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Iridium-Catalyzed C−C Coupling of a Simple Propargyl Ether with Primary Alcohols: Enantioselective Homoaldol Addition via Redox-Triggered (*Z*)-Siloxyallylation

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Supporting Information

ABSTRACT: A chiral iridium complex formed *in situ* from $[Ir(cod)Cl]_2$ and (*R*)-H_8-BINAP is found to catalyze the direct enantioselective C−C coupling of a simple propargyl ether, $TIPSOCH_2C{\equiv}CH$, with primary alcohols to form γ-hydroxy (*Z*)-enol silanes with uniformly high enantioselectivity and complete alkene (*Z*)-stereoselectivity. As corroborated by deuterium labeling studies, these studies represent the first examples of 1,2-hydride shift-enabled π-allyl formation in the context of iridium catalysis.

Carbonyl addition ranks among the most broadly utilized methods for C−C bond formation.[1] Traditionally, the delivery of non-stabilized carbanions to carbonyl compounds has relied on the use of main-group organometallic reagents.[2] In a significant departure from classical carbonyl addition chemistry, we have developed a broad family of "*redox-triggered carbonyl additions*," wherein hydrogen transfer from alcohols to π-unsaturated reactants generates transient carbonyl−organometal pairs *en route* to products of C−C coupling.[3] By merging the characteristics of carbonyl addition and transfer hydrogenation in this way, the direct conversion of lower alcohols to higher alcohols is achieved in the absence of stoichiometric metals or discrete alcohol-to-carbonyl redox reactions.[3] For example, in the context of carbonyl allylation and crotylation,[4,5] these concepts have enabled a progression from the use of chiral allyl- and crotylmetal reagents to direct site-selective catalytic asymmetric conversions of primary alcohols to secondary homoallylic alcohols using abundant commodity chemical feedstocks, such as allyl acetate[6] or butadiene.[7]

In more recent work based on these principles, ruthenium catalysts were found to promote C−C bond formation between primary alcohols and *internal* alkynes.[8a,b,9] As corroborated by deuterium labeling studies, these transformations proceed by way of alkyne-to-allene isomerization. The intermediate allene then couples to the carbonyl partner through oxidative coupling[8a] or hydrometalative[8b] pathways. Remarkably, we found that propargyl ethers participate in ruthenium-catalyzed C−C couplings with primary alcohols through an entirely different mechanism involving an unprecedented 1,2-hydride shift-enabled π-allyl formation.[8c] These transformations deliver enantiomerically enriched γ-hydroxy-β-methyl enol silanes, but with poor control of enol (*E*:*Z*)-selectivity. Further, ruthenium-based catalysts failed to promote the C−C coupling of the *terminally unsubstituted* propargyl ethers. Here, demonstrating the generality of this new pathway for π-allyl formation and overcoming the aforesaid limitations in scope, we report that chiral iridium complexes catalyze the direct C−C coupling of the simple propargyl ether **1a**, $TIPSOCH_2C{\equiv}CH$ (TIPS = $^iPr_3Si$), with primary alcohols **2a**−**2l** to form γ-hydroxy (*Z*)-enol silanes **3a**−**3l** with uniformly high enantioselectivity and complete enol (*Z*)-stereoselectivity. These processes represent a divergence from the classical acetylide addition chemistry of terminal alkynes,[10,11] allowing propargyl ethers to serve as homoenolate equivalents[12,13] in the absence of stoichiometric metals (Figure 1).

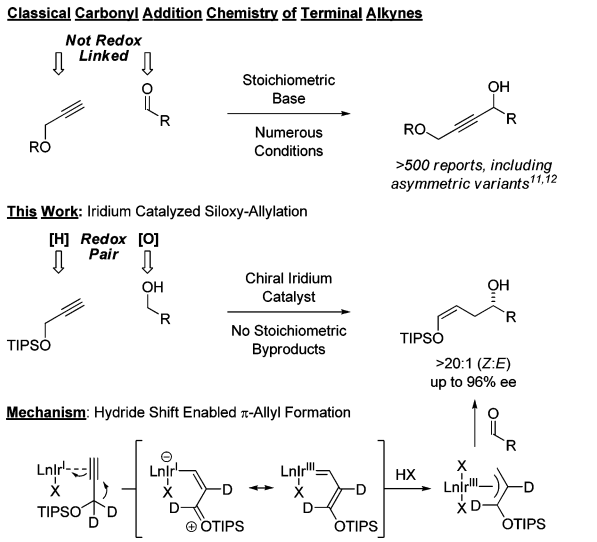

Figure 1. Classical and redox-triggered carbonyl addition chemistry of terminal alkynes.

Initial experiments involved exposure of propargyl ether **1a** (300 mol%) to *p*-bromobenzyl alcohol **2c** (100 mol%) in the presence of $[Ir(cod)Cl]_2$ (2.5 mol%) and (*R*)-BINAP (5 mol %) in toluene solvent at 95 °C. The desired product of C−C coupling, γ-hydroxy enol silane **3c**, was formed with complete enol (*Z*)-stereoselectivity in 14% isolated yield and 87% ee (Table 1, entry 1). It was found that Bu_4NI (10 mol%) and Ph_3CCO_2H (5 mol%) each have a beneficial effect on conversion. When they were used together, a 47% isolated

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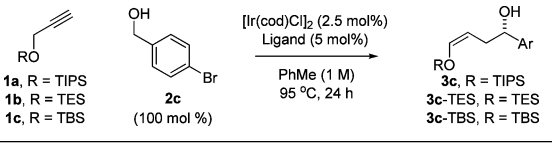
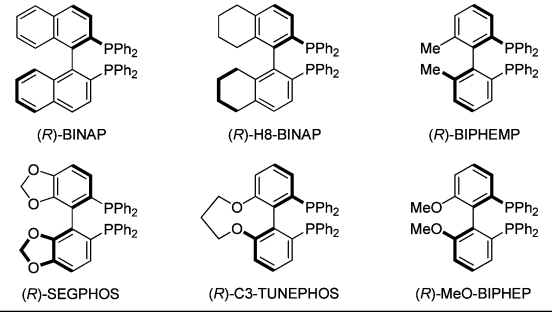
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 1. Selected Optimization Experiments in the Enantioselective Coupling of Propargyl Ether 1 and *p*-Bromobenzyl Alcohol 2c To Form γ-Hydroxy Enol Silane 3c[a]



Entry	1	Ligand	Bu_4NI	Ph_3CCO_2H	3c (Yield, *Z*:*E*)	ee%
1	**1a**, 300 mol%	(*R*)-BINAP	-	-	14%, >20:1	87
2	**1a**, 300 mol%	(*R*)-BINAP	10 mol%	-	21%, >20:1	92
3	**1a**, 300 mol%	(*R*)-BINAP	-	5 mol%	23%, >20:1	87
4	**1a**, 300 mol%	(*R*)-BINAP	10 mol%	5 mol%	47%, >20:1	90
5	**1a**, 300 mol%	(*R*)-H_8-BINAP	10 mol%	5 mol%	55%, >20:1	91
6	**1a**, 400 mol%	(*R*)-BINAP	10 mol%	5 mol%	64%, >20:1	93
⇨ 7	**1a**, 400 mol%	**(*R*)-H_8-BINAP**	**10 mol%**	**5 mol%**	**86%, >20:1**	**91**
8	**1a**, 400 mol%	(*R*)-H_8-BINAP	10 mol%	-	38%, >20:1	88
9	**1a**, 400 mol%	(*R*)-H_8-BINAP	-	5 mol%	58%, >20:1	85
10	**1a**, 400 mol%	(*R*)-SEGPHOS	10 mol%	5 mol%	30%, >20:1	96
11	**1a**, 400 mol%	(*R*)-MeO-BIPHEP	10 mol%	5 mol%	47%, >20:1	94
12	**1a**, 400 mol%	(*R*)-C3-TUNEPHOS	10 mol%	5 mol%	32%, >20:1	91
13	**1a**, 400 mol%	(*R*)-BIPHEMP	10 mol%	5 mol%	48%, >20:1	86
14[b]	**1a**, 400 mol%	(*R*)-H_8-BINAP	-	5 mol%	83%, >20:1	84
15	**1b**, 400 mol%	(*R*)-H_8-BINAP	10 mol%	5 mol%	36%, >20:1	90
16	**1c**, 400 mol%	(*R*)-H_8-BINAP	10 mol%	5 mol%	56%, >20:1	91

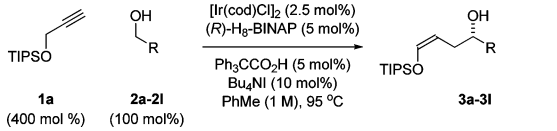


[a]Yields are of material isolated by silica gel chromatography and represent the average of two runs. Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See Supporting Information for further details. [b]$[Ir(cod)I]_2$.

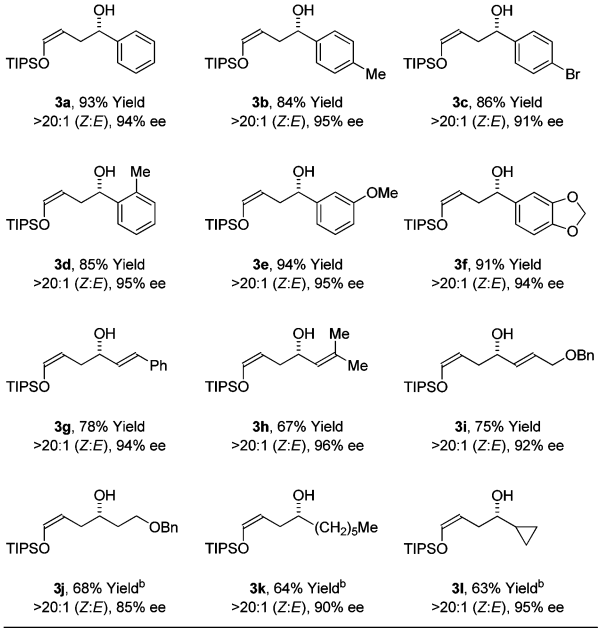
yield of **3c** was obtained, and the level of enantiomeric enrichment increased to 90% ee (Table 1, entries 2–4). Conversion was enhanced further by increasing the loading of propargyl ether **1a** (400 mol%) and using the chiral iridium catalyst modified by (*R*)-H_8-BINAP (Table 1, entries 5–7). Under these conditions, γ-hydroxy enol silane **3c** was formed in 86% isolated yield with complete enol (*Z*)-stereoselectivity and 91% ee (Table 1, entry 7). These optimal conditions require the additives Bu_4NI (10 mol%) and Ph_3CCO_2H (5 mol%) (Table 1, entries 8 and 9). Only selected examples of the many phosphine ligands evaluated in this study are shown (Table 1, entries 10–13). While other ligands could enforce higher enantioselectivities in certain cases, the highest isolated yield of **3c** was obtained using the iridium catalyst modified by (*R*)-H_8-BINAP (Table 1, entry 7). Notably, a comparable isolated yield of **3c** could be obtained using the iridium catalyst generated *in situ* from $[Ir(cod)I]_2$ (2.5 mol%) and (*R*)-H_8-BINAP in the absence of Bu_4NI (Table 1, entry 14), suggesting the role of Bu_4NI involves formation of an iodide modified iridium catalyst. A proposed catalytic mechanism accounting for the role of both Bu_4NI and Ph_3CCO_2H is provided (*vide infra*). Silyl ethers **1b** (TES = Et_3Si) and **1c** (TBS = $^tBuMe_2Si$) gave diminished yields of the siloxyallylation products **3c**-TES and **3c**-TBS, respectively (Table 1, entries 15 and 16). Finally, it should be noted that the internal alkyne $TIPSOCH_2C{\equiv}CMe$, which under the conditions of ruthenium catalysis reacts efficiently with primary alcohols to form products of siloxycrotylation, does not engage in C–C coupling under the present conditions of iridium catalysis.

To evaluate the scope of this process, optimal conditions were applied to the coupling of propargyl ether **1a** to alcohols **2a–2l** (Table 2). Benzylic alcohols **2a–2f** were converted to

Table 2. Enantioselective Iridium-Catalyzed C–C Coupling of Propargyl Ether 1a with Alcohols 2a–2l To Form Products of (*Z*)-Siloxyallylation, γ-Hydroxy Enol Silanes 3a–3l[a]



2a, R = Ph; **2b**, R = 4-MePh; **2c**, R = 4-BrPh
2d, R = 2-MePh; **2e**, R = 3-MeOPh; **2f**, R = 5-benzodioxole
2g, R = HC=CHPh; **2h**, R = HC=CMe$_2$; **2i**, R = HC=CCH$_2$OBn
2j, R = (CH$_2$)$_2$OBn; **2k**, R = (CH$_2$)$_5$Me; **2l**, R = *c*-Pr



3a, 93% Yield, >20:1 (*Z*:*E*), 94% ee
3b, 84% Yield, >20:1 (*Z*:*E*), 95% ee
3c, 86% Yield, >20:1 (*Z*:*E*), 91% ee
3d, 85% Yield, >20:1 (*Z*:*E*), 95% ee
3e, 94% Yield, >20:1 (*Z*:*E*), 95% ee
3f, 91% Yield, >20:1 (*Z*:*E*), 94% ee
3g, 78% Yield, >20:1 (*Z*:*E*), 94% ee
3h, 67% Yield, >20:1 (*Z*:*E*), 96% ee
3i, 75% Yield, >20:1 (*Z*:*E*), 92% ee
3j, 68% Yield[b], >20:1 (*Z*:*E*), 85% ee
3k, 64% Yield[b], >20:1 (*Z*:*E*), 90% ee
3l, 63% Yield[b], >20:1 (*Z*:*E*), 95% ee

[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details. [b]Adamantane carboxylic acid was used instead of Ph_3CCO_2H.

adducts **3a–3f**, respectively, in excellent isolated yield, complete enol (*Z*)-stereoselectivity and uniformly high levels of enantioselectivity. As illustrated by the conversion of benzylic alcohol **2d** to adduct **3d**, *ortho*-substitution is tolerated. Allylic alcohols **2g–2i** were converted to adducts **3g–3i**, respectively, in good isolated yields with complete enol (*Z*)-stereoselectivity and enantioselectivities greater than 90% ee. For aliphatic alcohols **2j–2l**, slightly lower isolated yields were obtained in the formation adducts **3j–3l**, but high levels of stereoselectivity persisted. Increased loadings of propargyl ether **1a** did not enhance the isolated yield of **3j–3l**. To verify the absolute stereochemical assignment of adducts **3a–3l**, compound **3a** was subjected to hydrolysis followed by borohydride reduction to form the previously reported compound, (*S*)-1-phenylbutane-1,4-diol.[14] The functional group array embodied by γ-hydroxy enol silanes **3a–3l** offer numerous possibilities for

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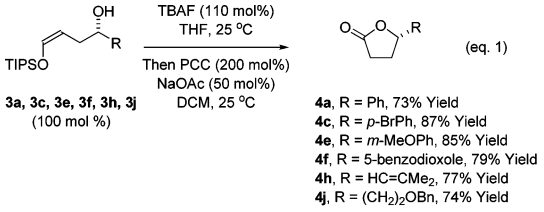
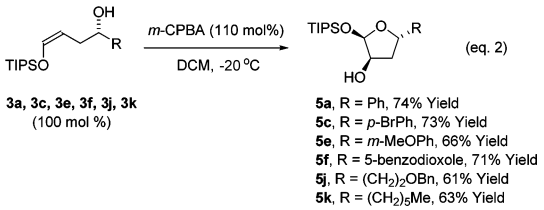
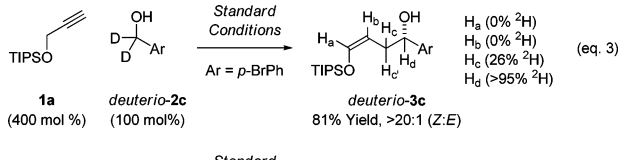
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

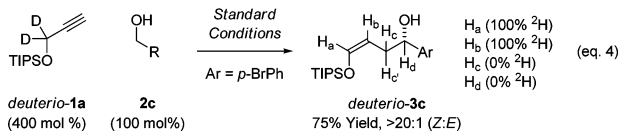
elaboration. For example, treatment of adducts **3a**, **3c**, **3e**, **3f**, **3h** and **3j** with TBAF followed by pyridinium chlorochromate (PCC) mediated oxidation provides the enantiomerically enriched γ-lactones **4a**, **4c**, **4e**, **4f**, **4h**, and **4j** (eq 1).[8c] Additionally, peracid-mediated epoxidation of adducts **3a**, **3c**, **3e**, **3f**, **3j**, and **3k**, occurs in a highly diastereoselective manner to furnish the trisubstituted furans **5a**, **5c**, **5e**, **5f**, **5j**, and **5k**, (eq 2).[13]





Deuterium labeling experiments were performed to probe the catalytic mechanism. Exposure of propargyl ether **1a** to *deuterio*-**2c** under standard conditions provided *deuterio*-**3c**, for which deuterium is observed at the allylic (26% ^{2}H) and carbinol (>95% ^{2}H) positions (eq 3). Coupling of the



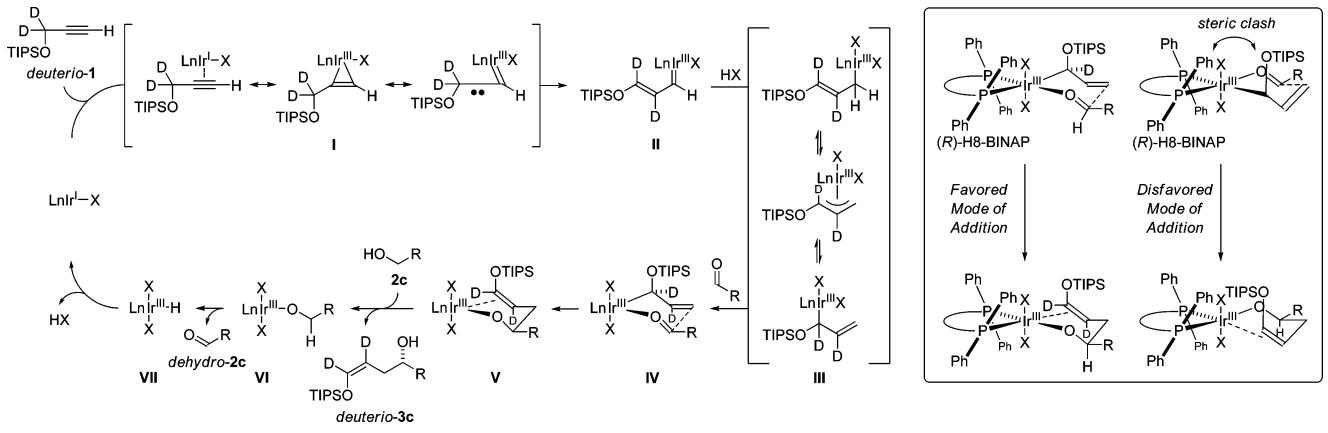


deuterated propargyl ether *deuterio*-**1a** with alcohol **2c** under standard reaction conditions provided *deuterio*-**3c**, for which complete deuterium incorporation is observed at each vinylic position (eq 4). In both reactions, the pattern of deuterium incorporation was as determined by ^{1}H and ^{2}H NMR and analyses.

These data corroborate the indicated catalytic mechanism involving 1,2-hydride shift enabled π-allyl formation (Scheme 1). Specifically, alkyne complexation by low-valent iridium induces 1,2-hydride shift to form vinylcarbene **II**. The n→σ* interaction of the oxygen lone pair with the propargylic C−H bond is crucial in terms of promoting 1,2-hydride shift, as in the absence of the ether functional group products of (*Z*)-siloxyallylation are not observed. Related 1,2-hydride shifts have been observed in metal-catalyzed cycloisomerizations of *N*-tethered 1,6-enynes,[15] including iridium-catalyzed reactions.[16] Protonation of vinylcarbene **II** delivers the siloxyallyliridium complex **III**. Aldehyde association triggers carbonyl addition through the closed, chair-like transition structure **IV**. A model accounting for the absolute stereochemistry and (*Z*)-enol selectivity is provided (Scheme 1). Addition occurs by way of the σ-allyliridium haptomer where iridium is attached to the oxygen-bearing carbon, presumably due to the negative inductive effect of oxygen and formation of a less-congested C−C bond. The resulting homoallylic iridium alkoxide **V** exchanges with a reactant alcohol **2c** to release the product of (*Z*)-siloxyallylation **3c**. β-Hydride elimination of the primary iridium alkoxide **VI** provides the aldehyde *dehydro*-**2c** and the iridium(III) hydride complex **VII**. Finally, H-X reductive elimination returns iridium to its low-valent form to close the catalytic cycle.

In summary, we report the direct iridium-catalyzed C−C coupling of a simple propargyl ether, TIPSOCH$_2$C≡CH, with primary alcohols **2a**−**2l** to form products of siloxyallylation, γ-hydroxy (*Z*)-enol silanes **3a**−**3l**. Uniformly high levels of enantioselectivity and complete enol (*Z*)-stereoselectivity are observed. As corroborated by deuterium labeling studies, these transformations proceed through a novel 1,2-hydride shift mechanism that converts a metal bound alkyne to a vinyl carbene that protonates to form a nucleophilic π-allyliridium complex. These processes represent a departure from the classical carbonyl addition chemistry of terminal alkynes and raise numerous possibilities for the development of related C−C couplings beyond stoichiometric carbanions.

Scheme 1. General Catalytic Mechanism As Corroborated by Deuterium Labeling Experiments and Model Accounting for Absolute Stereochemistry and Enol (*Z*)-Selectivity



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■ ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data; HPLC traces corresponding to racemic and enantiomerically enriched samples (PDF)

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Notes

The authors declare no competing financial interest.

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