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Ruthenium Catalyzed Diastereo- and Enantioselective Coupling of Propargyl Ethers with Alcohols: Siloxy-Crotylation via Hydride Shift Enabled Conversion of Alkynes to π-Allyls

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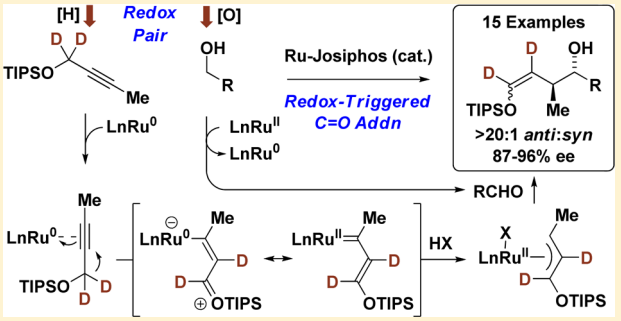
Supporting Information

ABSTRACT: The first enantioselective carbonyl crotylations through direct use of alkynes as chiral allylmetal equivalents are described. Chiral ruthenium(II) complexes modified by Josiphos (SL-J009-1) catalyze the C−C coupling of TIPS-protected propargyl ether **1a** with primary alcohols **2a**−**2o** to form products of carbonyl siloxy-crotylation **3a**−**3o**, which upon silyl deprotection-reduction deliver 1,4-diols **5a**−**5o** with excellent control of regio-, *anti*-diastereo-, and enantioselectivity. Structurally related propargyl ethers **1b** and **1c** bearing ethyl- and phenyl-substituents engage in diastereo- and enantioselective coupling, as illustrated in the formation of adducts **5p** and **5q**, respectively. Selective *mono*-tosylation of diols **5a**, **5c**, **5e**, **5f**, **5k**, and **5m** is accompanied by spontaneous cyclization to deliver the *trans*-2,3-disubstituted furans **6a**, **6c**, **6e**, **6f**, **6k**, and **6m**, respectively. Primary alcohols **2a**, **2l**, and **2p** were converted to the siloxy-crotylation products **3a**, **3l**, and **3p**, which upon silyl deprotection-lactol oxidation were transformed to the *trans*-4,5-disubstituted γ-butyrolactones **7a**, **7l**, and **7p**. The formation of **7p** represents a total synthesis of (+)-*trans*-whisky lactone. Unlike closely related ruthenium catalyzed alkyne-alcohol C−C couplings, deuterium labeling studies provide clear evidence of a novel 1,2-hydride shift mechanism that converts metal-bound alkynes to π-allyls in the absence of intervening allenes.



INTRODUCTION

Polyketides and their semisynthetic congeners are used extensively in human medicine.[1] With one exception,[2] all commercial polyketides derive from soil bacteria, yet less than 5% of soil bacteria are amenable to culture, with many phyla having eluded culture entirely.[3] As techniques for bacterial culture improve, the number of medicinally relevant polyketides is anticipated to expand. Presently, all polyketides used in human medicine, again with one exception,[3] are prepared via fermentation or through modification of fermentation products.[1] Although *de novo* chemical synthesis offers a gateway to otherwise inaccessible structural variants, conceptual advances beyond the first-generation lexicon of synthetic methods are required for the design of more efficient, cost-effective routes to these important secondary metabolites.[1d]

Among methods for *de novo* polyketide construction,[4] diastereo- and enantioselective carbonyl crotylation has proven especially effective (Figure 1).[5] Beginning with the pioneering studies of Hoffmann,[6] the majority of asymmetric crotylation protocols employ crotylmetal reagents that incorporate chiral modifiers (Figure 1, eq A).[5] Catalytic enantioselective crotylations, including umpoled reactions of crotyl halides or carboxylates,[7,8] were subsequently developed. These too rely on the use of stoichiometric metals, specifically, crotylmetal reagents[5] or metallic terminal reductants.[7,8] In a significant departure from prior art, we have introduced the concept of engaging alcohols and π-unsaturated reactants as redox pairs for the generation of carbonyl−organometal pairs *en route* to products of carbonyl addition.[5k] On the basis of this concept of "redox-triggered carbonyl addition," reactions of primary alcohols with α-methyl allyl acetate[9a−c] or butadiene[9d−f] to form products of carbonyl crotylation were developed (Figure 1, eq B). *In this account, we report the first direct alkyne mediated carbonyl crotylations* (Figure 1, eq C).[10] These transformations display high levels of *anti*-diastereo- and enantioselectivity and operate through a novel mechanism wherein metal-bound alkynes are converted to π-allylmetal species in the absence of intervening allenes (Figure 1, eq D).

In recent work from our laboratory, ruthenium catalysts were found to promote the redox-triggered coupling of primary alcohols with allenes to form homoallylic alcohols.[11,12] During these studies, Obora and Ishii described the iridium catalyzed coupling primary alcohols with aryl propynes to form products of (α-aryl)allylation.[13] This work suggested the feasibility of a dual ruthenium-based catalytic cycle wherein alkyne-to-allene isomerization occurs in tandem with redox-triggered carbonyl addition. Two key modifications to our previously reported ruthenium(II) based catalyst fulfilled efforts toward this goal (Scheme 1). First, using the catalyst generated *in situ* upon acid

Received: July 30, 2015
Published: September 29, 2015

DOI: 10.1021/jacs.5b08019
J. Am. Chem. Soc. 2015, 137, 13066−13071

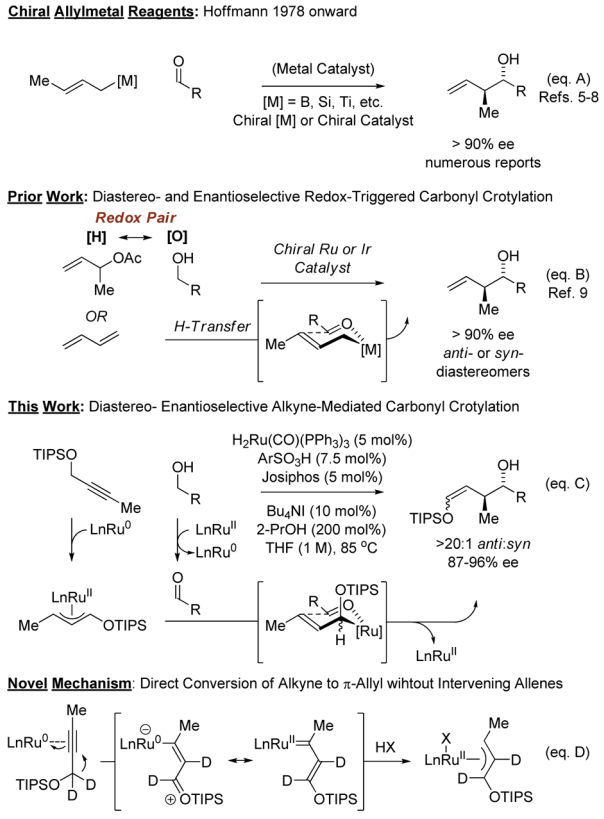
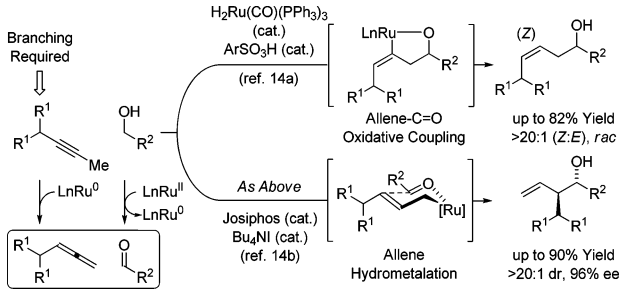


Figure 1. Overview of methods for carbonyl crotylation and the discovery of alkyne mediated crotylation.

base reaction of $H_2Ru(CO)(PPh_3)_3$ and 2,4,6-$(2\text{-}Pr)_3PhSO_3H$,[9e] ruthenium(0) species became accessible via H-X (X = $ArSO_3$) reductive elimination, enabling alkyne-to-allene isomerization by ruthenium(0) mediated propargyl C−H oxidative addition−reductive elimination pathways. Allenes generated under these conditions engage in ruthenium(0) mediated oxidative coupling with carbonyl partners to form linear (*Z*)-homoallylic alcohols.[14a] A second key modification to the catalyst involves the introduction of iodide and an electron rich chelating phosphine ligand, which suppresses oxidative coupling while maintaining catalytic alkyne-to-allene isomerization. Allenes generated under these conditions participate in hydrometallative pathways en route to branched homoallylic allylic alcohols.[14b] *It should be emphasized that in both cases isotopic labeling studies and other experiments corroborate intervention of allenes as discrete intermediates.*[14]

Scheme 1. Dual Ruthenium-Based Catalytic Cycles wherein Alkyne-to-Allene Isomerization Occurs in Tandem with Redox-Triggered C−C Bond Formation[a]

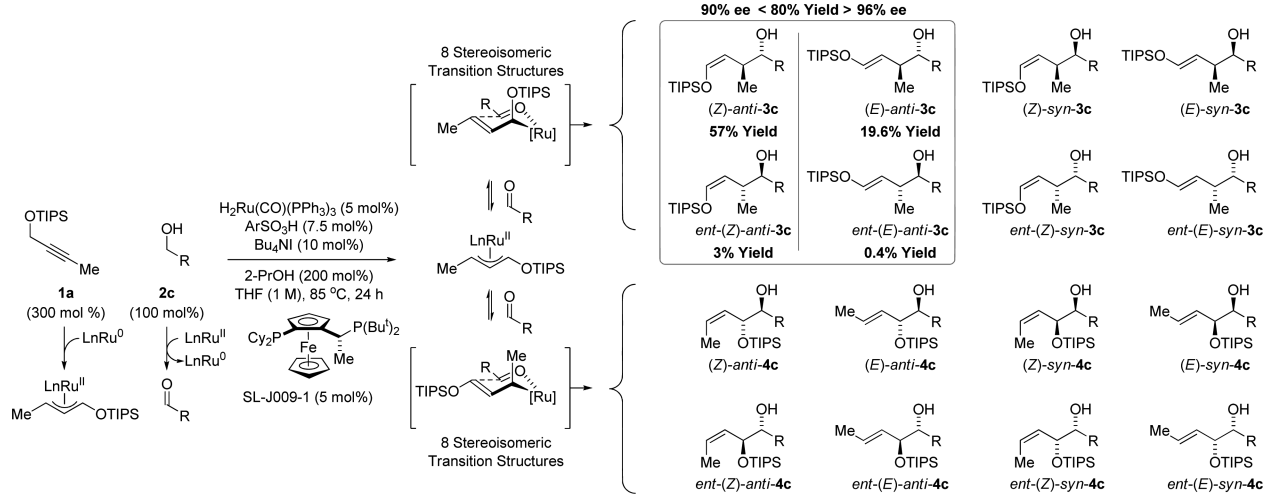


[a] $ArSO_3H$ = 2,4,6-$(2\text{-}Pr)_3PhSO_3H$.

RESEARCH DESIGN AND METHODS

For hydrometallative pathways *en route* to branched homoallylic allylic alcohols, the 2-alkyne must be branched at propargylic position to suppress numerous side-reactions. However, the TIPS-protected propargyl ether **1a** was not subject to this constraint. Exposure of propargyl ether **1a** to *p*-bromobenzyl alcohol **2c** under conditions used in the asymmetric couplings of 4-methyl-2-pentyne[14b] delivered the product of "siloxy-crotylation" **3c** with complete control of regio- and diastereoselectivity as a 3:1 (*Z*:*E*) mixture of olefin geometrical isomers in 70% isolated yield. The (*Z*)- and (*E*)-alkenes each displayed high levels of enantiomeric enrichment: 87% ee and 94% ee, respectively. This result was surprising given the large number of regio- and stereoisomers potentially formed in this transformation. Further optimization was undertaken.[15] Although (*Z*)- and (*E*)-selectivity was insensitive to variation of the ether

Scheme 2. Regio-, Diastereo-, and Enantioselectivity in the Redox-Triggered C−C Coupling of Propargyl Ether 1a and *p*-Bromobenzyl Alcohols 2c[a]



[a] $ArSO_3H$ = 2,4,6-$(2\text{-}Pr)_3PhSO_3H$. R = *p*-BrPh. Yield refers to a mixture (*Z*)-*anti*-**3c** and (*E*)-*anti*-**3c** and their enantiomers isolated by silica gel chromatography. See Supporting Information for further experimental details.

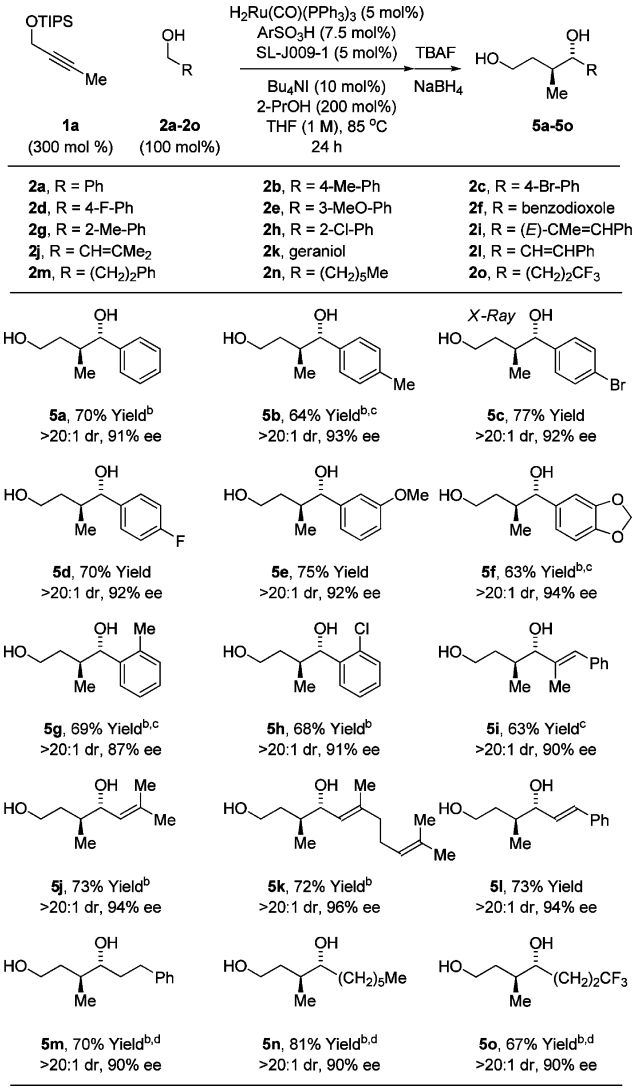
DOI: 10.1021/jacs.5b08019
J. Am. Chem. Soc. 2015, 137, 13066−13071

substituent, reactions conducted at lower temperatures and slightly higher loadings of 2,4,6-(2-Pr)$_3$PhSO$_3$H delivered (*Z*)- and (*E*)-*anti*-**3c** in 80% isolated yield and 90% ee and 96% ee, respectively (Scheme 2). The (*Z*)- and (*E*)- selectivity is inconsequential, as fluoride assisted cleavage of the enol in the presence of $NaBH_4$ enabled convergence of (*Z*)- and (*E*)-*anti*-**3c** to diol **5c** in quantitative yield and 92% ee.[16] The requirement of 2-propanol merits discussion. In the absence of 2-propanol, unreacted aldehyde accumulates due to competing transfer hydrogenation of propargyl ether **1a**. As the allylruthenium-aldehyde intermediates are generated in a pairwise manner, introduction of 2-propanol returns the aldehyde to the alcohol oxidation level, enabling reentry into the catalytic C−C coupling pathway.

Under these optimal conditions, propargyl ether **1a** was exposed to benzylic alcohols **2a**−**2h**, allylic alcohols **2i**−**2l**, and aliphatic alcohols **2m**−**2o** (Table 1). The respective enol silanes **3a**−**3o** were converted to diols **5a**−**5o**, which were formed with complete levels of regio- and *anti*-diastereoselectivity and uniformly high levels of enantioselectivity (87−96% ee). The stereochemical assignment of diols **5a**−**5o** was made in analogy to that determined for compound **5c** by single-crystal X-ray diffraction analysis. Both TBS and TBDPS ethers participate in coupling, but isolated yields were lower by roughly 20%. Application of these conditions to *O*-alkyl propargyl ethers led to complex mixtures. However, as illustrated in the coupling of ethyl- and phenyl-substituted propargyl alcohols **1b** and **1c**, variation of the acetylenic substituent is tolerated (see equations 1 and 2). Here, use of a BINAP modified ruthenium catalyst enables formation of adducts **5p** and **5q** in highly enantiomerically enriched form.

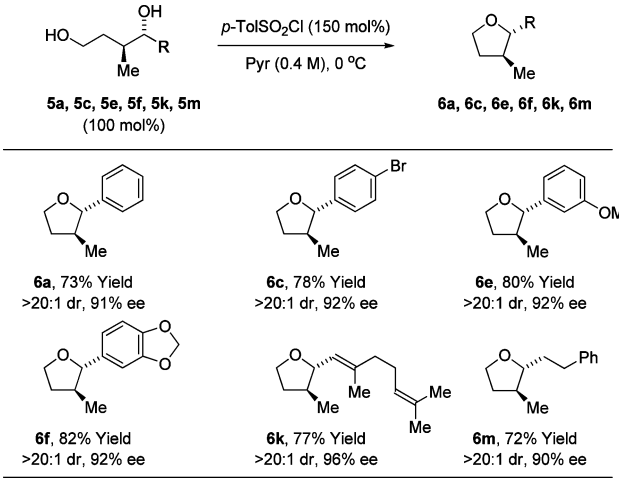
To illustrate the utility of this methodology, diols **5a**, **5c**, **5e**, **5f**, **5k**, and **5m** were exposed to *p*-toluenesulfonyl chloride in pyridine solvent, resulting in highly chemoselective *mono*-tosylation of the primary alcohol and spontaneous cyclization to form the corresponding *trans*-2,3-disubstituted furans **6a**, **6c**, **6e**, **6f**, **6k**, and **6m** (Table 2). Only in the formation of **6f** was any erosion in enantiomeric purity observed. Notably, 2,3-disubstituted furans that incorporate 3-methyl substituents

Table 1. Regio-, *anti*-Diastereo- and Enantioselective Coupling of Alkyne 1a with Alcohols 2a−2o To Form Diols 5a−5o[a]



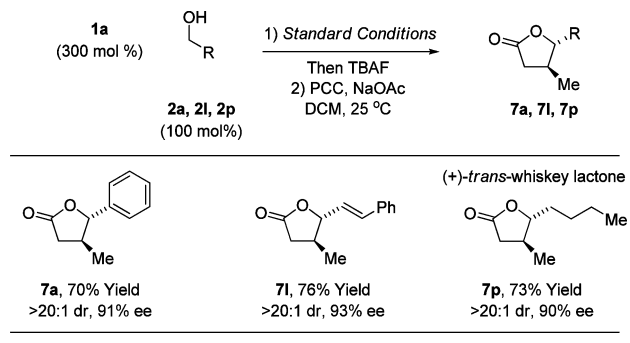
[a]Yields are of material isolated by silica gel chromatography. [b]48 h. See Supporting Information for further details. [c]$H_2Ru(CO)(PPh_3)_3$ (6 mol %), SL-J009−1 (6 mol %), $ArSO_3H$ (9 mol %), Bu_4NI (12 mol %). [d]2-PrOH was omitted.

Table 2. Conversion of Adducts 5a, 5c, 5e, 5f, 5k, and 5m to *trans*-2,3-Disubstituted Furans 6a, 6c, 6e, 6f, 6k, and 6m[a]



[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

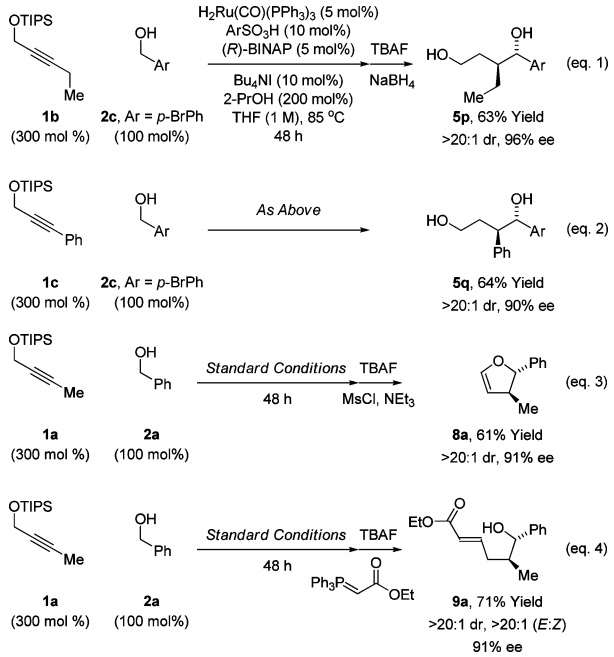
Table 3. Conversion of Alcohols 2a, 2l, and 2p to *trans*-4,5-Disubstituted γ-Butyrolactones 7a, 7l, and 7p[a]



[a]Yields are of material isolated by silica gel chromatography over the two-step sequence. See Supporting Information for further details.

DOI: 10.1021/jacs.5b08019
J. Am. Chem. Soc. 2015, 137, 13066−13071

appear frequently as substructures in type I polyketide natural products.[17] Coupling of primary alcohols **2a**, **2l**, and **2p** under standard conditions followed by exposure to TBAF led to crude hemiacetals, which upon treatment with pyridinium chlorochromate (PCC) delivered the *trans*-4,5-disubstituted γ-butyrolactones **7a**, **7l**, and **7p** (Table 3). The formation of **7p** represents a total synthesis of (+)-*trans*-whisky lactone.[18] Similarly, crude hemiacetals obtained in the aforesaid manner can be treated with mesyl chloride in the presence of triethylamine to form *trans*-4,5-disubstituted-2,3-dehydrofurans, as illustrated in the formation of **8a** (equation 3). Finally, crude hemiacetal can be treated with the indicated stabilized Wittig reagent to deliver the enoate **9a** with complete alkene (*E*)-stereoselectivity (equation 4).

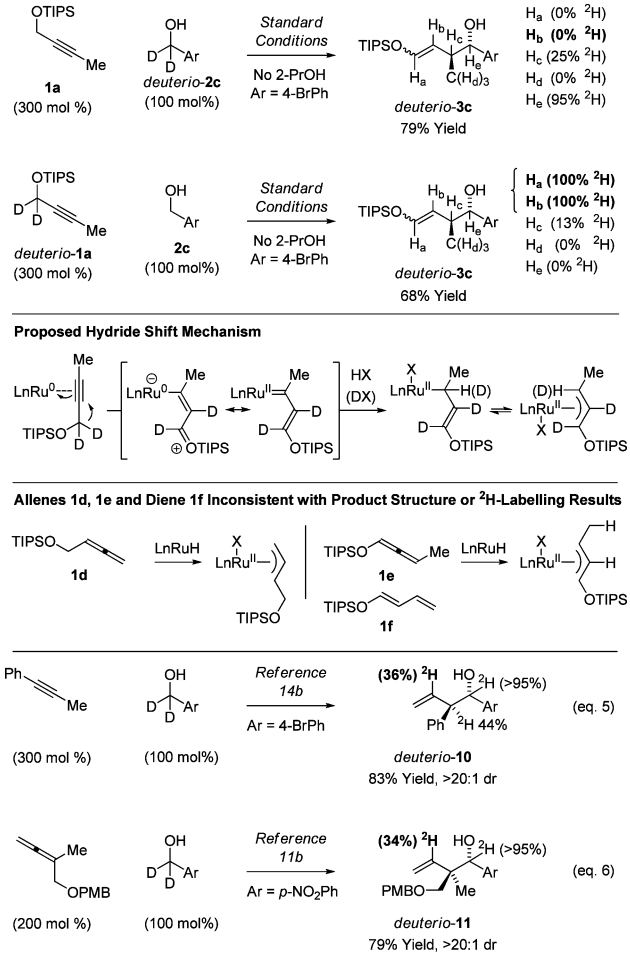


MECHANISM

Unlike the asymmetric couplings of 4-methyl-2-pentyne,[14b] the products obtained in reactions of propargyl ether **1a** are inconsistent with the intervention of a terminal allene such as **1d**. Initially, it was assumed that siloxy-crotylation proceeded by way of the internal 1,3-disubstituted allene **1e** or diene **1f**. However, deuterium labeling studies exclude allene **1e** or diene **1f** as intermediates (Scheme 3).[19] If allene **1e** or diene **1f** were discrete intermediates, the reaction of propargyl ether **1a** should result in deuterium incorporation at H_b or H_d of adduct *deuterio*-**3c**, respectively, but it does not. Rather, the reaction of *deuterio*-**1a** with alcohol **2c** results in deuterium transfer to H_a and H_b of adduct *deuterio*-**3c**. These data clearly corroborate the indicated 1,2-hydride shift mechanism.[20−22] *To our knowledge, direct conversion of metal-bound alkynes to π-allyls via 1,2-hydride shift is unique.*

The question as to whether the 1,2-hydride shift mechanism is at all operative in related asymmetric alkyne−alcohol C−C couplings[14b] merits consideration. Here, it is instructive to consider the respective patterns of deuterium incorporation observed upon use of d_2-benzylic alcohols. For the related asymmetric alkyne−alcohol C−C couplings (equation 5),[14b] wherein hydrometalation of a discrete allene intermediate is proposed to generate a nucleophilic allylruthenium species, the pattern of deuterium closely resembles that observed in the parent allene-alcohol C−C couplings (equation 6).[11b] The analogous

Scheme 3. Deuterium Labelling Studies Exclude Allenes As Discrete Intermediates and Are Consistent with a Hydride Shift Mechanism[a]



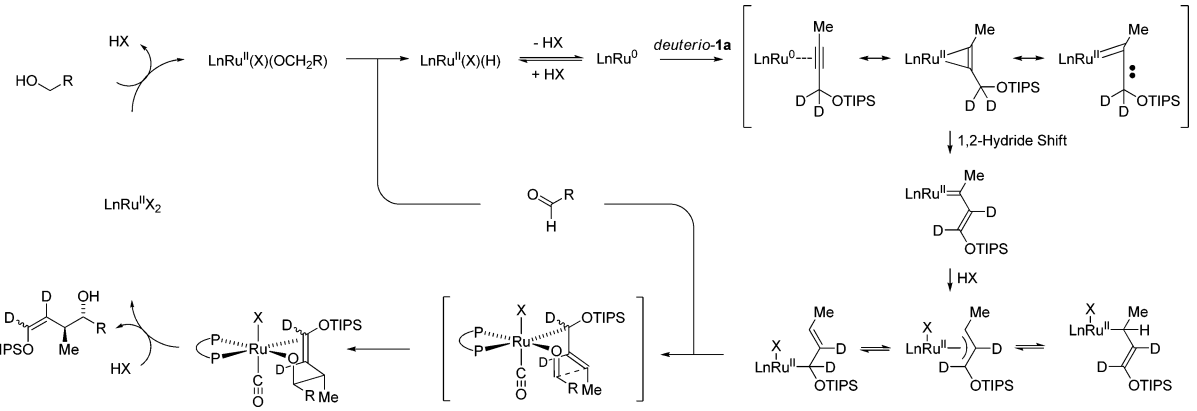
[a]Yields are of material isolated by silica gel chromatography. See Supporting Information for further details.

isotopic labeling experiment using propargyl ether **1a** does not result in deuterium incorporation at the interior vinylic position. These data exclude allene hydrometalation in the present couplings of propargyl ether **1a** and suggest the 1,2-hydride shift mechanism is likely inoperative in the previously developed alkyne-alcohol C−C couplings.[23]

On the basis of this novel pattern of reactivity, a general catalytic mechanism for asymmetric ruthenium catalyzed siloxy-crotylation via redox-triggered carbonyl addition was proposed (Scheme 4). A ruthenium(II) complex mediates alcohol dehydrogenation to form aldehyde and LnRu(II)HX. Elimination of HX delivers a zerovalent ruthenium complex that binds the π-acidic alkyne. A high degree of π-backbonding between ruthenium(0) and the bound alkyne promotes metallacyclopropene or carbenoid character which induces 1,2-hydride shift to form a vinyl carbene. The n → σ^* interaction between the oxygen lone pair and the propargylic C−H bond appears to be important in terms of promoting 1,2-hydride shift, as in the absence of the silyl ether alkyne-to-allene isomerization is observed.[14] Protonation of the vinyl carbene delivers a nucleophilic siloxy-substituted allylruthenium(II) complex. Aldehyde addition occurs by way of a Zimmerman−Traxler type transition structure from the σ-bound allylruthenium haptomer

DOI: 10.1021/jacs.5b08019
J. Am. Chem. Soc. 2015, 137, 13066−13071

Scheme 4. General Catalytic Mechanism As Corroborated by Deuterium Labeling Experiments



wherein ruthenium resides at the oxygen-bearing carbon atom. This haptomeric preference is presumably due to the negative inductive effect of oxygen. Protonolytic cleavage of the resulting homoallylic ruthenium(II) alkoxide releases the product and regenerates the starting ruthenium(II) complex.

CONCLUSIONS

In summary, we report a direct alkyne-mediated carbonyl (siloxy)crotylation via redox-triggered carbonyl addition that is enabled through a unique 1,2-hydride-shift mechanism. This method directly converts primary alcohols to secondary alcohols bearing a propionate-based monoketide structural motif. Complete levels of regio- and *anti*-diastereoselectivity are accompanied by uniformly high levels of enantioselectivity using a Josiphos (SL-J009-1) modified ruthenium(II) catalyst. Deuterium labeling studies corroborate a novel catalytic mechanism wherein 1,2-hydride migration of a ruthenium-bound alkyne forms an α,β-unsaturated carbene, which upon protonation delivers a 1,3-disubstituted π-allylruthenium complex. Thus, metal-bound alkynes are directly converted to chiral allylmetal species in the absence of intervening allenes. The present transformation contributes to a growing body of redox-neutral catalytic C−C bond formations that merge the characteristics of carbonyl addition transfer hydrogenation.[5k]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b08019.

Experimental procedures and spectroscopic data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS), including images of NMR spectra (PDF)

Single crystal X-ray diffraction data for **5c** (CIF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The Robert A. Welch Foundation (F-0038) and the NIH-NIGMS (RO1-GM069445) and the Center for Green Chemistry and Catalysis are acknowledged for partial support of this research.

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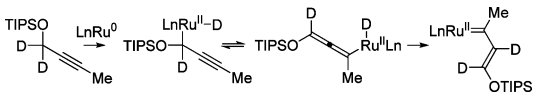

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DOI: 10.1021/jacs.5b08019
J. Am. Chem. Soc. 2015, 137, 13066−13071