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Enantioselective Iridium-Catalyzed Allylation of Acetylenic Ketones via 2-Propanol-Mediated Reductive Coupling of Allyl Acetate: C14-C23 of Pladienolide D

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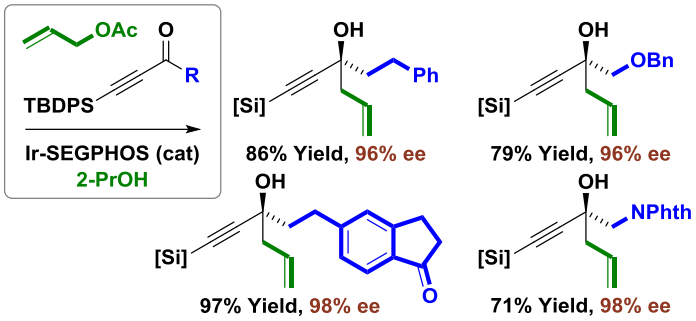
<Graphical Abstract>

Alkyne-Directed Chemo- and Enantioselectivity. Highly enantioselective catalytic reductive coupling of allyl acetate with acetylenic ketones occurs in a chemoselective manner in the presence of aliphatic or aromatic ketones. This method was used to construct C14-C23 of pladienolide D in half the steps previously required.

Keywords: Enantioselective, Iridium, Ketone Allylation, π-allyl, Transfer Hydrogenation.



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Enantioselective Iridium-Catalyzed Allylation of Acetylenic Ketones via 2-Propanol-Mediated Reductive Coupling of Allyl Acetate: C14-C23 of Pladienolide D**

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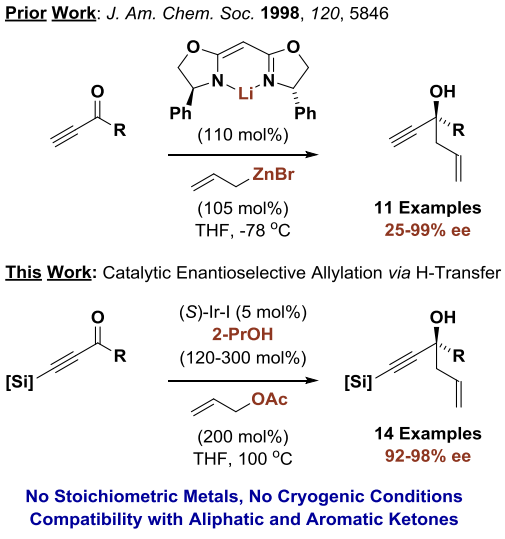
The catalytic enantioselective addition of *C*-nucleophiles to ketones represents a persistent challenge in chemical synthesis.[1] Differentiation of the acyl substituents by the chiral catalyst is often incomplete, leading to low C=O π-facial enantioselectivities. Additionally, for stabilized *C*-nucleophiles, ketone addition is frequently reversible, which erodes kinetic stereoselectivity. Consequently, work in this area is relegated to the use of non-stabilized *C*-nucleophiles in the form of stoichiometric organometallic reagents or related metalloids, which are often prepared via successive transmetallation.[2,3] In the specific context of enantioselective ketone allylation, reagents based on B, Si, and Sn have been described.[4] Metal-catalyzed carbonyl reductive couplings of π-unsaturated feedstocks potentially provides an alternative to the use of premetalated *C*-nucleophiles.[5] However, the requisite reductants utilized in these processes are typically metallic (Zn, Mn), pyrophoric ($ZnEt_2$, BEt_3), expensive or mass-intensive (R_3SiH).[6] To address these limitations, we have developed metal-catalyzed carbonyl reductive couplings that utilize elemental hydrogen, 2-propanol or formate as terminal reductant, as well as related hydrogen auto-transfer processes wherein alcohols serve as hydrogen donor and carbonyl proelectrophile.[7] While this technology has enabled diverse catalytic enantioselective aldehyde allylations[7f] and propargylations,[7g] asymmetric transfer hydrogenative allylations of ketones are restricted to vicinal dicarbonyl compounds.[8]

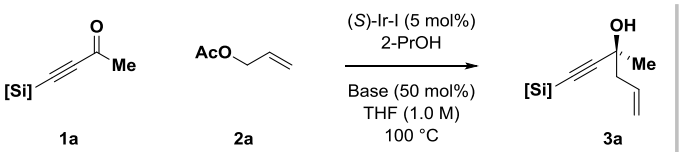
Figure 1. Asymmetric allylation of acetylenic ketones.



It was posited that acetylenic ketones might participate in efficient alcohol-mediated carbonyl allylation due to electrophilic activation associated with the negative inductive effect of the alkyne.[9] Although isolated examples have been reported,[10] only one systematic study on the asymmetric allylation of acetylenic ketones appears in the literature, which exploits an allylzinc reagent bound by a stoichiometric quantities of a chiral modifier.[11] Given this lack of prior art and the utility of the resulting 1,5-enynes *vis-á-vis* diverse carbophilic metal-catalyzed transformations,[12] the 2-propanol-mediated transfer hydrogenative allylation of acetylenic ketones was explored. Here, we report that such processes not only occur with high levels of enantioselectivity, but may be conducted in a chemoselective manner in the presence of aliphatic and aromatic ketones (Figure 1).

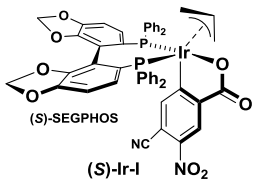
Guided by our prior work on the transfer hydrogenative allylation of acetylenic aldehydes,[9] methyl ketone **1a** (100 mol%, [Si] = $^{i}Pr_3Si$) was exposed to allyl acetate **2a** (200 mol%) and 2-propanol (200 mol%) in the presence of Cs_2CO_3 (50 mol%) and the commercially available π-allyliridium-*C*,*O*-benzoate modified by (*S*)-SEGPHOS, (S)-Ir-**I** (5 mol%), in anhydrous THF (Table 1, entry 1). The desired product of ketone allylation **3a** was not observed. However, upon introduction of water (100 mol%), which may facilitate alkoxide exchange at the metal center and solubilize the carbonate base, the tertiary homoallylic alcohol **3a** was obtained in 44% yield in highly enantiomerically enriched form (Table 1, entry 2). The mass balance in this experiment consisted primarily of unreacted **1a** and the corresponding product of silyl cleavage. As acetylenic C-H moieties are not tolerated by the iridium catalyst, an effort was made to accelerate carbonyl addition with respect silyl cleavage through the introduction of a more inductive silyl groups. While use of the triphenylsilyl group, as in **1a** ([Si] = Ph_3Si), only exacerbated silyl cleavage to prevent formation of **3a** (Table 1, entry 3), the corresponding *tert*-butyl-diphenylsilyl compound, **1a** ([Si] = $^{t}BuPh_2Si$), better balanced inductive activation and stability toward cleavage, enabling formation of **3a** in 48% yield (Table 1, entry 4). While adjusting the loading of water did not increase efficiency (Table 1, entries 5 and 6), decreased loadings of 2-propanol (120 mol%) and use of a slightly weaker base, K_2CO_3 (50 mol%) each led to modest improvements (Table 1, entries 7 and 8). Finally, introduction of 3-NO_2-4-CN-BzOH (10 mol%), which presumably stabilizes the catalyst and attenuates silyl cleavage by buffering the medium, led to a much cleaner reaction, delivering **3a** in 66% yield and 96% enantiomeric excess (Table 1, entry 9).

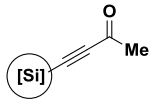
Table 1. Selected optimization experiments in the enantioselective π-allyliridium-*C*,*O*-benzoate catalyzed allylation of acetylenic ketone **1a**.[a]



1a (100 mol %) **2a** (300 mol %) **3a**

Entry	[Si]	Base	2-PrOH	H_2O	Yield (%)	ee (%)
1	$^{i}Pr_3Si$	Cs_2CO_3	200 mol%	---	---	---
2	$^{i}Pr_3Si$	Cs_2CO_3	200 mol%	100	44	96
3	Ph_3Si	Cs_2CO_3	200 mol%	100	---	---
4	$^{t}BuPh_2Si$	Cs_2CO_3	200 mol%	100	48	94
5	$^{t}BuPh_2Si$	Cs_2CO_3	200 mol%	200	37	94
6	$^{t}BuPh_2Si$	Cs_2CO_3	200 mol%	50	39	94
7	$^{t}BuPh_2Si$	Cs_2CO_3	120 mol%	100	50	94
8	$^{t}BuPh_2Si$	K_2CO_3	120 mol%	100	53	94
9[b]	$^{t}BuPh_2Si$	K_2CO_3	120 mol%	100	66	94

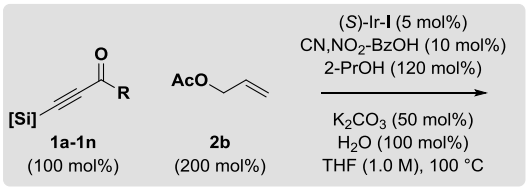




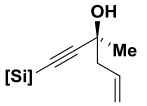
[Si] Too Electron Rich: Insufficient C=O Electrophilicity
[Si] Too Electron Deficient: Silyl Cleavage Forms Acetylenic C-H, a Catalyst Poison

[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details. [b]3-NO_2-4-CN-BzOH (10 mol%).

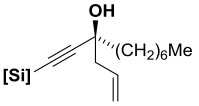
Table 2. Enantioselective π-allyliridium-*C*,*O*-benzoate catalyzed allylation of acetylenic ketones **1a-1n** via 2-propanol-mediated reductive coupling with allyl acetate **2a**.[a]



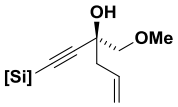
1a-1n (100 mol%) **2b** (200 mol%)



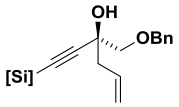
3a, 66% Yield, 94% ee
[Si] = $^{t}BuPh_2Si$



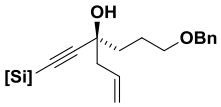
3b, 57% Yield, 98% ee
[Si] = $^{t}BuPh_2Si$



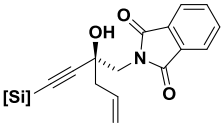
3c, 63% Yield, 94% ee
[Si] = $^{i}Pr_3Si$



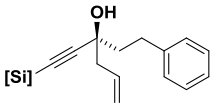
3d, 79% Yield, 96% ee
[Si] = $^{i}Pr_3Si$



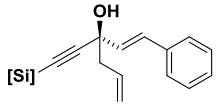
3e, 77% Yield, 95% ee
[Si] = $^{t}BuPh_2Si$



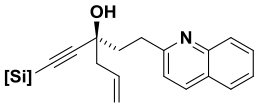
3f, 71% Yield, 98% ee
[Si] = $^{t}BuPh_2Si$



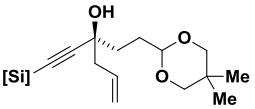
3g, 86% Yield, 96% ee
[Si] = $^{t}BuPh_2Si$, **X-RAY**



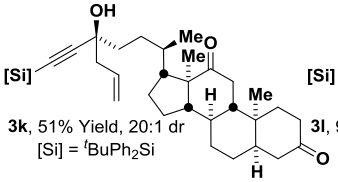
3h, 64% Yield, 93% ee
[Si] = $^{t}BuPh_2Si$



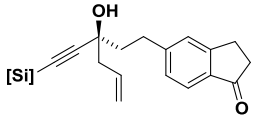
3i, 79% Yield, 96% ee
[Si] = $^{t}BuPh_2Si$



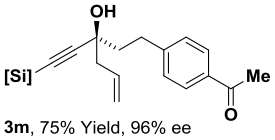
3j, 60% Yield, 92% ee
[Si] = $^{t}BuPh_2Si$



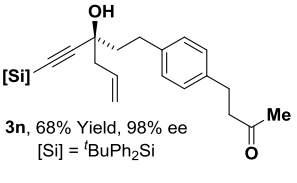
3k, 51% Yield, 20:1 dr
[Si] = $^{t}BuPh_2Si$



3l, 97% Yield, 98% ee
[Si] = $^{t}BuPh_2Si$



3m, 75% Yield, 96% ee
[Si] = $^{t}BuPh_2Si$



3n, 68% Yield, 98% ee
[Si] = $^{t}BuPh_2Si$

[a]Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details.

With these optimal conditions in hand, the enantioselective allylation of diverse acetylenic ketones was explored (Table 2). While simple alkyl-substituted acetylenic ketones **1a** and **1b** provide moderate yields of the corresponding tertiary homoallylic alcohols **3a** and **3b**,

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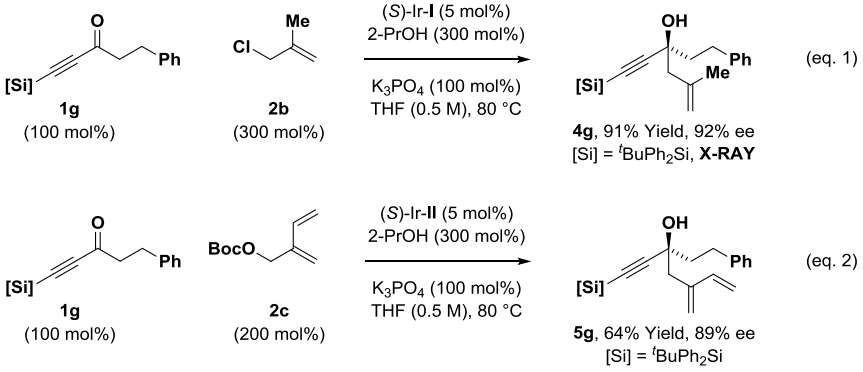
acetylenic ketones **1c**-**1g**, which incorporate substituents that exert a negative σ-inductive effect, deliver the tertiary homoallylic alcohols **3c**-**3g**, respectively, excellent yields. For α-alkoxy ketones **1c** and **1d**, which exert a relatively strong negative σ-inductive effect, the less inductive and more stable $^{i}Pr_3Si$ moiety can be used instead of the $^{t}BuPh_2Si$ moiety. Remarkably, ketone **1h**, which incorporate acetylenic and vinylic acyl substituents, is an effective partner of carbonyl allylation, forming the tertiary propargylic-allylic-homoallylic alcohol **3h** in good yield. Tolerance of *N*-heterocycles and acetals are illustrated by the formation of **3i** and **3j**, respectively. Perhaps most significant, however, are the reactions of ketones **1k**-**1n**. The acetylic ketone moieties of **1k**-**1n** undergo completely chemoselective allylation in the presence of aliphatic or aromatic ketone moieties to form **3k**-**3n** as single constitutional isomers. For all adducts **3a**-**3n**, uniformly high levels of enantioselectivity are observed. In lower yielding transformations, unreacted ketone along with trace quantities of *tert*-butyldiphenylsilanol (<5 %) were observed. The absolute stereochemistry of tertiary alcohols **3a**-**3n** was assigned in analogy to that determined for adducts **3g**, which was determined by single crystal X-ray diffraction analysis. Aryl substituted acetylenic ketones did not participate in allylation. Additionally, formation of compounds **3a**-**3n** from the propargyl alcohols corresponding to ketones **1k**-**1n** via hydrogen auto-transfer was inefficient, as the negative inductive effect of the alkyne impedes dehydrogenation. Finally, acetylenic ketones are competent partners in related enantioselective transfer hydrogenative allylations. For example, exposure of acetylenic ketone **1g** to methallyl chloride **2b** and 2-propanol (300 mol%) in the presence of (S)-Ir-**I** (5 mol%) provides the product of methallylation **4g** in 91% yield and 92% ee (eq. 1).[13] Additionally, the reductive coupling of acetylenic ketone **1g** with isoprenyl *tert*-butoxy carbonate **2c** mediated by 2-propanol (300 mol%) and catalyzed by the corresponding (*S*)-DM-SEGPHOS-modified catalyst (*S*)-Ir-**II** (5 mol%) provides the product of isoprenylation **5g** in 64% yield and 89% ee (eq. 1).[14]



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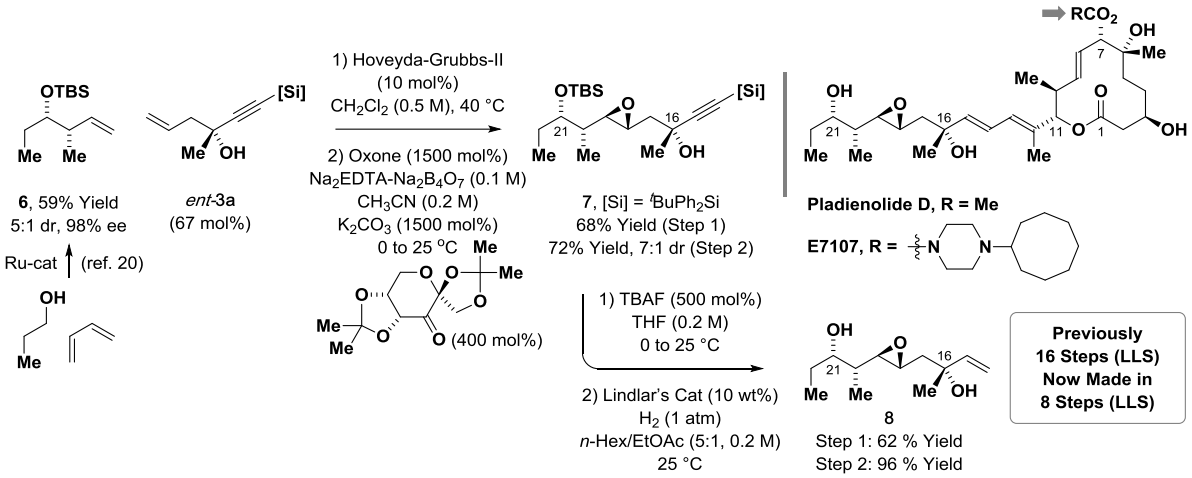
Scheme 1. Enantioselective synthesis of C14-C23 side chain of pladienolide D.



The utility of the present ketone allylation method to natural product total synthesis is illustrated by the rapid conversion of adduct *ent*-**3a** to the C14-C23 side chain of pladienolide D (Scheme 1). The pladienolides were isolated in 2004 from the culture broth of Mer-11107, an engineered strain of Streptomyces platensis,[15] and were found to inhibit the proliferation of multiple drug resistant human cancer cells with low nanomolar IC_{50} values.[16] These compounds operate through a novel mechanism of action, involving binding to the splicing factor 3b (SF3b) subunit of the spliceosome.[17] Clinical evaluation of pladienolide analogue E7107 was undertaken but discontinued due to vision loss.[18] More recently, however, clinical trials were initiated with another pladienolide analogue, H3B-8800, which was granted orphan drug status by the FDA in August 2017 for treatment of myelogenous leukemia and chronic myelomonocytic leukemia.[19] Cross-metathesis of *ent*-**3a** with compound **6** (conveniently prepared via butadiene-mediated crotylation of propanal),[20] followed by Shi epoxidation[21] of the resulting olefin, delivers acetylenic epoxide **7** with high levels of stereocontrol. To corroborate the stereochemical assignment of acetylenic epoxide **7**, it was subjected to silyl deprotection and Lindlar reduction to furnish the previously reported tertiary allylic alcohol **8**,[21] which embodies C14-C23 of pladienolide D. Whereas the prior synthesis of tertiary allylic alcohol **8** required 16 steps (LLS), the present synthesis of **8** is completed in only 8 steps (LLS).

In summary, we report the first catalytic enantioselective allylations of acetylenic ketones. Specifically, using the commercially available π-allyliridium-*C*,*O*-benzoate modified by (*S*)-SEGPHOS, (*S*)-Ir-I, as catalyst, allyl acetate **2a** engages acetylenic ketones **1a**-**1n** in enantioselective 2-propanol-mediated reductive coupling to form tertiary propargyl alcohols **3a**-**3n**. Additionally, owing the highly chemoselective nature of this process, we demonstrate that

acetylenic ketones undergo allylation in the presence of aliphatic or aromatic ketone functional groups to form single constitutional isomers. Using this protocol, a concise enantioselective synthesis of C14-C23 side chain of pladienolide D is achieved. More broadly, these studies contribute to a growing body of alcohol-mediated carbonyl additions that collectively signify a departure from the use of premetalated reagents C-C bond formation.[5d]

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