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Catalytic Enantioselective Allylations of Acetylenic Aldehydes *via* 2-PropanolMediated Reductive Coupling

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Abstract

Cyclometalated π-allyliridium *C,O*-benzoates modified by (*S*)-SEGPHOS or (*S*)-Cl,OMe-BIPHEP catalyze enantioselective 2propanol-mediated reductive couplings of diverse non-metallic allyl pronucleophiles with the acetylenic aldehyde TIPSC≡CCHO. Absolute stereochemistry of the resulting secondary homoallylic-propargylic alcohols were assigned using Rychnovsky's competing enantioselective conversion (CEC) method.

Graphical Abstract

Despite decades of study on enantioselective carbonyl allylation, crotylation, and related syntheses of homoallylic alcohols,[1] the asymmetric allylation of acetylenic aldehydes (ynals) has received relatively little attention. To date, only two systematic studies of asymmetric ynal allylation appear in the literature,[2] along with isolated examples involving reagents based on boron,[3] tin[4] and zinc.[5] These methods invariably require cryogenic conditions and the use of premetalated reagents, which limits their utility. Our laboratory has

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The authors declare no competing financial interest.

Supporting Information Available. Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). Single crystal X-ray diffraction data. Conversion and selectivity data for the CEC reactions in Scheme 2. This material is available free of charge *via* the internet at http://pubs.acs.org.

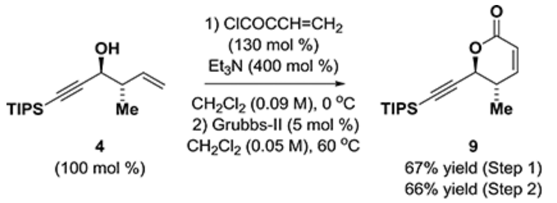
developed the first alcohol-mediated carbonyl reductive couplings,[6] including highly enantioselective carbonyl allylations and propargylations.[6d] These processes do not require cryogenic conditions and exploit tractable non-metallic allyl pronucleophiles, for example, allyl acetate. In connection with collaborative efforts toward the total synthesis of phosdiecin A,[7] a systematic study of enantioselective, iridium-catalyzed ynal reductive couplings mediated by 2-propanol was undertaken. Here, we report that the acetylenic aldehyde TIPSC≡CCHO participates in a diverse range of allylative carbonyl additions to form highly enantiomerically enriched secondary homoallylic-propargylic alcohols.[8] Additionally, as an inversion in enantiofacial selectivity was previously observed in response to the steric features of the allyl donor,[9] Rychnovsky's competing enantioselective conversion (CEC) method was used to corroborate absolute stereochemistry, and, in doing so, was expanded to encompass a diverse set of chiral propargyl alcohols.

Due to the high kinetic reactivity of alkynes under the conditions of iridium catalysis, it was necessary to evaluate terminally substituted ynals **1a-1d** for their ability to participate in the parent enantioselective reductive iridiumcatalyzed carbonyl allylation mediated by 2-propanol.[10] For this purpose, the chromatographically purified cyclometallated **π**-allyliridium *C,O*-benzoate complexes (*S*)-Ir-**I** and (*S*)-Ir-**II**, modified by (*S*)-Cl-MeO-BIPHEP and (*S*)-SEGPHOS, respectively, were utilized. Acetylenic aldehydes **1a** and **1b** bearing terminal phenyl and silyloxymethyl moieties, respectively, decomposed upon exposure to the standard reaction conditions, and the desired products of carbonyl allylation were not observed (Table 1, entries 1–4). It was reasoned that a more sterically demanding substituent at the alkyne terminus would mask the alkyne and mitigate decomposition. Indeed, the acetylenic aldehyde **1c** bearing a 2-(2-silyloxy)propyl substituent provided the desired product of allylation **3c** in modest yield, but with excellent levels of enantiomeric enrichment (Table 1, entries 5 and 6). A series of trialkylsilyl-terminated acetylenic aldehydes **1d-1f** were evaluated. While the TMS-substituted acetylenic aldehyde **1d** decomposed upon exposure to allylation conditions (Table 1, entries 7 and 8), the TBS-substituted acetylenic aldehyde **1e** provided highly enantiomerically enriched allylation product **3e**, albeit in poor yield (Table 1, entries 9 and 10). Finally, using the TIPS-substituted acetylenic aldehyde **1f**, the targeted product of allylation **3f** could be obtained in good yields and excellent enantioselectivities (Table 1, entries 11 and 12). Optimal results were obtained using the catalyst (*S*)-Ir-**I** modified by (*S*)-Cl-MeO-BIPHEP. The optical rotation of **3f** matched the literature value,[11] and its absolute stereochemical assignment is consistent with the enantiofacial preference generally observed in related aldehyde allylations catalyzed by (*S*)-Ir**I** and (*S*)-Ir-**II**.[6d,10]

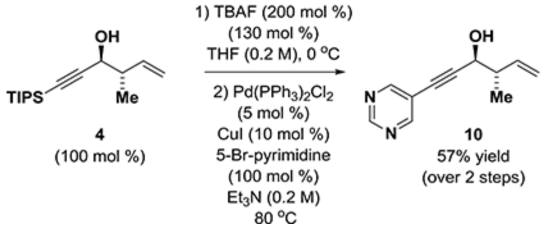
The TIPS-substituted acetylenic aldehyde **1f** was reacted with a range of allyl pronucleophiles **2a-2f** to assess the diversity of products potentially accessible (Scheme 1). Beyond allylation,[10] *anti*-diastereo- and enantioselective crotylation to form compound **4** occurred in good yield with excellent control of relative and absolute stereochemistry.[12] Similarly, methallylation of aldehyde **1f** delivered adduct **5** in good yield with high levels of enantiomeric enrichment.[13] Using dimethylallene **2d** as the pronucleophile, *tert*-prenylation of aldehyde **1f** occurs efficiently and, as anticipated on the basis of prior observations,[9] with inversion of enantiofacial selectivity. Aldehyde **1f** reacts with vinyl aziridine **2e** to form the product of α-(aminomethyl)allylation **7** in an *anti*-diastereo- and enantioselective manner.[14] Finally, using allyl donor **2f**, which incorporates a 3-(6-methoxypyridine) substituent, the product of α-(aryl)allylation **8** is formed with good levels of stereoselectivity.[15] Attempted reactions from the propargyl alcohol oxidation level were less efficient (20% lower yields), as the inductive effect of the alkyne raises the barrier for alcohol dehydrogenation.[16]

The configuration of the alcohol products were analyzed using the CEC method (Scheme 2).[17] Enantioselective acylation of the chiral nonracemic alcohols with (*R*)- or (*S*)HBTM, Birman's catalyst,[18] are anticipated to proceed with higher conversions with the stereochemically matched catalyst. In the event, the acylation catalyzed by (*R*)-HBTM was faster for alcohols **3f**, **4**, **5**, and **8**, indicating these alcohols are of the (*S*)-configuration, that is, the configuration of the alcohols are forward, as shown. Acylation of alcohol **7** was anomalously fast and unselective, and no assignment could be made. Alcohol **6**, the *tert*-prenylation product, was problematic. Acylation of alcohol **6** was essentially unselective at room temperature. At 0 °C, alcohol **6** showed modestly higher conversion with the (*R*)-HBTM catalyst. The standard mnemonic suggests that the alcohol should be of the (*S*)-configuration, however, X-ray analysis establishes an (*R*)-configuration.[19] Empirically, while the CEC method is useful for alcohols that display reasonable selectivity at room temperature, lowering the temperature to augment selectivity in normally unselective CEC substrates should be avoided.

To illustrate how homoallylic-propargylic alcohols **3d**, **4-8** might serve as building blocks in chemical synthesis, the product of *anti*-crotylation, compound **4**, was converted to the acrylic ester and subjected to ring-closing metathesis to form the α,β-unsaturated δ-lactone **9**(eq 1).[6c] Alternatively, removal of the TIPS-protecting group of compound **4** using TBAF followed by Sonogashira coupling of the crude terminal alkyne with 5-bromopyrimidine provides the heteroaryl-substituted alkyne **10** in good yield over two steps(eq 2).



(1)



(2)

To conclude, despite decades of study on asymmetric carbonyl allylation, only two systematic studies on ynal electrophiles appear in the literature, which require cryogenic conditions and premetalated reagents.[2] Here, using the concept of alcohol-mediated carbonyl addition, we report general catalytic enantioselective methods for ynal allylations that are non-cryogenic and utilize nonmetallic pronucleophiles. Additionally, the CEC method for determination of absolute stereochemistry was applied to homoallylic-propargylic alcohols **3f**, **4-6**, **8** and, notwithstanding compound **6**, which bears a quaternary carbon directly adjacent to the carbinol stereocenter, was proven effective for this class of secondary alcohols. Future studies will be focused on the development of related C-C bond forming transfer hydrogenations, including transfer hydrogenative imine additions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

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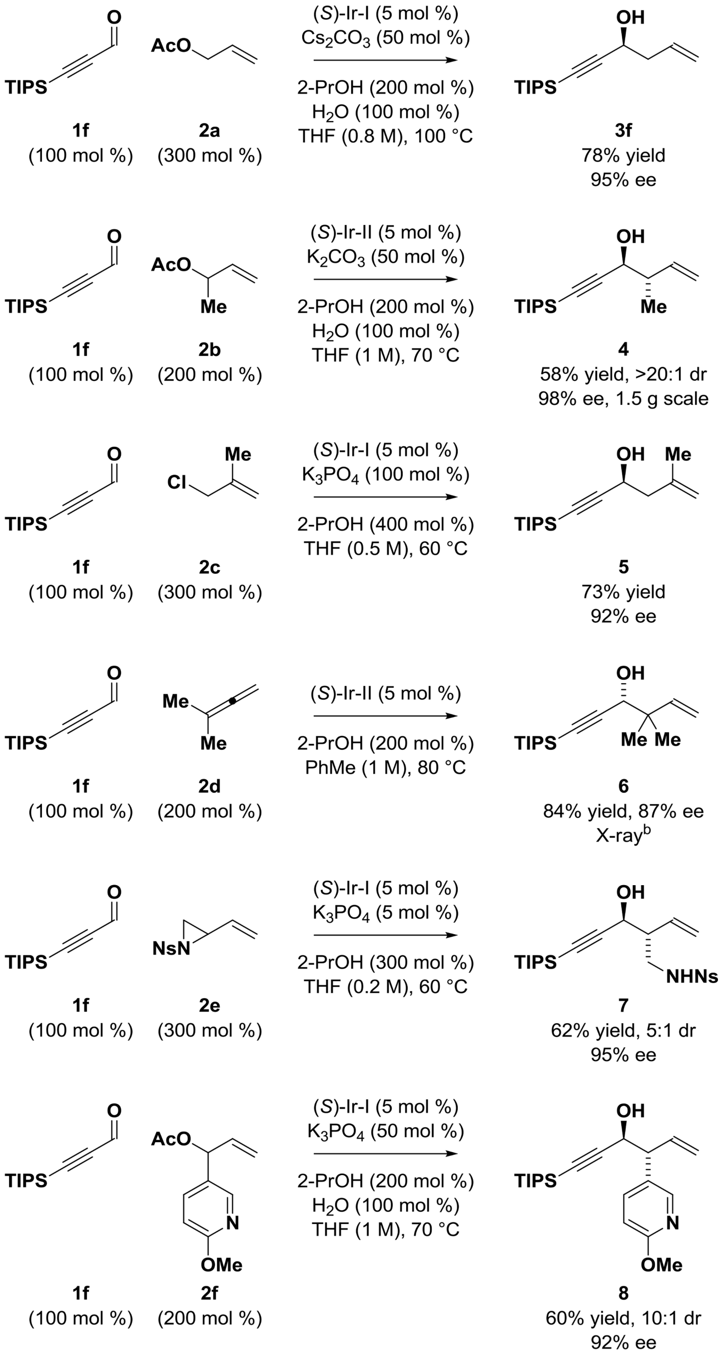
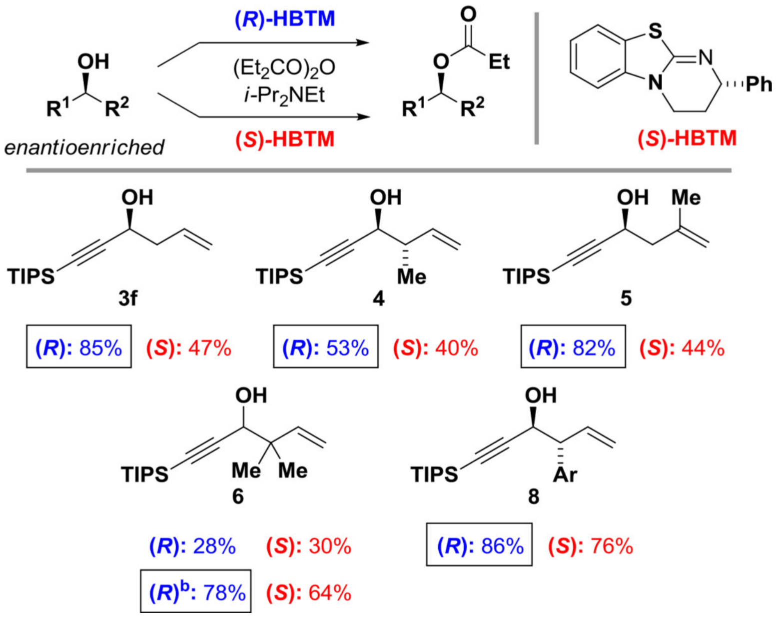


Scheme 1.

Enantioselective iridium-catalyzed reductive couplings of ynal **1f** with allyl pronucleophiles **2a**-**2f** to form homoallylic-propargylic alcohols **3f**, **4-8**.[a]

[a]Yields are of material isolated by silica gel chromatography. Enantioselectivity was determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details. [b]XRay data obtained after removal of the TIPS group and conversion to the 3,5-dinitrobenzoate.



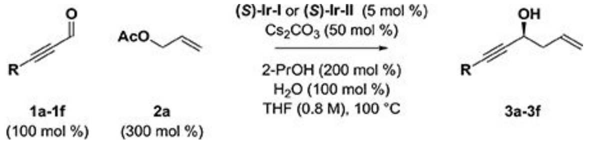
Scheme 2.

Analysis of alcohol configurations using the competing enantioselective conversion (CEC) method.[a]

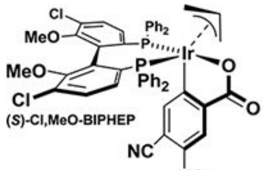
[a]Parallel acylation reaction were run with (*R*)- *or* (*S*)-HBTM catalyst (10 mol %), DIPEA (300 mol %) and propionic anhydride (300 mol %) at room temperature. The conversions were analyzed by ^{1}H NMR after 1560 min. With the directing group to the left, faster reactions with the (*R*)HBTM indicate that the alcohol configuration is forward. See Supporting Information for more details. [b]0 °C, HBTM (26 mol %).

Table 1.

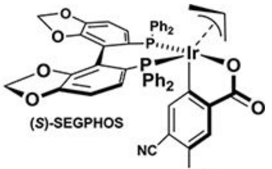
Enantioselective iridium-catalyzed allylation of ynals **1a-1f** with allyl acetate via 2-propanol-mediated reductive coupling.[a]



entry	1a-1d	catalyst	yield (%)	ee (%)
1	**1a,** R = Ph	**(*S*)-Ir-I**	—	—
2	**1a,** R = Ph	**(*S*)-Ir-II**	—	—
3	**1b,** R = $CH_2OTBDPS$	**(*S*)-Ir-I**	—	—
4	**1b,** R = $CH_2OTBDPS$	**(*S*)-Ir-II**	—	—
5	**1c,** R = CMe_2OTIPS	**(*S*)-Ir-I**	63	95
6	**1c,** R = CMe_2OTIPS	**(*S*)-Ir-II**	53	94
7	**1d,** R = TMS	**(*S*)-Ir-I**	—	—
8	**1d,** R = TMS	**(*S*)-Ir-II**	—	—
9	**1e,** R = TBS	**(*S*)-Ir-I**	24	94
10	**1e,** R = TBS	**(*S*)-Ir-II**	22	96
11	**1f,** R = TIPS	**(*S*)-Ir-I**	78	95
12	**1f,** R = TIPS	**(*S*)-Ir-II**	61	93



(S)-Ir-I



(S)-Ir-II

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