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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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Abstract

A chiral iridium complex formed *in situ* from $[\text{Ir}(\text{cod})\text{Cl}]_2$ and (*R*)-H₈-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 “*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 crotylmethyl 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 labelling 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 hydrometallative^{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

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Supporting Information Available: Experimental procedures and spectral data. HPLC traces corresponding to racemic and enantiomerically enriched samples. This material is available free of charge *via* the internet at <http://pubs.acs.org>.

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**, TIPSOCH₂C $\equiv$ CH (TIPS = *i*Pr₃Si), with primary alcohols **2a-2l** to form γ -hydroxy (*Z*)-enol silanes **3a-3l** with uniformly high enantioselectivities and complete enol (*Z*)-stereoselectivity. These processes represent a divergence from 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).

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 Bu₄NI (10 mol%) and Ph₃CCO₂H (5 mol%) each have a beneficial effect on conversion. When used together, a 47% isolated 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 8-9). 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 = *t*BuMe₂Si) 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 $\equiv$ 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, these optimal conditions were applied to the coupling of propargyl ether **1a** to alcohols **2a-2l** (Table 2). Benzylic alcohols **2a-2f** were converted to 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 well tolerated. Allylic alcohol **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 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 γ -lactones **5a**, **5c**, **5e**, **5f**, **5j** and **5k**, (eq. 2).¹³

Deuterium labelling 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 are 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, $\text{TIPSOCH}_2\text{C}\equiv\text{CH}$, 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 the chemistry of stoichiometric carbanions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

- (1). (a) Knochel, P.; Molander, GA. *Comprehensive Organic Synthesis*. 2nd. Elsevier; Oxford: 2014. Vols. 1 and Vol. 2(b) Otera, J. *Modern Carbonyl Chemistry*. Wiley-VCH; Weinheim, Germany: 2000.
- (2). Grignard V. *Compt. Rend.* 1900; 130:1322.
- (3). Ketcham JM, Shin I, Montgomery TP, Krische MJ. *Angew. Chem., Int. Ed.* 2014; 53:9142. Review:
- (4). Herold T, Hoffmann RW. *Angew. Chem., Int. Ed.* 1978; 17:768. For the seminal report on enantioselective carbonyl allylation using chirally modified allyl metal reagents, see.
- (5). (a) Yamamoto Y, Asao N. *Chem. Rev.* 1993; 93:2207. For selected reviews on enantioselective carbonyl allylation and crotylation, see. (b) Ramachandran PV. *Aldrichim. Acta.* 2002; 35:23.(c) Kennedy JWJ, Hall DG. *Angew. Chem., Int. Ed.* 2003; 42:4732.(d) Denmark SE, Fu J. *Chem. Rev.* 2003; 103:2763. [PubMed: 12914480] (e) Yu C-M, Youn J, Jung H-K. *Bull. Korean Chem.*

- Soc. 2006; 27:463.(f) Marek I, Sklute G. Chem. Commun. 2007:1683.(g) Hall DG. Synlett. 2007:1644.(h) Li J, Menche D. Synthesis. 2009:2293.(i) Leighton JL. Aldrichim. Acta. 2010; 43:3.(j) Yus M, González-Gómez JC, Foubelo F. Chem. Rev. 2011; 111:7774. [PubMed: 21923136] (k) Pasco M, Gilboa N, Mejuch T, Marek I. Organometallics. 2013; 32:942.
- (6). (a) Kim IS, Ngai M-Y, Krische MJ. J. Am. Chem. Soc. 2008; 130:6340. For catalytic enantioselective carbonyl allylation *via* redox-triggered couplings of primary alcohols and allyl acetate, see. [PubMed: 18444616] (b) Kim IS, Ngai M-Y, Krische MJ. J. Am. Chem. Soc. 2008; 130:14891. [PubMed: 18841896] (c) Dechert-Schmitt A-MR, Schmitt DC, Krische MJ. Angew. Chem., Int. Ed. 2013; 52:3195.(d) Shin I, Wang G, Krische MJ. Chem. Eur. J. 2014; 20:13382. [PubMed: 25169904]
- (7). (a) Zbieg JR, Yamaguchi E, McInturff EL, Krische MJ. Science. 2012; 336:324. [PubMed: 22442385] (b) McInturff EL, Yamaguchi E, Krische MJ. J. Am. Chem. Soc. 2012; 134:20628. [PubMed: 23234459]
- (8). (a) Park BY, Nguyen KD, Chaulagain MR, Komanduri V, Krische MJ. J. Am. Chem. Soc. 2014; 136:11902. [PubMed: 25075434] (b) Liang T, Nguyen KD, Zhang W, Krische MJ. J. Am. Chem. Soc. 2015; 137:3161. [PubMed: 25734220] (c) Liang T, Zhang W, Chen T-Y, Nguyen KD, Krische MJ. J. Am. Chem. Soc. 2015; 137:13066. [PubMed: 26418572]
- (9). Obora Y, Hatanaka S, Ishii Y. Org. Lett. 2009; 11:3510. Obora and Ishii report an iridium catalyzed C-C coupling of 1-aryl-1-propynes with primary alcohols to furnish racemic products of carbonyl α -(aryl)allylation. Deuterium labeling studies were not performed, however, related products are formed in iridium and ruthenium catalyzed C-C couplings of primary alcohols with allenes, where pathways involving allene hydrometalation have been corroborated: and literature cited in reference 8a. [PubMed: 19719194]
- (10). (a) Miura T, Nishida Y, Murakami M. J. Am. Chem. Soc. 2014; 136:6223. Indirect use of 1-alkynes in carbonyl allylation is achieved through their conversion to allylboron reagents *via* tandem alkyne hydroboration-alkene isomerization, see. [PubMed: 24735355] (b) Miura T, Nishida Y, Morimoto M, Murakami M. J. Am. Chem. Soc. 2013; 135:11497. [PubMed: 23886015]
- (11). (a) Niwa S, Soai K. J. Chem. Soc., Perkin Trans. 1. 1990:937.(b) Ramos Tombo GM, Didier E, Loubinoux B. Synlett. 1990:547.(c) Li Z, Upadhyay V, DeCamp AE, DiMichele L, Reider PJ. Synthesis. 1999:1453.(d) Tan L, Chen C.-y. Tillyer RD, Grabowski EJJ, Reider PJ. Angew. Chem. Int. Ed. 1999; 38:711.(e) Frantz DE, Fässler R, Carreira EM. J. Am. Chem. Soc. 1999; 121:11245.
- (12). Kimura, M. Comprehensive Organic Synthesis. 2nd. Knochel, P.; Molander, GA., editors. Elsevier; Oxford: 2014. p. 606-628.Review:
- (13). Kang JY, Connell BT. J. Am. Chem. Soc. 2010; 132:7826. [PubMed: 20481562]
- (14). See Supporting Information for the determination of absolute stereochemistry
- (15). Fürstner A, Stelzer F, Szillat H. J. Am. Chem. Soc. 2001; 123:11863. [PubMed: 11724592]
- (16). (a) Barbazanges M, Augé M, Moussa J, Amouri H, Aubert C, Desmarets C, Fensterbank L, Gandon V, Malacria M, Ollivier C. Chem. Eur. J. 2011; 17:13789. [PubMed: 22052592] (b) Shibata T, Kobayashi Y, Maekawa S, Toshida N, Takagi K. Tetrahedron. 2005; 61:9018.(c) Dieckmann M, Jang Y-S, Cramer N. Angew. Chem. Int. Ed. 2015; 54:12149.

Classical Carbonyl Addition Chemistry of Terminal Alkynes **This Work:** Iridium Catalyzed Siloxy-Allylation **Mechanism:** Hydride Shift Enabled π -Allyl Formation

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

Scheme 1.

General catalytic mechanism as corroborated by deuterium labeling experiments and model accounting for absolute stereochemistry and enol (*Z*)-selectivity.

Selected optimization experiments in the enantioselective coupling propargyl ether **1a** and *p*-bromobenzyl alcohol **2c** to form γ -hydroxy enol silane **3c**.^a

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^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.

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

		<p>[Ir(cod)Cl]₂ (2.5 mol%) (R)-H₈-BINAP (5 mol%) Ph₃CCO₂H (5 mol%) Bu₄NI (10 mol%) PhMe (1 M), 95 °C</p>	<p>3a-3l</p>												
<p>1a (400 mol %)</p>	<p>2a-2l (100 mol %)</p>														
<p>2a, R = Ph 2d, R = 2-MePh 2g, R = HC=CHPh 2j, R = (CH₂)₂OBn</p>	<p>2b, R = 4-MePh 2e, R = 3-MeOPh 2h, R = HC=CMe₂ 2k, R = (CH₂)₅Me</p>	<p>2c, R = 4-BrPh 2f, R = 5-benzodioxole 2i, R = HC=CCH₂OBn 2l, R = c-Pr</p>													
<table border="0"> <tr> <td> 3a, 93% Yield >20:1 (Z:E), 94% ee </td> <td> 3b, 84% Yield >20:1 (Z:E), 95% ee </td> <td> 3c, 86% Yield >20:1 (Z:E), 91% ee </td> </tr> <tr> <td> 3d, 85% Yield >20:1 (Z:E), 95% ee </td> <td> 3e, 94% Yield >20:1 (Z:E), 95% ee </td> <td> 3f, 91% Yield >20:1 (Z:E), 94% ee </td> </tr> <tr> <td> 3g, 78% Yield >20:1 (Z:E), 94% ee </td> <td> 3h, 67% Yield >20:1 (Z:E), 96% ee </td> <td> 3i, 75% Yield >20:1 (Z:E), 92% ee </td> </tr> <tr> <td> 3j, 68% Yield^b >20:1 (Z:E), 85% ee </td> <td> 3k, 64% Yield^b >20:1 (Z:E), 90% ee </td> <td> 3l, 63% Yield^b >20:1 (Z:E), 95% ee </td> </tr> </table>				 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
 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													
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^bAdamantane carboxylic acid was used instead of Ph₃CCO₂H.

^aYields are of material isolated by silica gel chromatography. See Supporting Information for further experimental details.