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Cyclometallated Iridium-PhanePhos Complexes Are Active Catalysts in Enantioselective Allene-Fluoral Reductive Coupling and Related Alcohol-Mediated Carbonyl Additions that Form Acyclic Quaternary Carbon Stereocenters

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Abstract

Iridium complexes modified by PhanePhos catalyze the 2-propanol-mediated reductive coupling of diverse 1,1-disubstituted allenes **1a–1u** with fluoral hydrate **2a** to form CF₃-substituted secondary alcohols **3a–3u** that incorporate acyclic quaternary carbon-containing stereodiads. By exploiting concentration-dependent stereoselectivity effects related to the interconversion of kinetic (*Z*)- and thermodynamic (*E*)- σ -allyliridium isomers, adducts **3a–3u** are formed with complete levels of branched regioselectivity and high levels of *anti*-diastereo- and enantioselectivity. The utility of this method for construction of CF₃-oxetanes and CF₃-azetidines is illustrated by the formation of **4a** and **6a**, respectively. Studies of the reaction mechanism aimed at illuminating the singular effectiveness of PhanePhos as a supporting ligand in this and related transformations have led to the identification of a chromatographically stable cyclometallated iridium-(*R*)-PhanePhos complex Ir-PP-**I** that is catalytically competent for allene-fluoral reductive coupling and previously reported transfer hydrogenative C-C couplings of dienes or CF₃-allenes with methanol. Deuterium labelling studies, reaction progress kinetic analysis (RPKA) and computational studies corroborate a catalytic mechanism involving rapid allene hydrometalation followed by turnover-limiting carbonyl addition. A computationally determined stereochemical

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ASSOCIATED CONTENT

Supporting Information. Experimental procedures and spectral data. HPLC traces of racemic and enantiomerically enriched products. Crystallographic data for the 3,5-dinitrobenzoate of **3d** and the cyclometallated iridium-(*R*)-PhanePhos complex Ir-PP-**I**. Reaction progress kinetic analysis data and data pertaining to computational studies. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

Notes.

The authors declare no competing financial interest.

model shows the *ortho*-CH₂ group of the cyclometallated iridium-PhanePhos complex plays a key role in directing diastereo- and enantioselectivity. The collective data provide key insights into the structural-interactive features of allyliridium complexes required to enforce nucleophilic character, which should inform the design of related cyclometallated catalysts for umpoled allylation.

Graphical Abstract

Introduction

Diverse catalytic enantioselective methods enabling formation of quaternary carbon stereocenters that reside within *cyclic* frameworks have been reported.¹ In contrast, catalytic enantioselective methods that deliver *acyclic* quaternary carbon stereocenters remain relatively uncommon.^{1a,g,2,3} Even more elusive are asymmetric methods that deliver (a) acyclic quaternary carbon-containing stereopolyads³ or (b) fluorinated acyclic quaternary carbon-containing structural motifs.⁴ In the course of developing catalytic enantioselective carbonyl reductive couplings via alcohol-mediated hydrogen transfer or hydrogen auto-transfer,⁵ we recently developed enantioselective methods for the formation of acyclic quaternary carbon stereocenters that operate under non-cryogenic conditions and completely atom-efficient, bypassing the use of stoichiometric metals.⁶ In these processes, vinyl epoxides,^{6a} 1,3-dienes^{6b} and CF₃-allenes^{6c} serve as pronucleophiles.

In the latter two processes, iridium complexes modified by PhanePhos⁷ were uniquely effective in catalyzing highly regio- and stereoselective methanol-mediated formaldehyde additions.^{6b,c,8} Other chelating phosphine ligands were completely inactive in these processes. The singular effectiveness of the iridium-PhanePhos catalyst prompted further exploration of its capabilities and investigations into the precise nature of the catalytically active species. Here, we report that the iridium complex derived from [Ir(cod)Cl]₂ and PhanePhos catalyzes highly regio-, diastereo- and enantioselective allene-fluoral reductive couplings mediated by 2-propanol to form acyclic quaternary carbon-containing stereodiads.^{9,10,11,12} Of greater significance, these studies have led to the identification of a cyclometallated iridium-PhanePhos complex that is catalytically competent - not only in the present transformation, but also in previously reported iridium-PhanePhos catalyzed reactions developed in our laboratory.^{6b,c} This complex contributes to a growing collection of cyclometallated iridium complexes that display diverse catalytic activities (Figure 1).¹³

Research Design and Methods

Reaction Optimization, Scope and Applications.

Prior work in our laboratory on enantioselective iridium-PhanePhos catalyzed C-C coupling focused on methanol-mediated formaldehyde additions.^{6b,c} Steric issues posed by the formation of a more highly substituted quaternary carbon C-C bond prohibited reactions of higher aldehydes. It was posited that fluoral, a highly reactive carbonyl electrophile like formaldehyde, might participate in alcohol-mediated reductive coupling to provide acyclic quaternary carbon stereodiads incorporating a trifluoroethyl carbinol fragment.¹⁴ However, the feasibility of allene-fluoral reductive coupling was rendered uncertain by two issues. First, fluoral is only commercially available as the hydrate or hemiacetal, yet the vast majority of enantioselective metal-catalyzed fluoral additions require use of anhydrous fluoral.⁴ Secondly, high levels of stereoselectivity not only require discrimination of enantiotopic carbonyl π -faces, but intervention of a single geometrical isomer of the σ -allyliridium nucleophile. The latter issue is further complicated by the fact that hydroiridation of 1,1-disubstituted allenes occurs preferentially at the allene π -face proximal to the smaller allene substituent (Rs) to furnish the less stable (*Z*)- σ -allyliridium isomer. Hence, notwithstanding Curtin-Hammett effects,¹⁵ in order to form the quaternary carbon stereocenter with optimal levels of stereoselectivity, kinetic stereoselectivity favoring formation of the (*Z*)- σ -allyliridium isomer must either be preserved or equilibration between the (*Z*)- and (*E*)- σ -allyliridium isomers must be achieved prior to carbonyl addition with complete conversion to the latter (Figure 2). The difference in energy between (*Z*)- and (*E*)-2-phenyl-2-butenes is more than 1 Kcal/mol, and greater energetic differentiation is anticipated for the corresponding (*Z*)- and (*E*)- σ -allyliridium species.¹⁶

With these considerations in mind, the following series of experiments was performed (Figure 2). Allene **1a** (200 mol%), fluoral hydrate **2a** (100 mol%, 75 wt% in water) and 2-propanol (200 mol%) were exposed to the iridium catalyst derived from [Ir(cod)Cl]₂ (2.5 mol%) and (*R*)-PhanePhos (5 mol%) in *tert*-butanol (0.5 M) at 100 °C. In the absence of desiccant, only trace quantities of the targeted reductive coupling product **3a** was observed. However, upon addition of 4 Å molecular sieves, compound **3a** was formed in 43% yield as 5:1 mixture of diastereomers in 96% enantiomeric excess. In accord with our stereochemical analysis, it was reasoned that more dilute conditions might increase diastereoselectivity by decreasing the rate of carbonyl addition with respect to the rate of equilibration between the (*Z*)- and (*E*)- σ -allyliridium isomers.¹⁵ Indeed, in the event, diastereoselectivity was found to increase with increasing dilution and at 0.05 M a 13:1 diastereomeric ratio was observed without any erosion of enantioselectivity, although under these dilute conditions the isolated yield of **3a** suffered. In the course of our optimization experiments, we also observed that more Lewis basic solvents promote higher diastereoselectivities. This fact led us to explore the effect of halide additives. To our delight, introduction of Bu₄NCl (100 mol%) not only improved diastereoselectivity and but also increased the isolated yield of **3a**. At 0.2 M in the presence of Bu₄NCl, compound **3a** was formed in 78% yield as a 17:1 mixture of diastereomers with a 96% enantiomeric excess. Diastereoselectivity remained constant at 80, 90, and 100 °C, and at lower temperatures conversion decreased precipitously so diastereoselectivity was not calculated.

These optimized conditions were applied to the reductive coupling 1,1-disubstituted allenes **1a-1o** bearing aryl and methyl groups with fluoral hydrate **2a** (Table 1). Allenes **1b-1k** bearing aryl moieties with diverse substitution patterns and electronic properties are converted to adducts **3b-3k** in good yield with uniformly high levels of regio-, diastereo- and enantioselectivity. Notably, functional groups that are potentially susceptible to reduction, for example nitro groups (**3j**) and ketones (**3k**), remain intact. Heteroaryl-substituted allenes **1l-1o** are also effective partners for reductive coupling, providing adducts **3l-3o** with high levels of relative and absolute stereocontrol. For *N*-heterocycles at least one *ortho*-substituent adjacent to nitrogen is required for high levels of conversion.

To test the limits of stereoselectivity, 1,1-disubstituted allenes **1p-1u** bearing higher alkyl substituents were evaluated in reductive couplings to fluoral **2a** (Table 2). Remarkably, although increasing size of the alkyl moiety was anticipated to erode partitioning of the transient (*E*)- and (*Z*)- σ -allyliridium isomers, excellent levels of stereocontrol were retained in reactions of allenes **1p-1u** that incorporate linear alkyl groups. In contrast, attempted reactions of allenes bearing branched alkyl groups, for example, cycloalkyl moieties, were lowyielding and non-diastereoselective. The absolute stereochemical assignment of all adducts **3a-3u** is made in analogy to that established for the 3,5-dinitrobenzoate of **3d**, which was determined by single crystal X-ray diffraction analysis.

To briefly illustrate the utility of the reaction products, fluoral adduct **3a** was converted to the CF₃-oxetane **4a**, which bears a quaternary carbon stereocenter (eq. 1).¹⁷ Oxetanes have emerged as useful building blocks in medicinal chemistry due to their ability to serve as carbonyl and *gem*-dimethyl isosteres.¹⁸ Recently, CF₃-oxetanes were shown to function as a more polar *tert*-butyl isostere.¹⁹ To prepare CF₃-oxetane **4a**, fluoral adduct **3a** was transformed to the mesylate and subjected to ozonolysis conditions. The resulting primary alcohol was exposed to sodium hydride to provide oxetane **4a** (eq. 1). As corroborated by the conversion of primary tosylate **5a** to oxetane **4a** (eq. 2), the formation of **4a** proceeds via secondary to primary methanesulfonate transfer. Just as trifluoroethylamines serve as amide bioisosteres,²⁰ CF₃-azetidines²¹ may be viewed as β -lactam mimics. To prepare CF₃-azetidine **6a**, fluoral adduct **3a** was converted the mesylate and subjected to ozonation conditions to deliver the corresponding aldehyde. Reductive amination-cyclization provided CF₃-azetidine **6a** (eq. 3).

Identification of A Catalytically Competent Cyclometallated Complex.

Insight into the unusual effectiveness of the iridium-PhanePhos catalyst was essential in terms of formulating an accurate interpretation of the catalytic mechanism. Products of allene-fluoral reductive coupling were not formed upon use of other chelating phosphine ligands such as BINAP or SEGPHOS under otherwise identical conditions. The same is true for previously reported iridium-PhanePhos catalyzed couplings of methanol with 1,3-dienes^{6b} and CF₃-allenes.^{6c} Consequently, the fact that cyclometallated π -allyliridium *C,O*-benzoate complexes (Figure 1)^{13c} promote C-C coupling in the aforesaid processes (albeit with suboptimal levels of stereocontrol) was deemed significant. This observation raised the question of whether the unique topology of PhanePhos rendered this ligand susceptible to cyclometallation. Although cyclometallated complexes of PhanePhos have not been reported, a relatively short contact of 3.56 Å is found in the X-ray crystal structure of a palladium-PhanePhos complex²² between metal and the *ortho*-carbon atom of the cyclophane ring. For an iridium center, which has a larger atomic radius, one could easily imagine an agostic interaction or C-H oxidative addition to form a cyclometallated complex. With these thoughts in mind, an effort was made to prepare a cyclometallated iridium-PhanePhos complex and evaluate its catalytic activity.

In the event, heating a THF solution of [Ir(cod)Cl]₂ (100 mol%), (*R*)-PhanePhos (200 mol %) and allyl acetate (400 mol%) at 100 °C for one hour gave a yellow residue, which upon flash silica gel column chromatography delivered the 4-membered metallacycle Ir-PP-I in up to 60% yield. The structural assignment of Ir-PP-I was corroborated by single-crystal X-ray diffraction analysis (Figure 3). The cyclometallated iridium complex is of distorted octahedral geometry with the two phosphorus atoms of PhanePhos and acetate lying in the same plane and with the chloride and aryl moieties apical to the plane. The distance between the phosphorus atoms (3.34 Å) is noticeably less than that found in the related square planar

Pd(*rac*-PhanePhos)Cl₂ complex (3.62 Å).²² Additionally, the P–Ir–P “bite angle” (95.90°) is significantly compressed compared to that found in the palladium complex (103.69°).²² The P–Ir–C bond angle of the iridacycle is 67.95° with an Ir–C bond length of 2.04 Å. The bond length of the cyclometallated Ir–P is 2.24 Å, which is slightly shorter than the other Ir–P bond, which has a bond length of 2.26 Å. The differential trans influence of these two phosphorus atoms is reflected by the disparity between the two Ir–O bond lengths of the acetate moiety. The Ir–O bond that is trans to the activated phosphorus atom has bond length of 2.19 Å, which is slightly longer than the Ir–O bond trans to the non-cyclometallated phosphorus atom, which has a bond length of 2.15 Å.

To probe the catalytic competency of the cyclometallated complex, allene **1e** was exposed to fluoral hydrate **2a** in the presence of Ir-PP-I (5 mol%) under otherwise standard conditions. The product of reductive coupling **3e** was formed in 72% yield as a 14:1 diastereomeric ratio and 96% enantiomeric excess (eq. 4). Similarly, allene **1p** was exposed to fluoral hydrate **2a** in the presence of Ir-PP-I (5 mol%) under otherwise standard conditions to furnish the reductive coupling product **3p** in 62% yield as a 16:1 diastereomeric ratio and 93% enantiomeric excess (eq. 5). These data are in good alignment with the yields and stereoselectivities observed in reactions in which the catalyst is generated *in situ* from [Ir(cod)Cl]₂ (2.5 mol%) and (*R*)-PhanePhos (5 mol%) (Tables 1 and 2, respectively). The cyclometallated complex Ir-PP-I is also a competent catalyst in the previously reported iridium-PhanePhos catalyzed couplings of methanol with 1,3-dienes (eq. 6)^{6b} and CF₃-allenes (eq. 7).^{6c} These data (eq. 4–7) corroborate intervention of a cyclometallated catalyst related to Ir-PP-I in the present allene-fluoral reductive coupling and the previously reported transfer hydrogenative C–C couplings of dienes^{6b} or CF₃-allenes.^{6c} While roughly equivalent stereoselectivities are observed using the preformed complex Ir-PP-I, slightly lower yields are evident. This may be due to the fact that the catalyst generated *in situ* incorporates a monodentate chloride counterion, whereas Ir-PP-I contains a bidentate acetate counterion, which may inhibit catalysis.

Deuterium Labelling Studies and General Catalytic Mechanism.

To gain further insight into the catalytic mechanism, a series of deuterium labelling experiments were conducted (eq. 7 and 8). Exposure of fluoral hydrate **2a** to *deuterio-1a*, which incorporates a fully deuterated methyl group, under standard reaction conditions delivers *deuterio-3a* (eq. 7). Deuterium is completely retained at the methyl group and is not redistributed to any other position. This experiment demonstrates that the reaction does not proceed by way of allene-to-diene isomerization. Indeed, the isomeric diene was prepared and subjected to standard reaction conditions and was not a competent partner for C–C coupling. The coupling of **1a** and **2a** mediated by *d*8–2-propanol under otherwise standard conditions delivers *deuterio-3a'* (eq. 8). Deuterium is incorporated exclusively at the interior vinylic position (15% 2H). Exchange between iridium-hydrides and the deuterium atoms of D₂O is well-documented,²³ and incomplete deuterium incorporation is likely due to H–D exchange with *tert*-butanol or water associated with aqueous fluoral hydrate. Consistent with this hypothesis, when the reaction is conducted in *d*10-*tert*-butanol or toluene, enhanced levels of deuterium incorporation are observed (eq. 8).

The collective data are consistent with the indicated catalytic mechanism (Scheme 1). Entry into the catalytic cycle is achieved via C-H oxidative addition of the *ortho*-C-H bond of PhanePhos to iridium(I). Allene hydrometallation from the resulting iridium(III) hydride **I** delivers the kinetic (*Z*)- σ -allyliridium isomer **IIa**. Isomerization to the thermodynamically preferred (*E*)- σ -allyliridium isomer **IIb** is followed by association of fluoral and carbonyl addition to furnish the homoallylic iridium(III) alkoxide **IV**. Alkoxide exchange with 2-propanol releases the product of carbonyl addition **3a**. β -Hydride elimination from the 2-propoxy iridium(III) species **V** regenerates the iridium(III) hydride **I** to close the catalytic cycle. Knowing that the active catalyst is a cyclometallated halide containing iridium(III) complex, one can better understand how halides “tune” the environment at the iridium center to influence reactivity and selectivity. In the present transformation, the additive Bu_4NCl may assist by preserving chloride at the iridium(III) center, while in previously reported couplings of methanol with CF_3 -allenes,^{6c} Bu_4NI likely substitutes the chloride at iridium(III).

Reaction Progress Kinetic Analysis.

To gain further mechanistic insight, reaction progress kinetic analysis (RPKA) was applied to the coupling of allene **1a** with fluoroaldehyde **2a** to form adduct **3a**.^{24,25} Due to the volatile nature of the reactants and the complex equilibria between fluoral, fluoroal hydrate and hemiacetals that arise upon addition of 2-propanol and *tert*-butanol, the progress of a single reaction could not be monitored. Therefore, a series of reactions were conducted in parallel, and for each successive time point an individual reaction was stopped and the extent of product formation was determined by GC analysis using an internal standard. As each data point derives from a separate experiment the quality of the data were not ideal, nevertheless, several significant conclusions could be drawn.

The results of experiments carried out using the “different excess” protocol elucidate the order in allene **1a** and fluoroaldehyde **2a** (Figure 5). The observed overlap between data sets indicates zero-order kinetics in allene, since the rate of product formation is not effected by the change of initial concentration of allene (Figure 5, left). In contrast, higher concentrations of **2a** result in faster rates of product formation, which suggests a positive order in fluoroal (Figure 5, middle). Evaluation of the effect of increasing catalyst loading using Burés method²⁶ suggests the reaction is first order in catalyst (Figure 5, right). Furthermore, results of a set of experiments performed using the “same excess” protocol indicate minimal catalyst deactivation occurs (see Supporting Information). These data

corroborate a catalytic mechanism involving rapid allene hydrometalation followed by turnover-limiting carbonyl addition (Scheme 1). These data also implicate the π -allyliridium species, which could be detected via high resolution mass spectrometry as the catalyst resting state.

Computational Studies.

Initial computational studies were aimed at formulating a unified stereochemical model accounting for relative and absolute stereochemistry in the present and prior^{6b,c} iridium-(*R*)-PhanePhos catalyzed transfer hydrogenative carbonyl additions (eq. 4–7). Accordingly, 48 different conformations based on a Zimmerman-Traxler-type transition structure²⁷ were thus computationally analyzed to identify the transition state with the lowest energy barrier (see Supporting Information). In the most favored transition state (Figure 6), the σ -allyl occupies a coordination site that minimizes steric repulsion with the CH₂ moiety of the cyclophane ethano-linkage that resides *ortho* to iridium. At the same time, nonbonded interactions between the terminal aryl moiety of the σ -allyl and the cyclometallated phenyl ring are decreased. The carbonyl electrophile, fluoral, can then enter the coordination site *trans* to the PPh₂ moiety of the iridacycle and *syn* to Ir-Cl with the CF₃ pointing away from the Ir center. The orientation of the fluoral C-H bond suggests possible intervention of a formyl C-H bond with the chloride ligand.²⁸ Addition of the σ -allyl to the *Si*-face of the carbonyl through a closed transition structure defines enantiotopic π -facial selectivity. This model is also applicable to iridium-(*R*)-PhanePhos-catalyzed couplings of methanol with 1,3-dienes^{6b} and CF₃-allenes.^{6c}

Computational studies were used to further assess the veracity of our interpretation of the catalytic mechanism (Scheme 2). Allene hydrometallation from intermediate **I**, an iridium(III) hydride-allene complex, delivers the kinetic (*Z*)- σ -allyliridium isomer **IIb**, which can interconvert with the thermodynamically preferred (*E*)- σ -allyliridium isomer **IIa**. The Curtin–Hammett situation¹⁵ favors the reaction to proceed by association of fluoral to **IIa** followed by carbonyl addition via **TS2-*E*** to furnish the homoallylic iridium(III) alkoxide **IVa**. Alkoxide exchange with 2-propanol releases the product of carbonyl addition **3a** and regenerates the iridium(III) hydride coordinated with an allene after β -hydride elimination to close the catalytic cycle. Consistent with the excellent levels of diastereo- and enantioselectivity that are observed, the transition state leading to the disfavored enantiomer, **TS2-*E*-2R3S**, requires the fluoral carbonyl group to become *anti*-periplanar to Ir-Cl bond, which results in a higher energy barrier due to the increased steric interactions with the cyclometallated phenyl ring and the *ortho*-CH₂ group of the PhanePhos ligand. Within the same core geometry at iridium, the second lowest transition state, **TS2-*Z*-2S3S**, will afford a diastereomer from the (*Z*)-isomer (**IIb**) with the same stereoselectivity for the allylation of fluoral. Notably, both computational studies and RPKA implicate rapid allene hydrometallation followed by turnover-limiting carbonyl addition with the allyliridium species as a potential catalyst resting state.

Conclusions

In summary, we report a highly regio- and enantioselective iridium catalyzed allene-fluoral reductive coupling mediated by 2-propanol. This method enables generation of enantiomerically enriched quaternary carbon stereocenters in the context of a CF₃-bearing stereodiad. Of greater significance, we have identified a chromatographically stable cyclometallated iridium-(*R*)-PhanePhos complex Ir-PP-I that is catalytically competent in the present allene-fluoral reductive couplings as well as previously reported iridium-PhanePhos catalyzed C-C couplings of methanol with dienes^{6b} or CF₃-allenes.^{6c} These findings suggest that cyclometallated iridium-PhanePhos complexes akin to Ir-PP-I may constitute a privileged catalyst class. A catalytic mechanism involving rapid allene hydrometalation followed by turnover-limiting carbonyl addition was corroborated by deuterium labelling studies, reaction progress kinetic analysis (RPKA) and DFT calculations. Computational studies also were used to formulate a unified stereochemical that accounts for the origins of enantioselectivity in the present fluoral-allene reductive couplings and previously reported iridium-PhanePhos catalyzed C-C couplings of methanol with dienes^{6b} or CF₃-allenes.^{6c} Future studies will focus on the discovery and development of related umpoled allylations²⁹ via alcohol-mediated carbonyl addition catalyzed by cyclometallated iridium-PhanePhos complexes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Diverse catalytic activities of cyclometallated iridium complexes and the identification of a catalytically competent cyclometallated iridium-PhanePhos complex.

Figure 2.

Relative and absolute stereoselection in 2-propanol-mediated reductive couplings of allenes with fluoral hydrate via concentration-dependent diastereoselectivity.^a

Figure 3. Structure of the cyclometallated iridium-(*R*)-PhanePhos complex Ir-PP-I as determined by single crystal X-ray diffraction.^a

Figure 4.

Corroboration of catalytic competency of Ir-PP-I for all iridium-(*R*)-PhanePhos-catalyzed transfer hydrogenative carbonyl additions.^a

Figure 5.

Product formation as monitored by GC analysis in reactions carried out utilizing “different excess” protocol. $[cat] = 0.005$ M; $[TBAC] = 0.1$ M; $[2\text{-propanol}] = 0.2$ M; (a) $[1a]_0 = 0.2$ M, $[2a]_0 =$ as noted; (b) $[2a]_0 = 0.1$ M, $[1a]_0 =$ as noted. (c) Time adjustment of product formation in varying catalyst loading reactions as monitored by GC analysis. $[1a] = 0.2$ M; $[2a] = 0.1$ M; $[TBAC] = 0.1$ M; $[2\text{-propanol}] = 0.2$ M; $[cat] =$ as noted.

Figure 6.

Computationally determined stereochemical model accounting for relative and absolute stereochemistry for all iridium-(*R*)-PhanePhos catalyzed transfer hydrogenative carbonyl additions.^a

Scheme 1.

Proposed catalytic mechanism for iridium-PhanePhos catalyzed allene-fluoral reductive coupling mediated by 2-propanol.

Scheme 2.

Computationally determined energy profiles of the proposed catalytic mechanism.^a

Table 1.

Variation of aryl substituent in iridium-catalyzed coupling of allenes **1a-1o** with fluoral hydrate **2a** to form adducts **3a-3o** bearing acyclic quaternary carbon stereocenters.^a

1a , Ar = Ph 1d , Ar = 4-Br-Ph 1g , Ar = 3-MeO-Ph 1j , Ar = 3-NO ₂ -Ph 1m , Ar = 5-(2-MeO-Pyr)	1b , Ar = 4-F-Ph 1e , Ar = 4-MeO-Ph 1h , Ar = 3,5-Cl ₂ -Ph 1k , Ar = 4-COMe-Ph 1n , Ar = 5-(2-Me-Pym)	1c , Ar = 4-Cl-Ph 1f , Ar = 3-NHAc-Ph 1i , Ar = 2-F-Ph 1l , Ar = 3-Thienyl 1o , Ar = 4-(6-MeO-Quin)
 3a , 78% Yield, 17:1 dr 96% ee	 3b , 81% Yield, 19:1 dr 96% ee	 3c , 72% Yield, 18:1 dr 96% ee
 3d , 85% Yield, 19:1 dr 96% ee (2 mmol scale, X-Ray)	 3e , 79% Yield, 14:1 dr 96% ee	 3f , 64% Yield, 11:1 dr 90% ee
 3g , 76% Yield, 18:1 dr 96% ee	 3h , 71% Yield, 19:1 dr 95% ee	 3i , 58% Yield, 13:1 dr 96% ee
 3j , 74% Yield >20:1 dr, 96% ee	 3k , 86% Yield, 20:1 dr 96% ee	 3l , 68% Yield, 13:1 dr 94% ee ^b
 3m , 68% Yield, 19:1 dr 97% ee	 3n , 69% Yield, 15:1 dr 96% ee	 3o , 70% Yield, >20:1 dr 95% ee

^aDiastereoselectivity determined by ¹⁹F NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. Yields of material isolated by silica gel chromatography. ^b8 hr. See Supporting Information for further experimental details.

Table 2.

Variation of alkyl substituent in iridium-catalyzed coupling of allenes **1p-1u** with fluoral hydrate **2a** to form adducts **3p-3u** bearing acyclic quaternary carbon stereocenters.^a

1p , R = Et 1s , R = (CH ₂) ₃ NPhth	1q , R = CH ₂ OTIPS 1t , R = (CH ₂) ₂ 4-F-Ph	1r , R = (CH ₂) ₃ OTIPS 1u , R = (CH ₂) ₃ CO ₂ Et
 3p , 76% Yield, 12:1 dr 93% ee	 3q , 58% Yield, 20:1 dr 99% ee	 3r , 84% Yield, 10:1 dr 95% ee
 3s , 81% Yield, 15:1 dr 93% ee	 3t , 72% Yield, 11:1 dr 96% ee	 3u , 65% Yield, 9:1 dr 96% ee

^aDiastereoselectivity determined by ¹⁹F NMR of crude reaction mixtures. Enantioselectivities were determined by chiral stationary phase HPLC analysis. Yields of material isolated by silica gel chromatography. See Supporting Information for further experimental details.