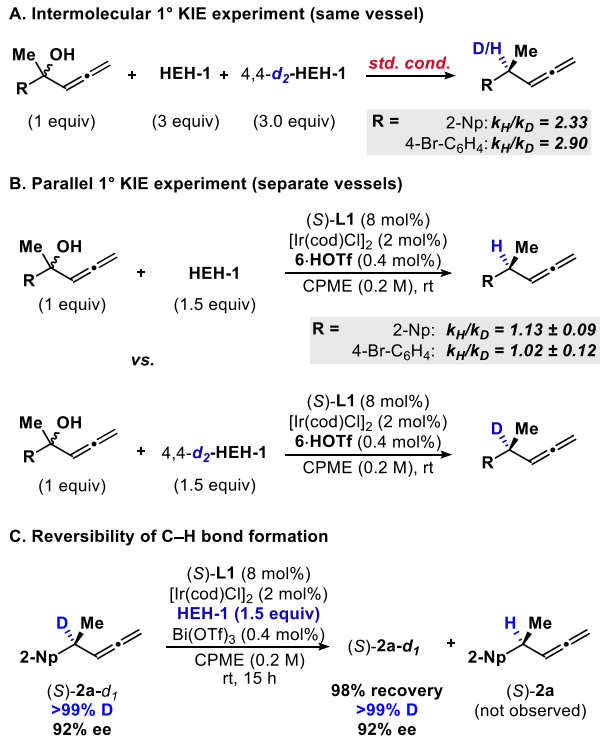


The proposed reductive deoxygenation resembles an S_N1-type reaction that is likely to proceed via a mechanism involving turnover-limiting ionization of the tertiary alcohol motif.[38] In line with this hypothesis, a series of kinetic isotope effect (KIE) studies were first conducted to determine if 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-d_2-**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

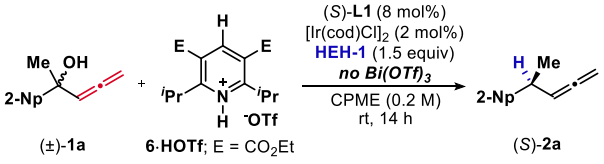
acid promoter for the reductive deoxygenation. Indeed, when as little as 0.3 mol% of **6·HOTf** was employed in place of $Bi(OTf)_3$, nearly identical yield, regioselectivity, enantioselectivity and intermolecular KIE values were obtained in comparison to the standard conditions (Table 3). Fortunately, **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.



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]

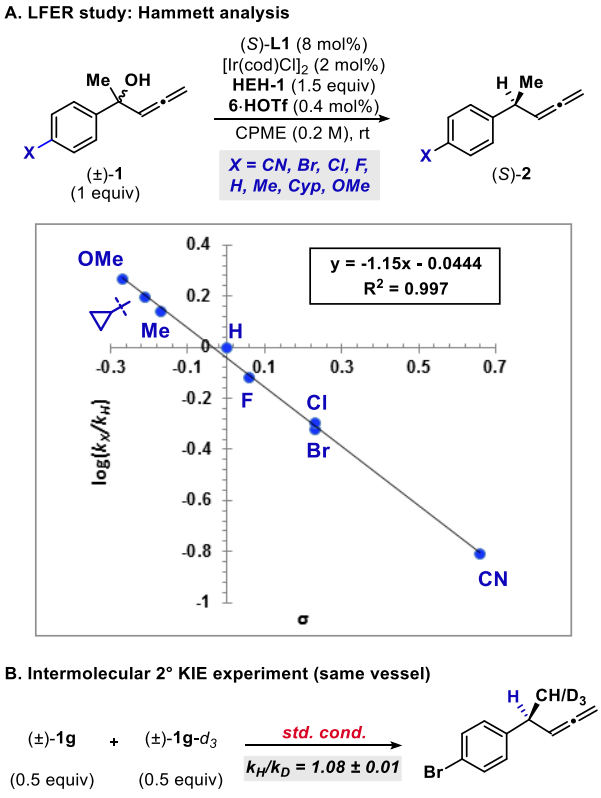


entry	**6·HOTf** (mol%)	(*S*)-**2a** (%)[b,c]	rr **2a**:**2a**[b]	ee (%)[d]
1	1.2	80	>20:1	84
2	0.8	84	>20:1	87
3[e]	0.4	86	>20:1	91
4[f]	0.3	84	>20:1	92
5	0	0	–	–

[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.

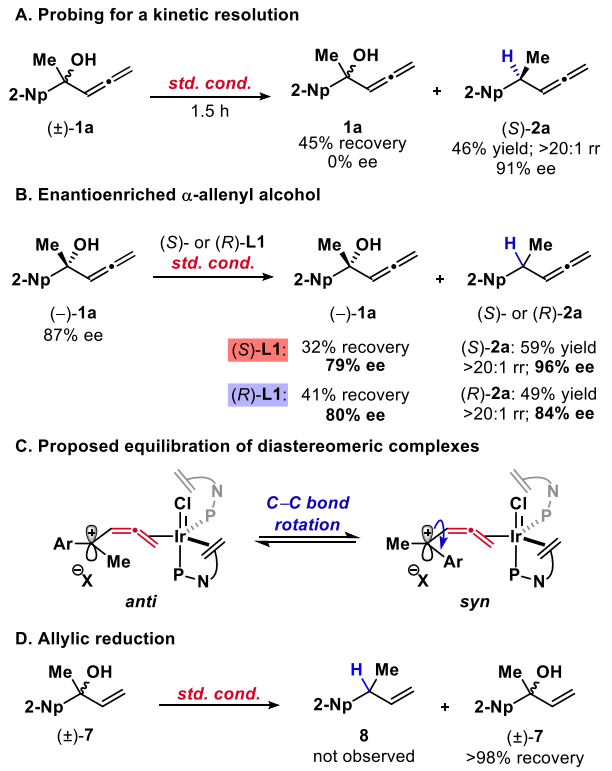


The observation of a linear free-energy dependence in this context provides strong evidence for positive charge accumulation in the turnover-limiting transition state, which is consistent with an S_N1-type ionization step. In order to further study the nature of the turnover-limiting step, a β secondary 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.



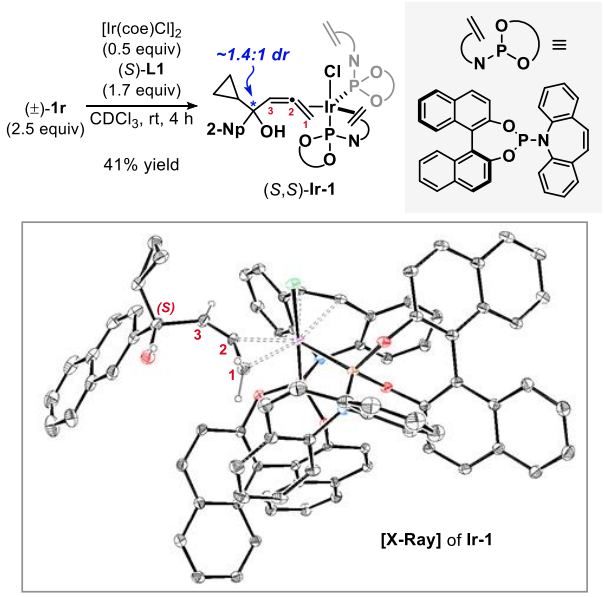
In separate experiments, product (*S*)-**2a** was obtained in 59% yield with 96% ee using (*S*)-**L1**, while (*R*)-**2a** was obtained in 49% yield with opposite absolute stereochemistry (-84% ee) when (*R*)-**L1** was used. These results suggest that the reaction is non-stereospecific, and enantioselectivity 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 $CDCl_3$ 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

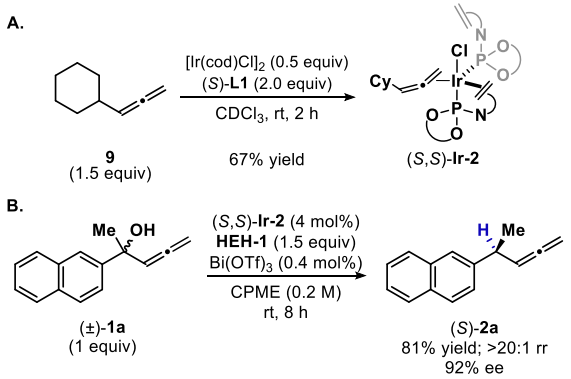
allene is further from the metal center than the central carbon (C_1–Ir = 2.167 Å vs. C_2–Ir = 2.095 Å).

Scheme 7. Synthesis of an η^2-allene Ir(I) complex bearing a coordinated substrate molecule.



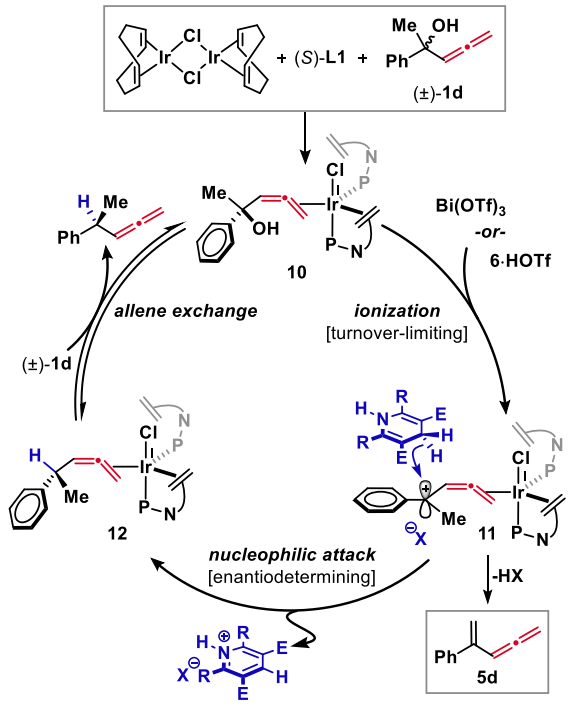
In order to examine the reversibility of allene binding which acts to facilitate catalyst turnover, known complex (*S*,*S*)-**Ir-2** bearing η^2-coordinated unfunctionalized allene **9** was prepared (Scheme 8A),[47] and shown to act as an effective pre-catalyst (4 mol%) for the asymmetric reductive 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_N1-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).

AUTHOR INFORMATION

Corresponding Author

*erickm.carreira@org.chem.ethz.ch

ORCID

Mayuko Isomura: 0000-0002-6235-5937
David A. Petrone: 0000-0001-9867-9178
Erick M. Carreira: 0000-0003-1472-490X

Author Contributions

§ These authors contributed equally.

Notes

The authors declare no competing financial interests.

ACKNOWLEDGEMENTS

ETH Zürich and the Swiss National Science Foundation (200020_152898) are gratefully acknowledged for financial support. MI thanks the Funai Foundation for a Funai Overseas Scholarship. DAP thanks the National Sciences and Engineering Research Council of Canada for a postdoctoral fellowship. The authors thank Michael Solar and Dr. N. Trapp (ETH Zürich) for X-ray analysis, Dr. M.-O. Ebert, R. Arnold, R. Frankenstein, and S. Burkhardt for NMR measurements, and Oswald L. Greter for HRMS measurements and analysis. Dr. Ivan Franzoni (NuChem Therapeutics) and Simon L. Rössler (ETH Zürich) are thanked for helpful discussions and Greta Vastakaite is thanked for assistance with SFC and HPLC separations. This manuscript is dedicated to Professor Mark Lautens on the occasion of his 60th birthday.

REFERENCES

[1] a) Norris, J. On the Nonexistence of Trivalent Carbon. *Am. Chem. J.* **1901**, *25*, 117; b) Kehrman, F.; Wentzel, F. Uever die Basischen Eigenschaften des Kohlenstoffs und die Constitution des Sogenannten Triphenylmethyls. *Chem. Ber.* **1901**, *34*, 3815.

[2] Naredla, R.R.; Klumpp, D.A. Contemporary Carbocation Chemistry: Applications in Organic Synthesis. *Chem. Rev.* **2013**, *113*, 6905.

[3] For selected examples, see: a) Mühlthau, F.; Schuster, O.; Bach, T. High Facial Diastereoselectivity in Intra- and Intermolecular Reactions of Chiral Benzylic Cations. *J. Am. Chem. Soc.* **2005**, *127*, 9348; b) Stadler, D.; Bach, T. Concise Stereoselective Synthesis of (−)-Podophyllotoxin by an Intermolecular Iron(III)-Catalyzed Friedel–Crafts Alkylation. *Angew. Chem., Int. Ed.* **2008**, *47*, 7557; d) Rubenbauer, P.; Herdtweck, E.; Strassner, T.; Bach, T. $Bi(OTf)_3$-Catalyzed Diastereoselective S_N1-Type Reactions of Chiral Propargylic Acetates. *Angew. Chem. Int. Ed.* **2008**, *47*, 10106; d) Chung, J. Y.; Mancheno, D.; Dormer, P. G.; Variankaval, N.; Ball, R. G.; Tsou, N. N. Diastereoselective Friedel-Crafts Alkylation of Indoles with Chiral α-Phenyl Benzylic Cations. Asymmetric Synthesis of Anti-1,1,2-Triarylalkanes. *Org. Lett.* **2008**, *10*, 3037; e) Cakir, S. P.; Stokes, S.; Sygula, A.; Mead, K. T. Evidence for π-Stacking as a Source of Stereocontrol in the Synthesis of the Core Pyranochromene Ring System Common to Calyxin I, Calyxin J, and Epicalyxin J. *J. Org. Chem.* **2009**, *74*, 7529; f) Devoust, M.; Kitching, J. A.; Fleming, M. J.; Lautens, M. Diastereoselective Benzylic Arylation of Tetralins. *Chem. Eur. J.* **2010**, *16*, 50; g) Li, G.-X.; Qu, J. Friedel–Crafts Alkylation of Arenes with Epoxides Promoted by Fluorinated Alcohols or Water. *Chem. Commun.* **2010**, *46*, 2653; h) Medeiros, M.R.; Narayan, R. S.; McDougal, N. T.; Schaus, S. E.; Porco, J. A., Jr. Skeletal Diversity via Cationic Rearrangements of Substituted Dihydropyrans. *Org. Lett.* **2010**, *12*, 3222; i) Medjahdi, M.; Gonzalez-Gomez, J. C.; Foubelo, F.; Yus, M. Concise Route to (–)- and (+)-Aphanorphine. *Eur. J. Org. Chem.* **2011**, 2230; j) Liebert, C.; Brinks, M. K.; Capacci, A. G.; Fleming, M.J.; Lautens, M. Diastereoselective Intramolecular Friedel–Crafts Alkylation of Tetralins. *Org. Lett.* **2011**, *13*, 3000; k) Guin, J.; Besnard, C.; Pattison, P.; Lacour, J. Highly Selective Additions of Hydride and Organolithium Nucleophiles to Helical Carbenium Ions. *Chem. Sci.* **2011**, *2*, 425.

[4] a) Brak, K.; Jacobsen, E.N. Asymmetric Ion-Pairing Catalysis. *Angew. Chem. Int. Ed.* **2012**, *52*, 534; b) Ungarean, C.N.; Southgate, E.H.; Sarlah, D. Enantioselective Polyene Cyclizations. *Org. Biomol. Chem.* **2016**, *14*, 5454.

[5] a) Guo, Q.-X.; Peng, Y.-G.; Zhang, J.-W.; Song, L.; Feng, Z.; Gong, L.-Z. Highly Enantioselective Alkylation Reaction of Enamides by Brønsted-Acid Catalysis. *Org. Lett.* **2009**, *11*, 4620; b) Wilcke, D.; Herdtweck, E.; Bach, T. Enantioselective Brønsted Acid Catalysis in the Friedel-Crafts Reaction of Indoles with Secondary ortho-Hydroxybenzylic Alcohols. *Synlett* **2011**, 1235; c) Rueping, M.; Uria, U.; Lin, M.;Y. Atodiresei, I. Chiral Organic Contact Ion Pairs in Metal-Free Catalytic Asymmetric Allylic Substitutions. *J. Am. Chem. Soc.* **2011**, *133*, 3732; d) Wang, S.-G.; Han, L.; Zeng, M.; Sun, F.-L.; Zhang, W.; You, S.- L. Enantioselective Synthesis of Fluorene Derivatives by Chiral *N*-Triflyl Phosphoramide Catalyzed Double Friedel–Crafts Alkylation Reaction. *Org. Biomol. Chem.* **2012**, *10*, 3202; e) Tsuji, N.; Kennemur, J.L.; Buyck, T.; Lee, S.; Prévost, S.; Kaib, P.S.J.; Bykov, D.; Farès, C.; List, B. Activation of Olefins via Asymmetric Brønsted Acid Catalysis. *Science* **2018**, *359*, 1501.

[6] Surendra, K.; Corey, E. J. Highly Enantioselective Proton-Initiated Polycyclization of Polyenes. *J. Am. Chem. Soc.* **2012**, *134*, 11992.

[7] The use of organocatalysts to generate chiral nucleophiles in asymmetric S_N1-type reactions has also been reported, yet generation of chirality at the electrophilic component remains a challenge. For examples, see: a) Fu, T.-h.; Bonaparte, A.; Martin, S. F. Synthesis of β-Heteroaryl Propionates via Trapping of Carbocations with π-Nucleophiles. *Tetrahedron Lett.* **2009**, *50*, 3253; b) Brown, A.R.; Kuo, W.-H.; Jacobsen, E.N. Enantioselective Catalytic α-Alkylation of Aldehydes via an S_N1 Pathway. *J. Am Chem. Soc.* **2010**, *132*, 9286; c) Bergonzini, G.; Vera, S.; Melchiorre, P. Cooperative Organocatalysis for the Asymmetric γ Alkylation of α-Branched Enals. *Angew. Chem, Int. Ed.* **2010**, *49*, 9685; d) Trifonidou, M.; Kokotos, C. G. Enantioselective Organocatalytic α-Alkylation of Ketones by S_N1-Type Reaction of Alcohols. *Eur. J. Org. Chem.* **2012**, *2012*, 1563.

[8] a) Braun, M.; Kotter, W. Titanium(IV)-Catalyzed Dynamic Kinetic Asymmetric Transformation of Alcohols, Silyl Ethers,

and Acetals under Carbon Allylation. *Angew. Chem. Int. Ed.* **2004**, *43*, 514; b) Zhao, W.; Wang, Z.; Chu, B.; Sun. J. Enantioselective Formation of All-Carbon Quaternary Stereocenters from Indoles and Tertiary Alcohols Bearing A Directing Group. *Angew. Chem. Int. Ed.* **2015**, *54*, 1910.

[9] Jørgensen recently proposed tertiary carbocations resulting from enamine oxidation as intermediates in asymmetric oxidative α-couplings of racemic aldehydes, see: Leth, L.A.; Næsborg, L.; Reyes-Rodríguez, G.J.; Tobiesen, H.N.; Iversen, M.V.; Jørgensen, K.A. Enantioselective Oxidative Coupling of Carboxylic Acids to α-Branched Aldehydes. *J. Am. Chem. Soc.* **2018**, *140*, 12687.

[10] Wendlandt, A.E.; Vangal, P.; Jacobsen, E.N. Quaternary Stereocenters via an Enantioconvergent Catalytic S_N1 Reaction. *Nature* **2018**, *556*, 447.

[11] Petrone, D.A.; Isomura, M.; Franzoni, I.; Rössler, S.L.; Carreira, E.M. Allenylic Carbonates in Enantioselective Iridium-Catalyzed Alkylations. *J. Am. Chem. Soc.* **2018**, *140*, 4697.

[12] a) Pearson, A.J. Transition Metal-Stabilized Carbocations in Organic Synthesis. In *The Chemistry of the Metal–Carbon Bond*, Hartley, F.R., Ed.; Wiley: New York; Vol. 4, 889; b) Pearson, A.J. Iron-Stabilized Carbocations as Intermediates for Organic Synthesis. *Science.* **1984**, *223*, 895.

[13] For an example of diastereocontrol over the Nazarov cyclization via chelation to a Lewis acid, see: Huang, J.; Frontier, A.J. Development of a Nazarov Cyclization/Wagner−Meerwein Rearrangement Sequence for the Stereoselective Synthesis of Spirocycles. *J. Am. Chem. Soc.* **2007**, *129*, 8060.

[14] Siehl, H.-U.; Mayr, H. Stable Vinyl Cations. Direct Spectroscopic Observation of Vinyl-Substituted Vinyl Cations. *J. Am. Chem. Soc.* **1982**, *104*, 909.

[15] For a review on stable carbocations, see: Olah, G.A.; Prakash Reddy, V.; Prakash, G.K.S. Long-Lived Cyclopropylcarbinyl Cations. *Chem. Rev.* **1992**, *92*, 69.

[16] These cations have been proposed as intermediates in Nazarov electrocyclizations. See: a) Cordier, P.; Aubert, C.; Malacria, M.; Lacôte, E.; Gandon, V. Silver and Brønsted Acid Catalyzed Nazarov-Type Cyclizations To Generate Benzofulvenes. *Angew. Chem. Int. Ed.* **2009**, *48*, 8757; b) Sai, M.; Matsubara, S. Lithium(1+)-Catalyzed Nazarov-Type Cyclization of 1-Arylbuta-2,3-dien-1-ols: Synthesis of Benzofulvene Derivatives. *Synlett*, **2014**, *2014*, 2067.

[17] Rössler, S.L.; Krautwald, S.; Carreira, E.M. Study of Intermediates in Iridium–(Phosphoramidite,Olefin)-Catalyzed Enantioselective Allylic Substitution. *J. Am. Chem. Soc.* **2017**, *139*, 3603.

[18] McCombie, S. W.; Motherwell, W. B.; Tozer, M. J. In Organic Reactions, Vol. *77*; Denmark, S. E., Ed.; Wiley: Hoboken, NJ, 2012; pp 161.

[19] For reviews, see: a) Herrmann, J.M.; König, B. Reductive Deoxygenation of Alcohols: Catalytic Methods Beyond Barton–McCombie Deoxygenation. *Eur. J. Org. Chem.* **2013**, *2013*, 7017; b) Tsuji, J.; Mandai, T. Palladium-Catalyzed Hydrogenolysis of Allylic and Propargylic Compounds with Various Hydrides. *Synthesis* **1996**, *1996*, 1; and references therein.

[20] For an example of asymmetric Pd-catalyzed reduction of allylic esters, see: Hayashi, T.; Iwamura, H.; Naito, M. Catalytic Asymmetric Reduction of Allylic Esters with Formic Acid Catalyzed by Palladium-MOP Complexes. *J. Am. Chem. Soc.* **1994**, *116*, 775.

[21] For examples of transition metal-catalyzed reductive deoxygenations not involving Lewis acid-catalysis, see: a) Nishibayashi, Y.; Shinoda, A.; Miyake, Y.; Matsuzawa, H.; Sato, M. Ruthenium-Catalyzed Propargylic Reduction of Propargylic Alcohols with Silanes. *Angew. Chem. Int. Ed.* **2006**, *45*, 4835; b) Yuki, M.; Miyake, Y.; Nishibayashi, Y. Preparation of Thiolate-Bridged Dinuclear Ruthenium Complexes Bearing a Phosphine Ligand and Application to Propargylic Reduction of Propargylic Alcohols with 2-Propanol. *Organometallics* **2010**, *29*, 5994; c) Foskey, T.J.A.; Heinekey, D.M.; Goldberg, K.I. Partial Deoxygenation of 1,2-Propanediol Catalyzed by Iridium Pincer Complexes. *ACS Catal.* **2012**, *2*, 1285; d) Dai, X.-J.; Li, C.-J. En Route to a Practical Primary Alcohol Deoxygenation. *J. Am. Chem. Soc.* **2016**, *138*, 5433; e) Bauer, J.O.; Chakraborty, S.; Milstein, D. Manganese-Catalyzed Direct Deoxygenation of Primary Alcohols. *ACS Catal.* **2017**, *7*, 4462; f) Yang, S.; Tang, W.; Yang, Z.; Xu, J. Iridium-Catalyzed Highly Efficient and Site-Selective Deoxygenation of Alcohols. *ACS Catal.* **2018**, *8*, 9320; For an example involving the stoichiometric reduction of an acetylene-Co complex, see: g) Nicholas, K.M.; Siegel, J. Synthesis of *sec*-Alkylacetylenes. Reduction of Cobalt Carbonyl Complexes of Acetylenic Alcohols. *J. Am. Chem. Soc.* **1985**, *107*, 4999.

[22] For select examples of direct, catalytic methods, see: a) Lee, J.-T.; Alper, H. The Hydridopentacyanocobaltate Anion Induced Deoxygenation of Allylic Alcohols Using β-Cyclodextrin as a Phase Transfer Agent. *Tetrahedron Lett.* **1990**, *31*, 4101; b) Gevorgyan, V.; Liu, J.-X.; Rubin, M.; Benson, S.; Yamamoto, Y. A Novel Reduction of Alcohols and Ethers with a $HSiEt_3$ Catalytic $B(C_6F_5)_3$ System. *Tetrahedron Lett.* **1999**, *40*, 8919; c) Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. Direct Reduction of Alcohols: Highly Chemoselective Reducing System for Secondary or Tertiary Alcohols Using Chlorodiphenylsilane with a Catalytic Amount of Indium Trichloride. *J. Org. Chem.* **2001**, *66*, 7741; d) Georgy, M.; Boucard, V.; Debleds, O.; Dal Zotto, C.; Campagne, J.-M. Gold(III)-Catalyzed Direct Nucleophilic Substitution of Propargylic Alcohols. *Tetrahedron*, **2009**, *65*, 1758; e) Wang, J.; Huang, W.; Zhang, Z.; Xiang, X.; Liu, R.; Zhou, X. $FeCl_3{\cdot}6H_2O$ Catalyzed Disproportionation of Allylic Alcohols and Selective Allylic Reduction of Allylic Alcohols and Their Derivatives with Benzyl Alcohol. *J. Org. Chem.* **2009**, *74*, 3299; f) Milne, J.E.; Storz, T.; Colyer, J.T.; Thiel, O.R.; Seran, M.D.; Larsen, R.D.; Murry, J.A. Iodide-Catalyzed Reductions: Development of a Synthesis of Phenylacetic Acids. *J. Org. Chem.* **2011**, *76*, 9519; g) Meyer, V.J.; Niggemann, M. Highly Chemoselective Calcium-Catalyzed Propargylic Deoxygenation. *Chem. Eur. J.* **2012**, *18*, 4687; h) Narayana Kumar, G.G.K.S.; Laali, K.K. Facile Coupling of Propargylic, Allylic and Benzylic Alcohols with Allylsilane and Alkynylsilane, and their Deoxygenation with Et_3SiH, Catalyzed by $Bi(OTf)_3$ in [BMIM][BF_4] Ionic Liquid (IL), with Recycling and Reuse of the IL. *Org. Biomol. Chem.* **2012**, *10*, 7347; i) Dobmeier, M.; Herrmann, J.M.; Lenoir, D.; König, B. Reduction of Benzylic Alcohols and α-Hydroxycarbonyl Compounds by Hydriodic Acid in a Biphasic Reaction Medium. *Beilstein J. Org. Chem.* **2012**, *8*, 330; j) Sawadjoon, S.; Lundstedt, A.; Samec, J.S.M. Pd-Catalyzed Transfer Hydrogenolysis of Primary, Secondary, and Tertiary Benzylic Alcohols by Formic Acid: A Mechanistic Study. *ACS Catal.* **2013**, *3*, 635; k) Drosos, N.; Morandi, B. Boron-Catalyzed Regioselective Deoxygenation of Terminal 1,2-Diols to 2-Alkanols Enabled by the Strategic Formation of a Cyclic Siloxane Intermediate. *Angew. Chem. Int. Ed.* **2015**, *54*, 8814; l) Yang, Z.; Kumar, R.K.; Liao, P.; Liu, Z.; Li, X.; Bi, X. Chemo- and Regioselective Reductive Deoxygenation of 1-en-4-yn-ols into 1,4-Enynes Through FeF_3 and TfOH co-Catalysis. *Chem. Commun.* **2016**, *52*, 5936.

[23] For asymmetric examples wherein the generated stereogenic unit is the carbon atom directly adjacent to the allene, see: a) Li, Q.; Fu, C.; Ma, S. Catalytic Asymmetric Allenylation of Malonates with the Generation of Central Chirality. *Angew. Chem. Int. Ed.* **2012**, *51*, 11783; b) Li, Q.;

Fu, C.; Ma, S. Palladium-Catalyzed Asymmetric Amination of Allenyl Phosphates: Enantioselective Synthesis of Allenes with an Additional Unsaturated Unit. *Angew. Chem. Int. Ed.* **2014**, *53*, 6511; c) Daum J.; Duan, X.; Zhou, J.; Fu, C.; Ma, S. Catalytic Enantioselective Simultaneous Control of Axial Chirality and Centra Chirality in Allenes. *Chin. J. Chem.* **2018**, *36*, 387; for non-asymmetric methods, see: d) Zhu, T.; Ma, S. 3,4-Alkadienyl Ketones via the Palladium-catalyzed Decarboxylative Allenylation of 3-Ooxocarboxylic Acids. *Chem. Commun.* **2017**, *52*, 6037; e) Gao, R.-D.; Zhai, Y.; You, S.-L.; Ma, S. Palladium-Catalyzed Intermolecular Dearomatic Allenylation of Hydrocycloalk[b]indoles with 2,3-Allenyl Carbonates. *Org. Chem. Front.* **2018**, *5*, 1664.

[24] For asymmetric examples wherein the generated stereogenic unit is the allene itself, see: Imada, Y.; Ueno, K.; Kutsuwa, K.; Murahashi, S.-I. Palladium-Catalyzed Asymmetric Alkylation of 2,3-Alkadienyl Phosphates. Synthesis of Optically Active 2-(2,3-Alkadienyl)malonates. *Chem. Lett.* **2002**, *31*, 140; b) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. Dynamic Kinetic Asymmetric Allylic Alkylations of Allenes. *J. Am. Chem. Soc.* **2005**, *127*, 14186; c) Nemoto, T.; Kanematsu, M.; Tamura, S.; Hamada, Y. Palladium-Catalyzed Asymmetric Allylic Alkylation of 2,3-Allenyl Acetates Using a Chiral Diaminophosphine Oxide. *Adv. Synth. Catal.* **2009**, *351*, 1773; d) Wan, B.; Ma, S. Enantioselective Decarboxylative Amination: Synthesis of Axially Chiral Allenyl Amines. *Angew. Chem. Int. Ed.* **2012**, *52*, 441.

[25] For an example of non-asymmetric substitution of racemic, tertiary α-allenyl acetates, see: a) Kezuka, S.; Kanemoto, K.; Takeuchi, R. Iridium Complex-Catalyzed Method for the Construction of a Quaternary Carbon Center α to Allene. *Tetrahedron Lett.* **2004**, *45*, 6403.

[26] a) Gaspard-Iloughmane, H.; Le Roux, C. Bismuth(III) Triflate in Organic Synthesis. *Eur. J. Org. Chem.* **2004**, *2004*, 2517; b) Ollevier, T. New Trends in Bismuth-Catalyzed Synthetic Transformations. *Org. Biomol. Chem.* **2013**, *11*, 2740.

[27] Mohr, J.T.; Moore, J.T.; Stoltz, B.M. Enantioconvergent Catalysis. *Beilstein J. Org. Chem.* **2016**, *12*, 2038.

[28] Luo, H.; Ma, S. CuI-Catalyzed Synthesis of Functionalized Terminal Allenes from 1-Alkynes. *Eur. J. Org. Chem.* **2013**, *2013*, 3041.

[29] a) Nakamura, K.; Ohno, A.; Oka, S. Reduction by a Model of NAD(P)H. 44. Transition Metal Catalyzed Reduction of Allylic Acetate. *Tetrahedron Lett.* **1983**, *24*, 3335; b) Chen, Z.; Dong, V.M. Enantioselective Semireduction of Allenes. *Nat. Commun.* **2017**, *8*, 784.

[30] Marcelli, T. Asymmetric Transfer Hydrogenations Using Hantzsch Esters. In *Enantioselective Organocatalyzed Reactions I*, Mahrwald, R., Ed.; Springer: New York; Vol. 1, 43.

[31] Ouellet, S.G.; Walji, A.M.; MacMillan, D.W.C. Enantioselective Organocatalytic Transfer Hydrogenation Reactions using Hantzsch Esters. *Acc. Chem. Res.* **2007**, *40*, 1327.

[32] Hamilton, J.Y.; Sarlah, D.; Carreira, E.M. Iridium-Catalyzed Enantioselective Allyl–Alkene Coupling. *J. Am. Chem. Soc.* **2014**, *136*, 3006.

[33] Shu, C.; Leitner, A.; Hartwig, J. F. Enantioselective Allylation of Aromatic Amines after In Situ Generation of an Activated Cyclometalated Iridium Catalyst. *Angew. Chem. Int. Ed.* **2004**, *43*, 4797.

[34] Tang, S.-B.; Zhang, X.; Tu, H.F.; You, S.-L. Regio- and Enantioselective Rhodium-Catalyzed Allylic Alkylation of Racemic Allylic Alcohols with 1,3-Diketones. *J. Am. Chem. Soc.* **2018**, *140*, 7737.

[35] Olah, G.A.; Berrier, A.L.; Field, L.D.; Prakash, G.K.S. A ^{13}C and ^{29}Si NMR Spectroscopic Study of α- and β-Trimethylsilyl-Substituted Carbocations. *J. Am. Chem. Soc.* **1982**, *104*, 1349.

[36] Mayr, H.; Förner, W.; von Ragué Schleyer, P. Methyl-Substituted Allyl Cations. A Comparison of Experimental Stability, Rotational Barrier, and Solvolysis Data with ab initio Calculation. *J. Am. Chem. Soc.* **1979**, *101*, 6032.

[37] a) Komeyama, K.; Morimoto, T.; Takai, K. A Simple and Efficient Iron-Catalyzed Intramolecular Hydroamination of Unactivated Olefins. *Angew. Chem. Int. Ed.* **2006**, *45*, 2938; b) Michaux, J.; Terrasson, V.; Marque, S.; Wehbe, J.; Prim, D.; Campagne, J.-M. Intermolecular $FeCl_3$-Catalyzed Hydroamination of Styrenes. *Eur. J. Org. Chem.* **2007**, *2007*, 2601; c) Marcyk, P.T.; Jeffries, L.R.; AbuSalim, D.I.; Pink, M.; Cook, S.P. *Angew. Chem. Int. Ed.* **2019**, *58*, 1727.

[38] *Modern Physical Organic Chemistry;* Anslyn, E.V., Dougherty, D.A., Eds.; University Science Books: Sausalito, CA, 2006.

[39] Simmons, E.M.; Hartwig, J.F. On the Interpretation of Deuterium Kinetic Isotope Effects in C–H Bond Functionalization by Transition-Metal Complexes. *Angew. Chem. Int. Ed.* **2012**, *51*, 3066.

[40] For an example of conjugate reduction using Hantzsch esters where hydride transfer is rate-limiting, see: Zhu, X.-Q.; Zou, H.-L.; Yuan, P.-W.; Liu, Y.; Cao, L.; Cheng, J.-P. A Detailed Investigation into the Oxidation Mechanism of Hantzsch 1,4-Dihydropyridines by Ethyl α-Cyanocinnamates and Benzylidenemalononitriles. *J. Chem. Soc. Perkin Trans. 2* **2000**, 1857.

[41] Hansch, C.; Leo, A.; Taft, R.W. A Survey of Hammett Substituent Constants and Resonance and Field Parameters. *Chem. Rev.* **1991**, *91*, 165.

[42] *Isotope Effects in Chemical Reactions*; Collins, C.J.; Bowman, N.S., Eds.; ACS Monograph; American Chemical Society: Washington, DC, 1970.

[43] The authors acknowledge an anonymous review for their insight into this section of the discussion.

[44] For selected examples, see: a) Krautwald, S.; Sarlah, D.; Schafroth, M. A.; Carreira, E. M. Enantio- and Diastereodivergent Dual Catalysis: α-Allylation of Branched Aldehdyes. *Science* **2013**, *340*, 1065; b) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. Iridium-Catalyzed Enantioselective Allylic Vinylation. *J. Am. Chem. Soc.* **2013**, *135*, 994; c) Hamilton, J. Y.; Sarlah, D.; Carreira, E. M. Iridium-Catalyzed Enantioselective Allylic Alkylation with Functionalized Organozinc Bromides. *Angew. Chem. Int. Ed.* **2015**, *54*, 7644; d) Breitler, S.; Carreira, E.M. Formaldehyde *N,N*-Dialkylhydrazones as Neutral Formyl Anion Equivalents in Iridium-Catalyzed Asymmetric Allylic Substitution. *J. Am. Chem. Soc.* **2015**, *137*, 5296; e) Sandmeier, T.; Krautwald, S.; Carreira, E. M. Stereoselective Synthesis of Piperidines by Iridium-Catalyzed Cyclocondensation. *Angew. Chem. Int. Ed.* **2017**, *56*, 11515; f) Sempere, Y.; Carreira, E. M. Trimethyl Orthoacetate and Ethylene Glycol Mono-Vinyl Ether as Enolate Surrogates in Enantioselective Iridium-Catalyzed Allylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 7654.

[45] Thermal ellipsoids are shown at the 20% probability level. Some hydrogen atoms and co-crystallized solvent molecules have been omitted for clarity in **Ir-1**.

[46] Brock, C.P.; Schweizer, W.B.; Dunitz, J.D. On the Validity of Wallach's Rule: on the Density and Stability of Racemic Crystals Compared with their Chiral Counterparts. *J. Am. Chem. Soc.* **1991**, *113*, 9811.

[47] Krautwald, S. Stereodivergent Dual Catalysis. Ph.D. Thesis, ETH Zürich, **2016**.

[48] a) Wabnitz, T.C.; Yu, J.-Q.; Spencer, J.B. Evidence That Protons Can Be the Active Catalysts in Lewis Acid Mediated Hetero-Michael Addition Reactions. *Chem. Eur. J.* **2004**, *10*, 484; b) Williams, D.B.G.; Lawton, M. Metal Triflates: On the

Question of Lewis Versus Brønsted Acidity in Retinyl Carbocation Formation. *J. Mol. Catal. A: Chem.* **2010**, *317*, 68; c) Dang, T.;T.; Boeck, F.; Hinterman, L. Hidden Brønsted Acid Catalysis: Pathways of Accidental or Deliberate Generation of Triflic Acid from Metal Triflates. *J.Org. Chem.* **2011**, *76*, 9353; d) Sletten, E.T.; Tu, Y.-J.; Schlegel, H.B.; Nguyen, H.M. Are Brønsted Acids the True Promoter of Metal-Triflate-Catalyzed
Glycosylations? A Mechanistic Probe into 1,2-cis-Aminoglycoside Formation by Nickel Triflate. *ACS Catal.* **2019**, *9*, 2110.

TOC Graphic: