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Asymmetric Ruthenium-Catalyzed Carbonyl Allylations by Gaseous Allene via Hydrogen Auto-Transfer: 1° vs 2° Alcohol Dehydrogenation for Streamlined Polyketide Construction

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Abstract

Iodide-bound ruthenium-JOSIPHOS complexes catalyze the redox-neutral C-C coupling of primary alcohols **2a**-**2r** with the gaseous allene (propadiene) **1a** to form enantiomerically enriched homoallylic alcohols **3a**-**3r** with complete atom-efficiency. Using formic acid as reductant, aldehydes *dehydro*-**2a** and *dehydro*-**2c** participate in reductive C-C coupling with allene to deliver adducts **3a** and **3c** with comparable levels of asymmetric induction. Deuterium labeling studies corroborate a mechanism in which alcohol dehydrogenation triggers allene hydroruthenation to form transient allylruthenium-aldehyde pairs that participate in carbonyl addition. Notably, due to a kinetic preference for primary alcohol dehydrogenation, chemoselective C-C coupling of 1°,2°-1,3-diols occurs in the absence of protecting groups. As illustrated by the synthesis of C7-C15 of spirastrellolide B and F (7 vs 17 steps), C3-C10 of cryptocarya diacetate (3 vs 7 or 9 steps), and a fragment common to C8′-C14′ of mycolactone F (1 vs 4 steps) and C22-C28 marinomycin A (1 vs 9 steps), this capability streamlines type I polyketide construction.

Graphical Abstract

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[§]Author Contributions

C.S. and E.O. contributed equally to this work.

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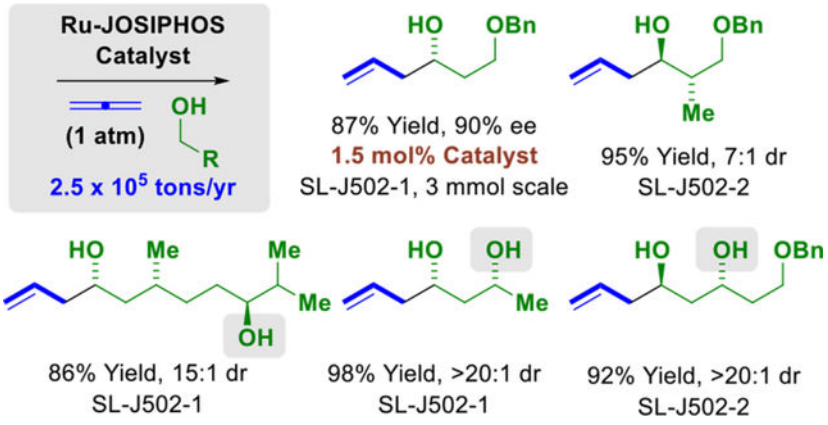
Supporting Information. Experimental procedures and spectroscopic data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS), including images of NMR spectra and HPLC traces for racemic and enantiomerically enriched compounds. Single-crystal X-ray diffraction data for the 3,5-dinitrobenzoate derived from compound **3g** (CCDC Deposition Number: 2172182). This information is available free of charge on the ACS Publications website.



Keywords

Ruthenium; allylation; enantioselective; alcohol dehydrogenation; polyketide; green chemistry; allene

Introduction

Polyketide natural products play a prominent role in human and veterinary medicine, as well as crop protection.[1] Manufacturing routes to commercial polyketides and their semi-synthetic congeners nearly all rely on fermentation.[2] *De novo* chemical synthesis potentially offers entry to otherwise inaccessible polyketide derivatives, yet despite advances in acyclic stereocontrol, especially in the area of aldol addition[3] and carbonyl allylation,[4] the classical lexicon of synthetic methods often does not deliver concise/scalable routes to these structurally complex compounds.[2] Aiming to address this deficiency, our laboratory has developed a family of catalytic C-C couplings for the enantioselective conversion of lower alcohols to higher alcohols via hydrogen auto-transfer and related metal-catalyzed carbonyl reductive couplings mediated by 2-propanol.[5,6] Of relevance to polyketide construction, these processes encompass iridium-catalyzed allylations, crotylations and propargylations.[5a]

Motivated by the prospect of exploiting a more abundant and cost-effective metal catalyst, our laboratory developed a new class of iodide-bound JOSIPHOS complexes.[7] These catalysts affect highly enantioselective couplings of primary alcohols with 1-aryl-1-propynes (to furnish products of carbonyl α-aryl-allylation[7a] or 2-butyne (to furnish tiglyl alcohols)[7b] and, most recently, reactions of 1,2- and 1,3-butadiene (to furnish products of carbonyl crotylation).[7c] The latter transformation suggests the feasibility of exploiting gaseous allene (propadiene) as a pronucleophile for the allylation of alcohol proelectrophiles. A racemic iridium-catalyzed reaction of this type was first reported by our laboratory in 2007.[8a] Enantioselective allene-mediated reductive allylations of aldehydes[8b] and ketones[8c] catalyzed by chiral iridium and copper complexes were disclosed in 2019 (Figure 1).

Here, we report the first ruthenium-catalyzed reactions of primary alcohols with gaseous allene to form homoallylic alcohols. Unlike enantioselective allene-mediated carbonyl allylations catalyzed by iridium[8b] or copper,[8c] the present ruthenium-catalyzed processes

are applicable to primary alcohol proelectrophiles. Furthermore, due to a kinetic preference for primary alcohol dehydrogenation, chemoselective C-C coupling of 1°,2°-diols occurs in the absence of protecting groups.[9] The impact of this capability on the efficiency of polyketide construction was explored, as illustrated in preparations of several previously described polyketide fragments. Specifically, C7-C15 of spirastrellolide B and F (7 vs 17 steps),[10a] C3-C10 of cryptocarya diacetate (3 vs 7 or 9 steps),[10b,c] C8′-C14′ of mycolactone F (1 vs 4 steps),[10d] and C22-C28 of marinomycin A (1 vs 9 steps)[10e] were each made in significantly fewer steps than previously possible. These data, along with prior work from our laboratory,[5] highlight how abundant π-unsaturated petrochemical feedstocks can function as surrogates to stoichiometric organometallic reagents, unlocking pathways for chemical synthesis of greater step- and atom-efficiency.[5b,11]

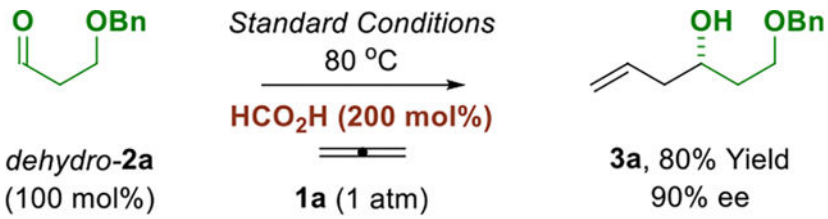
Results and Discussion

Our optimization experiments began with conditions identified for the reaction of primary alcohols with 1,2- and 1,3-butadiene (to furnish products of carbonyl crotylation).[7c] Thus, a pressure tube charged with alcohol **2a**, the iodide-containing complex $RuI(CO)_3(\eta^3\text{-}C_3H_5)$ (5 mol%), the JOSIPHOS ligand SL-J009-01 (5 mol%), trifluoroethanol (TFE) (300 mol%) (which is inert to ruthenium-catalyzed dehydrogenation)[12] and and THF (0.5 M) was back-filled with gaseous allene **1a**, sealed and placed in a 100 °C oil bath. To our surprise, only trace quantities of the targeted homoallylic alcohol **3a** were observed (Table 1, entry 1). By increasing the reaction temperature to 110 °C, alcohol **3a** could be formed in 20% yield and 74% ee (Table 1, entry 2). In an effort to improve the yield of **3a** and its level of enantiomeric enrichment, the JOSIPHOS ligands SL-J013-01 and SL-J502-01 were evaluated (Table 1, entries 3, 4). The JOSIPHOS SL-J502-01 proved to be superior, providing the alcohol **3a** in 75% yield and 85% ee (Table 1, entry 4). As revealed by a concise screening of solvent (Table 1, entries 4–7), reactions run in 1,2-diethoxyethane (DEE) at 0.1 M concentration enabled access to alcohol **3a** in 86% yield and 90% ee (Table 1, entry 7). In the absence of TFE, the yield of alcohol **3a** was dramatically diminished (Table 1, entry 8). Finally, as revealed in reactions of the corresponding chloride- and bromide-bound ruthenium catalysts (Table 1, entries 9, 10), iodide counterions are essential for maintaining optimal yields and enantioselectivities.[7a,13]

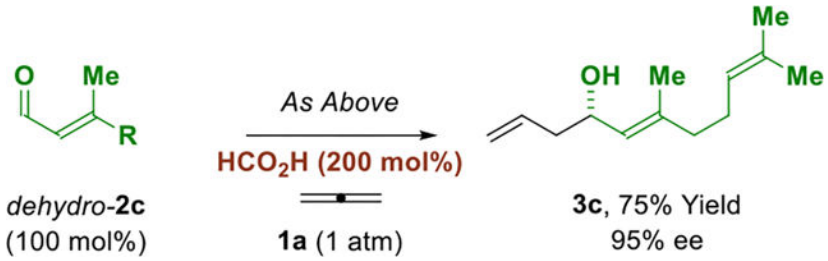
Optimal conditions identified for the ruthenium-JOSIPHOS-catalyzed C-C coupling of gaseous allene **1a** were applied to alcohols **2a**-**2g** (Table 2). The resulting homoallylic alcohols **3a**-**3g** were formed in good to excellent yields and enantioselectivities. As demonstrated by the formation of **3b**, primary alcohols with adjacent branched alkyl groups are tolerated. Geraniol **2c** is converted to adduct **3c** bearing 3 olefinic functional groups without competing alkene reduction or isomerization.[14] Heteroaromatic moieties are compatible with the conditions for catalytic C-C coupling, as demonstrated by the formation of adducts **3d**-**3g**. Finally, it is most notable that the reaction of **2a** at 3 mmol scale could be conducted at a catalyst loading of 1.5 mol% without any erosion in yield or enantioselectivity. The absolute stereochemical assignment of these adducts is made in analogy to that determined for compound **3g**, which was established by single crystal X-ray diffraction analysis.

To further explore the scope of this process, the reaction of alcohols **2h**-**2r**, which contain preexisting stereogenic centers and, in many cases, unprotected secondary hydroxyl groups, were explored (Table 2). Remarkably, exposure of (*R*)-1,3-butane diol **2h** to the optimized conditions for allene-mediated allylation delivered the homoallylic alcohol **3h** as single diastereomer in 98% yield. Use of the enantiomeric catalyst provided *epi*-**3h** in 96% yield as single diastereomer, thus revealing high levels of catalyst directed diastereoselectivity. Of direct relevance to polyketide total synthesis, the "Roche alcohol"[15] **2k** could be converted to adducts **3k** and *epi*-**3k** upon exposure to the enantiomeric ruthenium-JOSIPHOS catalysts without any epimerization of the methyl-bearing stereocenter, as determined by HPLC.[16] Compared to *epi*-**3k**, diastereoselectivity associated with the formation of adduct **3k** is lower, as the diastereofacial bias of the catalyst opposes the intrinsic Felkin-Anh selectivity of the aldehyde.[17] The reactions of alcohol **2r** (derived from pseudomonic acid A) to form **3r** and *epi*-**3r**, again underscore the applicability of this method to polyketide construction.

The ability to affect enantioselective allylation from the alcohol or carbonyl oxidation levels would lend further flexibility to this method. Whereas primary alcohols serve dually as reductant and carbonyl proelectrophile, direct use of aldehydes requires an exogenous reductant. It was found that reactions conducted in the presence of formic acid (200 mol%) at lower temperatures (80° C), but under otherwise identical conditions, enabled efficient allene-mediated allylation of aldehydes *dehydro*-**2a** and *dehydro*-**2c** to form adducts **3a** and **3c**, respectively, with good levels of enantiocontrol (eq. 1 and 2).



(eq. 1)



(eq. 2)

To demonstrate how the protecting group-free asymmetric allylation of primary alcohols in the presence of secondary alcohols streamlines *de novo* polyketide synthesis, the present method was used to prepare a known C7-C15 substructure of spirastrellolide B and F (Scheme 1).[10a] Thus, alcohol **2a** was subjected to standard conditions for enantioselective

allene-mediated carbonyl allylation on 500 mg scale at low loadings of catalyst (1.5 mol%) to form the homoallylic alcohol **3a** in 87% yield and 90% ee. Ozonolysis of **3a** accompanied by treatment of the ozonide with $NaBH_4$ delivered the 1°,2°-1,3-diol **2i**. Allene-mediated carbonyl allylation of diol **2i** delivered the 2°,2°-1,3-diol **3i** in 92% yield. Conversion of **3i** to the corresponding acetonide followed by treatment with ozone and $NaBH_4$ provided primary alcohol **4**, which upon asymmetric crotylation mediated by butadiene **1b** furnished compound **5**.[7c] Finally, successive treatment of **5** with ozone and $NaBH_4$ provides diol **6**, which encompasses C7-C15 of spirastrellolide B and F. Compound **6**, which was previously prepared by Sabitha and coworkers in 17 steps (longest linear sequence, LLS), is now accessible in 7 steps (LLS) via iterative alcohol-mediated C-C coupling. Further underscoring the increase in step-efficiency enabled by the present method, compound **3i** is itself a known C3-C10 substructure of cryptocarya diacetate that has been prepared on two prior occasions in 7 or 9 steps (LLS).[10b,c] Compound **3i** is now accessible in only 3 steps (LLS). Finally, compound **3h** is known fragment common to C8′-C14′ of mycolactone F[10d] and C22-C28 marinomycin A,[10e] which were prepared in 4 steps (LLS) and 9 steps (LLS), respectively. Compound **3h** is now accessible in only 1 step (LLS) via direct allylation of (*R*)-butanediol (Table 2).

A catalytic cycle has been posited and corroborated by a deuterium labelling experiment (Scheme 2). β-Hydride elimination from the pentacoordinate ruthenium(II) alkoxide **I** forms an aldehyde and a ruthenium(II) hydride **II**. Ruthenium(II) complexes such as alkoxide **I** are octahedral d^6 metal ions with vacant $d_{x^2-y^2}$ orbitals, which makes alkoxide β-hydride elimination especially facile. Allene **1a** suffers hydroruthenation by the ruthenium(II) hydride **II** to form the π-allylruthenium(II) complex **III**. Related stoichiometric reactions of $HXRu(CO)(PR_3)_3$ (X = Cl, Br) with allenes or dienes to form isolable π-allylruthenium species have been described.[18] Aldehyde addition from the σ-allylruthenium haptomer (not shown) through a six-centered transition structure provides the homoallylic ruthenium(II) alkoxide **IV**. Substitution of the homoallylic ruthenium(II) alkoxide **IV** with the reactant alcohol catalyzed by TFE closes the catalytic cycle. Entry into the catalytic cycle is envisioned to occur via protonation of the π-allylruthenium(II) precatalyst at carbon by TFE to furnish the transient ruthenium trifluoroethoxide, which is inert with respect to dehydrogenation due to inductive stabilization of the transition state for β-hydride elimination.[12] Incomplete transfer of deuterium from the reactant alcohol *deuterio*-**2a** to the interior vinylic position of the reaction product *deuterio*-**3a** is due (in part) to ^2H-^1H exchange of ruthenium(II) deuteride **II** with the hydroxyl protons of the reactant alcohol, TFE and adventitious water.[19] The persistence of deuterium at the carbinol position of *deuterio*-**3a** suggests that dehydrogenation of the secondary hydroxyl group is suppressed by chelation of the homoallylic olefin (as in complex **IV**), which blocks the otherwise open coordinate site required for β-hydride elimination.

Conclusion

In summary, polyketides have played a pervasive, longstanding role in medicine and agrochemistry, which, in turn, has inspired decades of research on the development of methods for their synthesis. Asymmetric protocols for carbonyl allylation figure prominently

among these methods, yet until work from our laboratory,[5] such methods have uniformly relied upon premetalated reagents or metallic reductants.[4] Here, using an iodide-bound ruthenium-JOSIPHOS complex recently developed in our laboratory, we report a catalytic method for enantioselective carbonyl allylation via hydrogen auto-transfer that is not only byproduct-free, but can be conducted from primary alcohol proelectrophiles in the presence of secondary alcohols. As illustrated in concise syntheses of multiple known polyketide substructures, these capabilities significantly enhance the efficiency of polyketide construction. More broadly, these data demonstrate how the native reducing ability of alcohols can be harnessed for the generation of transient organometallic nucleophiles to provide a path for chemical synthetic beyond stoichiometric organometallic reagents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(18). (a)Hiraki K; Ochi N; Sasada Y; Hayashida H; Fuchita Y; Yamanaka S Organoruthenium(II) Complexes Formed by Insertion Reactions of Some Vinyl Compounds and Conjugated Dienes into a Hydrido–Ruthenium Bond. J. Chem. Soc., Dalton Trans. 1985, 873–877.(b)Hill AF; Ho CT; Wilton-Ely JDET The Coupling of Methylene and Vinyl Ligands at a Ruthenium(II) Centre. Chem. Commun. 1997, 2207–2208.(c)Xue P; Bi S; Sung HHY; Williams ID; Lin Z; Jia G Isomerism of [Ru(η3-allyl)Cl(CO)(PPh3)2] Organometallics 2004, 23, 4735–4743.

(19). (a)Tse SKS; Xue P; Lin Z; Jia G Hydrogen/Deuterium Exchange Reactions of Olefins with Deuterium Oxide Mediated by the Carbonylchlorohydrido-tris(triphenylphosphine)ruthenium(II) Complex. Adv. Synth. Catal. 2010, 352, 1512–1522.(b)Isbrandt ES; Vandavasi JK; Zhang W; Jamshidi MP; Newman SG Catalytic Deuteration of Aldehydes with D2O. Synlett 2017, 28, 2851–2854.

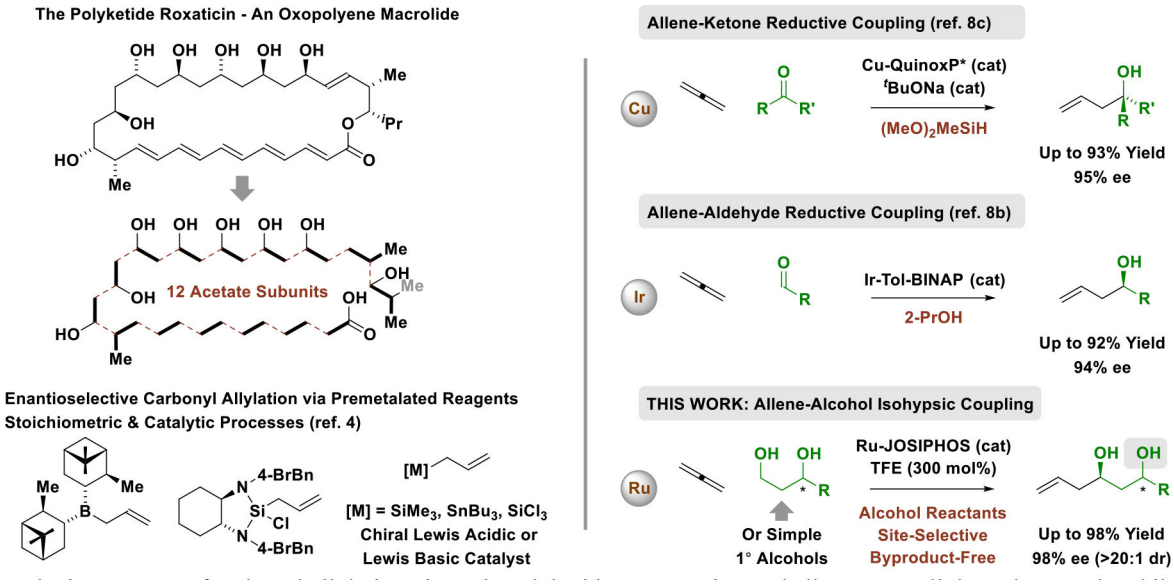
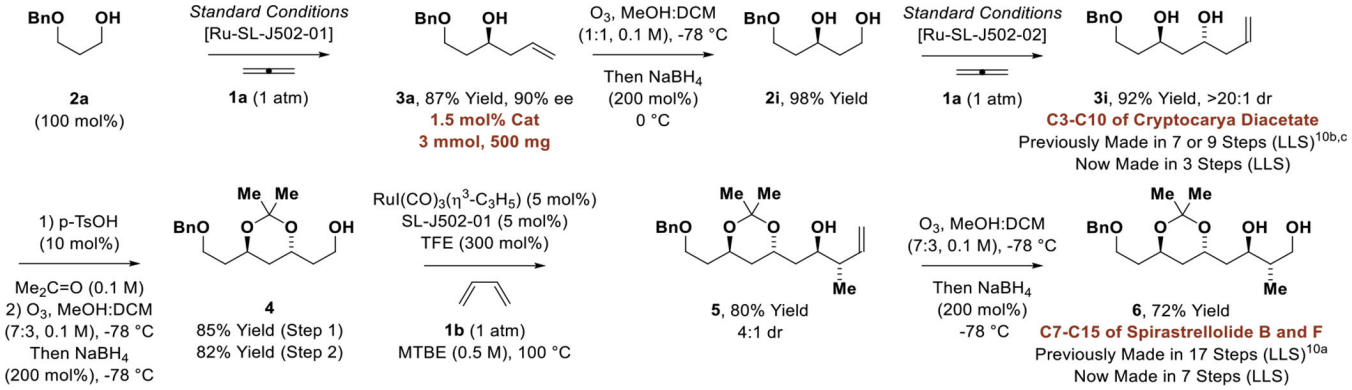


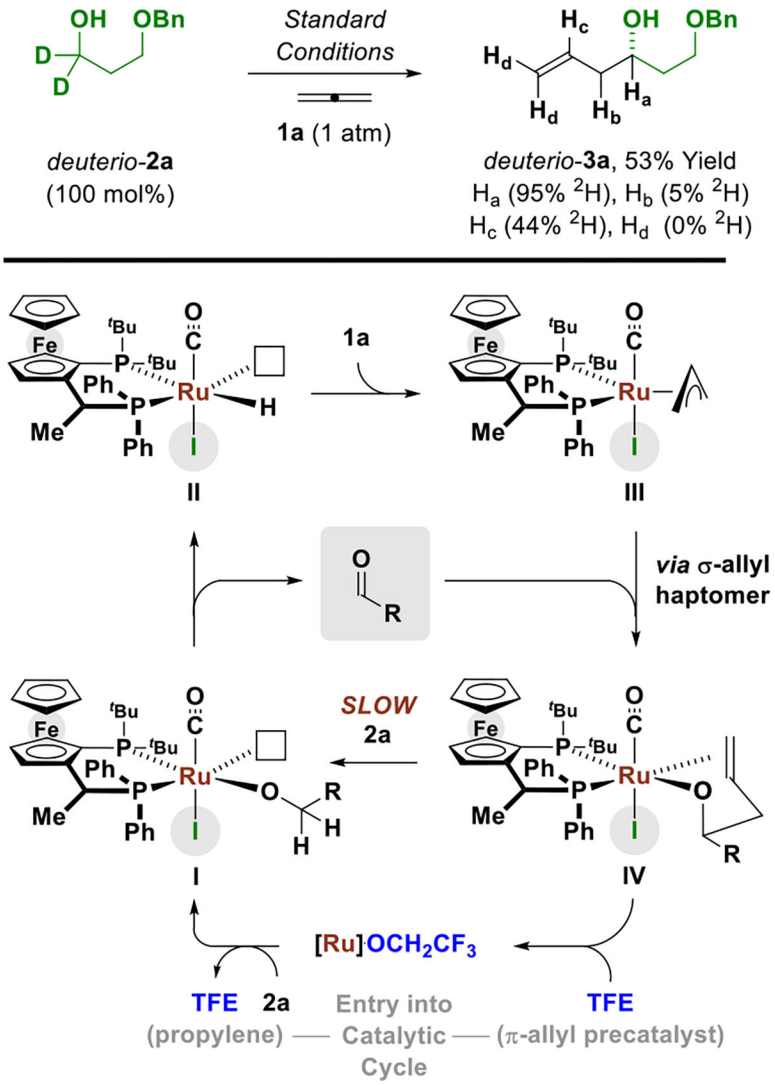
Figure 1.

The importance of carbonyl allylation vis-à-vis polyketide construction and allene as an allylmetal pronucleophile.



Scheme 1.

Streamlined polyketide construction via iterative allene-mediated allylation and crotylation.[a]

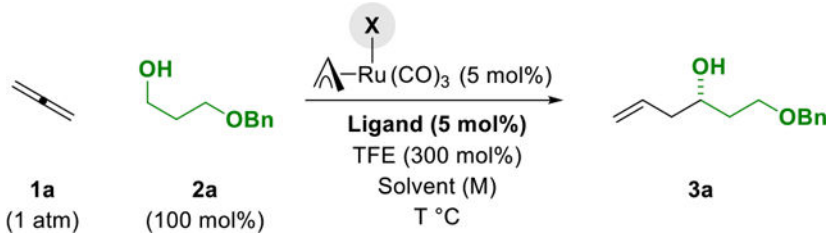


Scheme 2.

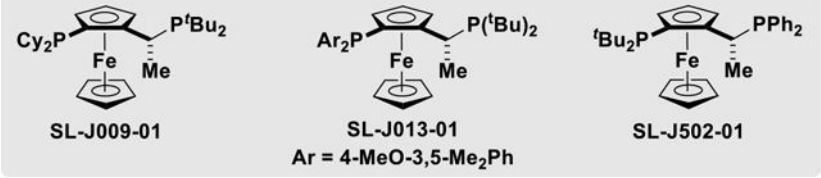
Proposed catalytic cycle as corroborated by a deuterium labeling experiment.

Table 1.

Selected optimization experiments in the ruthenium-JOSIPHOS-catalyzed C-C coupling of gaseous allene **1a** with alcohol **2a** to form homoallylic alcohol **3a**.[a]



Entry	T °C	X	Ligand	Solvent	Yield, ee
1	100	**I**	SL-J009-01	THF (0.5 M)	Trace
2	110	**I**	SL-J009-01	THF (0.5 M)	20%, 74%
3	110	**I**	SL-J013-01	THF (0.5 M)	65%, 69%
4	110	**I**	SL-J502-01	THF (0.5 M)	75%, 85%
5	110	**I**	SL-J502-01	MTBE (0.5 M)	78%, 87%
6	110	**I**	SL-J502-01	DEE (0.5 M)	88%, 88%
➡	**110**	**I**	**SL-J502-01**	**DEE (0.1 M)**	**86%, 90%**
7					
8[b]	110	**I**	SL-J502-01	DEE (0.1 M)	42%, 90%
9	110	CI	SL-J502-01	DEE (0.1 M)	Trace
10	110	Br	SL-J502-01	DEE (0.1 M)	29%, 75%

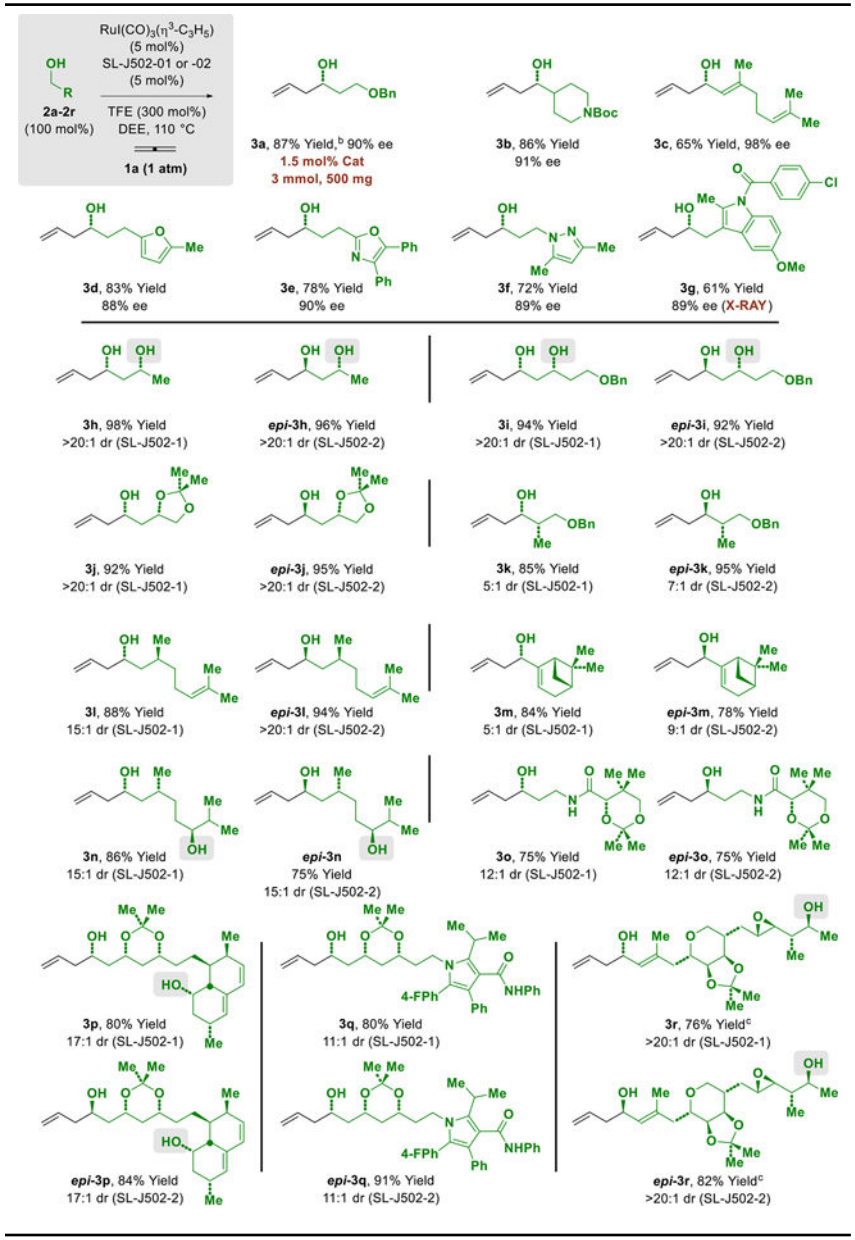


[a]Yields of material isolated by silica gel chromatography. Enantioselectivities were determined by HPLC analysis.

[b]TFE was omitted. See Supporting Information for further details.

Table 2:

Ruthenium-JOSIPHOS-catalyzed *C*-allylation of primary alcohols **2a-2r** mediated by gaseous allene.[a]



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[a] Yields of material isolated by silica gel chromatography. Enantioselectivities determined by HPLC analysis. Diastereoselectivities determined by ^{1}H NMR analysis of crude reaction mixtures.

[b] Ru-ligand (1.5 mol%).

[c] Ru-ligand (10 mol%), 80 °C. See Supporting Information for further details.