

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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S Supporting Information

ABSTRACT: A chiral iridium complex formed *in situ* from $[\text{Ir}(\text{cod})\text{Cl}]_2$ and (*R*)- H_8 -BINAP is found to catalyze the direct enantioselective C–C coupling of a simple propargyl ether, $\text{TIPSOCH}_2\text{C}\equiv\text{CH}$, 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 acetate⁶ 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**, $\text{TIPSOCH}_2\text{C}\equiv\text{CH}$ (TIPS = $^t\text{Pr}_3\text{Si}$), 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).

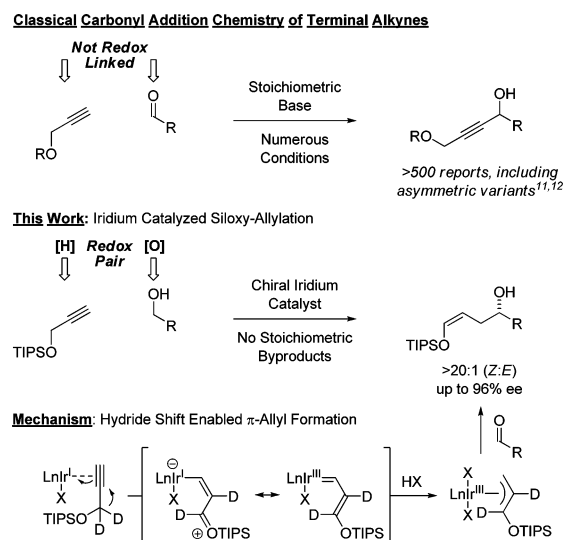


Figure 1. Classical and redox-triggered carbonyl addition chemistry of terminal alkynes.

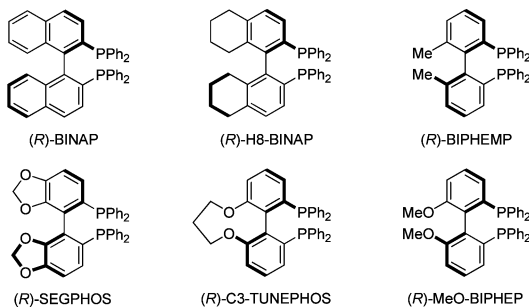
Initial experiments involved exposure of propargyl ether **1a** (300 mol%) to *p*-bromobenzyl alcohol **2c** (100 mol%) in the presence of $[\text{Ir}(\text{cod})\text{Cl}]_2$ (2.5 mol%) and (*R*)-BINAP (5 mol%) in toluene solvent at 95 °C. The desired product of C–C coupling, γ -hydroxy enol silane **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 $\text{Ph}_3\text{CCO}_2\text{H}$ (5 mol%) each have a beneficial effect on conversion. When they were used together, a 47% isolated

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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 ₄ NI	Ph ₃ CCO ₂ H	3c (Yield, Z:E)	ee%
1	1a, 300 mol%	(<i>R</i>)-BINAP	-	-	14%, >20:1	87
2	1a, 300 mol%	(<i>R</i>)-BINAP	10 mol%	-	21%, >20:1	92
3	1a, 300 mol%	(<i>R</i>)-BINAP	-	5 mol%	23%, >20:1	87
4	1a, 300 mol%	(<i>R</i>)-BINAP	10 mol%	5 mol%	47%, >20:1	90
5	1a, 300 mol%	(<i>R</i>)-H ₈ -BINAP	10 mol%	5 mol%	55%, >20:1	91
6	1a, 400 mol%	(<i>R</i>)-BINAP	10 mol%	5 mol%	64%, >20:1	93
→ 7	1a, 400 mol%	(<i>R</i>)-H ₈ -BINAP	10 mol%	5 mol%	86%, >20:1	91
8	1a, 400 mol%	(<i>R</i>)-H ₈ -BINAP	10 mol%	-	38%, >20:1	88
9	1a, 400 mol%	(<i>R</i>)-H ₈ -BINAP	-	5 mol%	58%, >20:1	85
10	1a, 400 mol%	(<i>R</i>)-SEGPHOS	10 mol%	5 mol%	30%, >20:1	96
11	1a, 400 mol%	(<i>R</i>)-MeO-BIPHEP	10 mol%	5 mol%	47%, >20:1	94
12	1a, 400 mol%	(<i>R</i>)-C3-TUNEPHOS	10 mol%	5 mol%	32%, >20:1	91
13	1a, 400 mol%	(<i>R</i>)-BIPHEMP	10 mol%	5 mol%	48%, >20:1	86
14 ^b	1a, 400 mol%	(<i>R</i>)-H ₈ -BINAP	-	5 mol%	83%, >20:1	84
15 ^b	1b, 400 mol%	(<i>R</i>)-H ₈ -BINAP	10 mol%	5 mol%	36%, >20:1	90
16	1c, 400 mol%	(<i>R</i>)-H ₈ -BINAP	10 mol%	5 mol%	56%, >20:1	91



^aYields 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*)-H₈-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 Bu₄NI (10 mol%) and Ph₃CCO₂H (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*)-H₈-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*)-H₈-BINAP in the absence of Bu₄NI (Table 1, entry 14), suggesting the role of Bu₄NI involves formation of an iodide modified iridium catalyst. A proposed catalytic mechanism accounting for the role of both Bu₄NI and Ph₃CCO₂H is provided (*vide infra*). Silyl ethers 1b (TES = Et₃Si) and 1c (TBS = ^tBuMe₂Si) 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 TIPSOCH₂C≡CMe,

which under the conditions of ruthenium catalysis reacts efficiently with primary alcohols to form products of siloxy-crotylation, 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

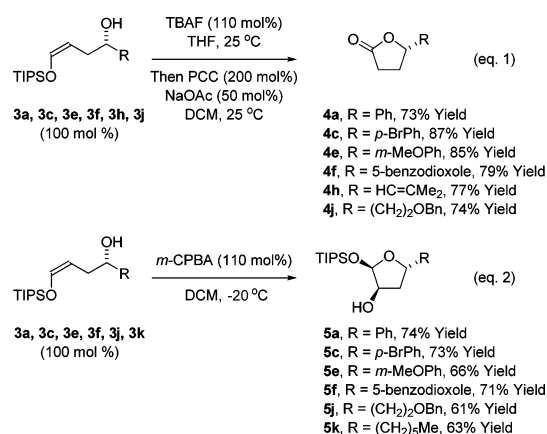
2a, R = Ph	2b, R = 4-MePh	2c, R = 4-BrPh
2d, R = 2-MePh	2e, R = 3-MeOPh	2f, R = 5-benzodioxole
2g, R = HC=CHPh	2h, R = HC=CMe ₂	2i, R = HC=CCH ₂ OBn
2j, R = (CH ₂) ₂ OBn	2k, R = (CH ₂) ₃ Me	2l, R = <i>c</i> -Pr

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

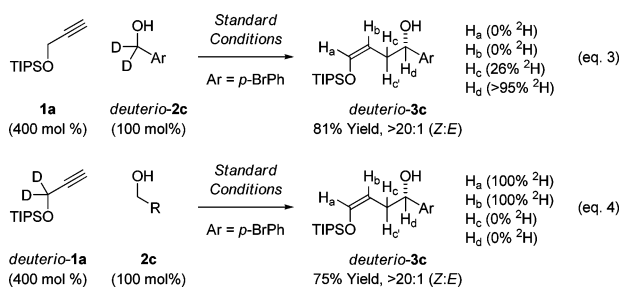
^aYields are of material isolated by silica gel chromatography. See [Supporting Information](#) for further experimental details. ^bAdamantane carboxylic acid was used instead of Ph₃CCO₂H.

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

elaboration. For example, treatment of adducts **3a**, **3c**, **3e**, **3f**, **3h** and **3j** with TBAF followed by pyridinium chlorochromate (PCC) mediated oxidation provides the enantioselectively enriched γ -lactones **4a**, **4c**, **4e**, **4f**, **4h**, and **4j** (eq 1).^{3c} 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% ²H) and carbinol (>95% ²H) positions (eq 3). Coupling of the



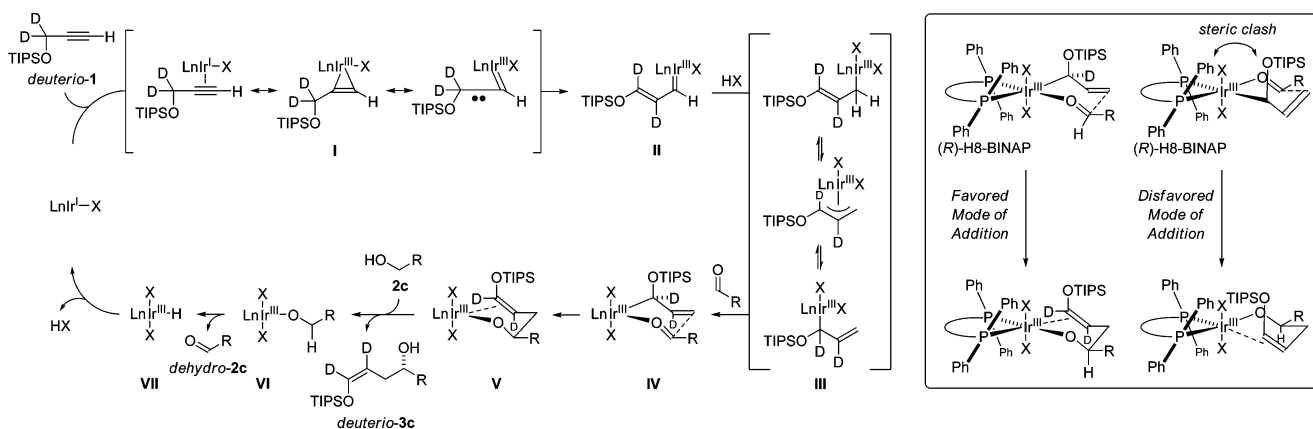
deuterated propargyl ether *deuterio-1a* with alcohol **2c** under standard reaction conditions provided *deuterio-3c*, for which complete deuterium incorporation is observed at each vinylic position (eq 4). In both reactions, the pattern of deuterium

incorporation was as determined by ¹H and ²H 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 $n \rightarrow \sigma^*$ 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, TIPSOCH₂C \equiv 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



■ ASSOCIATED CONTENT**📄 Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: [10.1021/jacs.5b12131](https://doi.org/10.1021/jacs.5b12131).

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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