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Ethanol: Unlocking an Abundant Renewable C_2-Feedstock for Catalytic Enantioselective C–C Coupling

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Abstract: *With annual production at >85 million tons/year, ethanol is the world's largest-volume renewable small molecule carbon source, yet its use as a C_2-feedstock in enantioselective C–C coupling is unknown. Here, the first catalytic enantioselective C–C couplings of ethanol are demonstrated in reactions with structurally complex, nitrogen-rich allylic acetates incorporating the top 10 N-heterocycles found in FDA-approved drugs.*

A 2017 BASF survey reveals that only 13% of the 20.8 million tons of carbon feedstocks used to manufacture organic chemicals were derived from renewable sources, with the remainder generated from crude oil (76%), natural gas (10%), or coal (1%).[1] Ethanol is produced at a rate of >85 million tons/year worldwide,[2] making it the largest-volume renewable small molecule feedstock. The vast majority of commercial ethanol is consumed as fuel. The goal of achieving sustainable, carbon-neutral routes to large-volume commodity chemicals using ethanol as a C_2-feedstock is highly underdeveloped and merits greater attention.[3] The Lebedev ethanol-to-butadiene process,[4] and more recent industrial efforts to launch ethanol-to-polyethylene processes,[5] underscore the feasibility of ethanol-based chemical manufacture. In the realm of commodity and fine chemical synthesis, ethanol use is relegated to the preparation of achiral C_2-compounds: ethyl halides, ethyl esters, diethyl ether, acetic acid, and ethyl amines.[2] Beyond ethanol-to-butanol[7,8] and other Guerbet-type reactions,[9] catalytic C–C couplings of ethanol are highly uncommon and largely limited to isolated examples in which racemic adducts are formed.[10,11] To our knowledge, catalytic enantioselective C–C couplings of ethanol are entirely absent from the chemical literature (Figure 1).[12] Here, in connection with our efforts to develop asymmetric alcohol-mediated carbonyl additions,[13] we report the first highly diastereo- and enantioselective conversions of ethanol to higher alcohols, which are achieved via catalytic C–C coupling with structurally complex nitrogen-rich allylic acetates, including those that

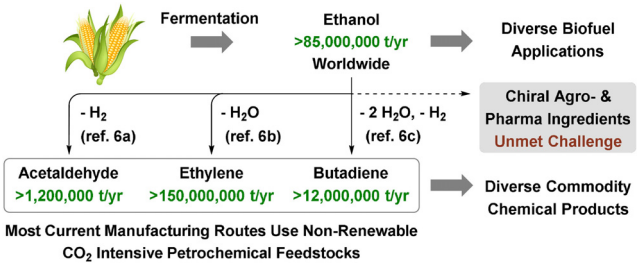
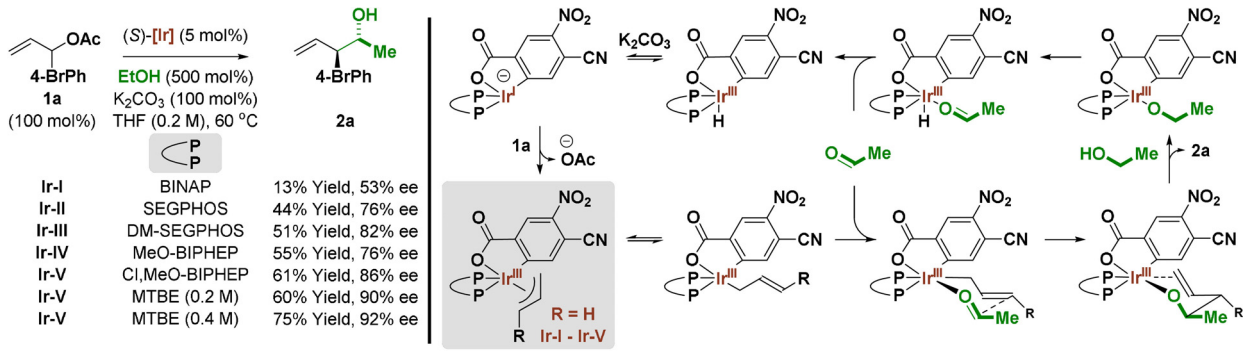


Figure 1. Opportunities for ethanol-based chemical manufacture.[6]



Scheme 1. Selected optimization experiments in the enantioselective π-allyliridium-*C*,*O*-benzoate-catalyzed coupling of ethanol with allylic acetate **1a** and general mechanism. 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.

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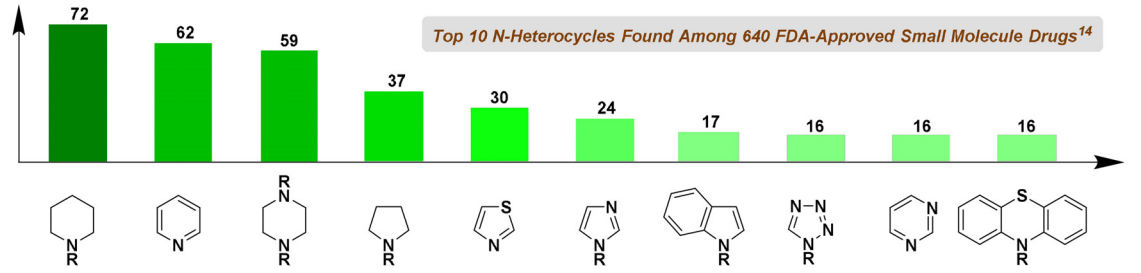
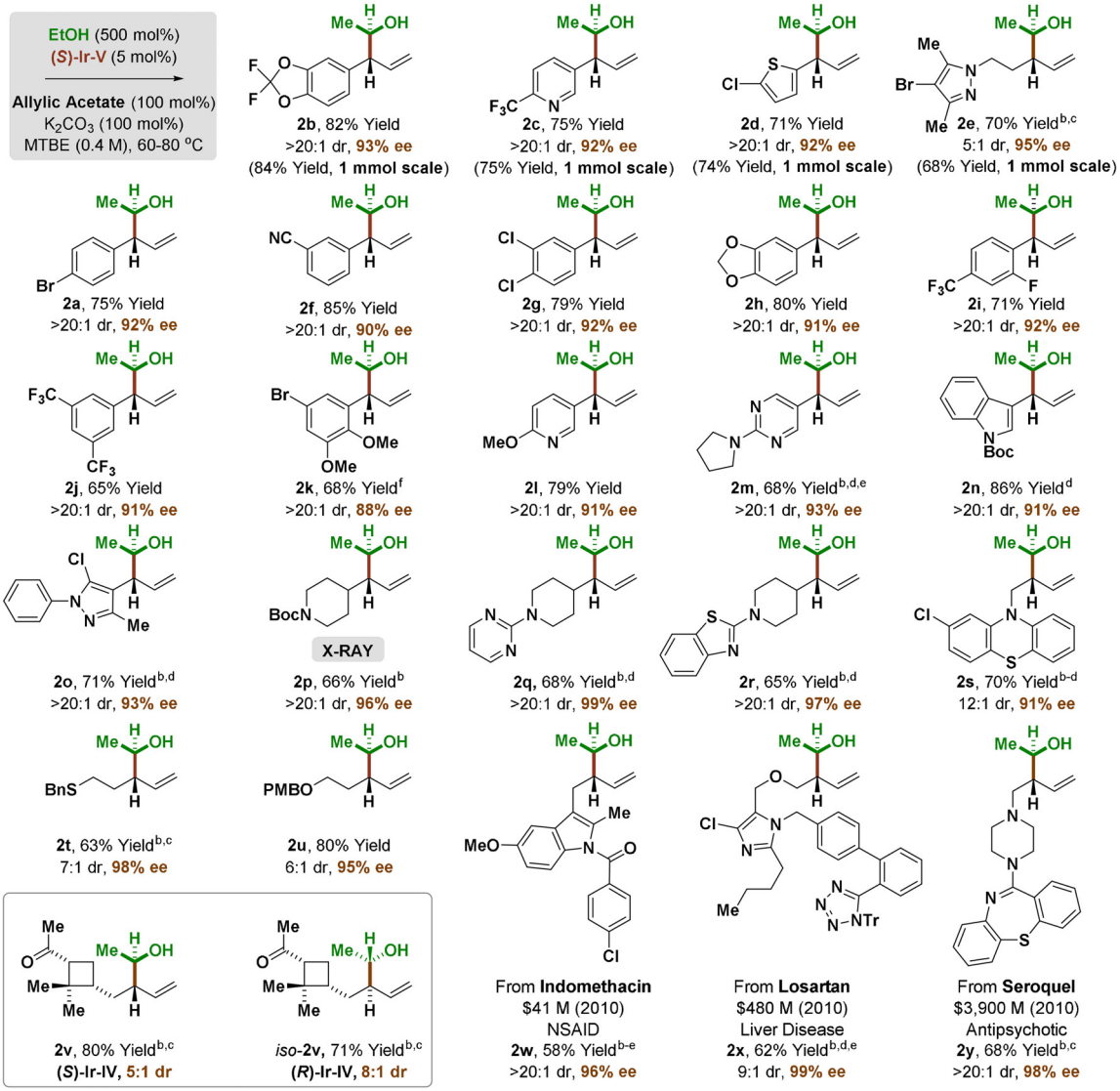
incorporate the top 10 most frequently encountered N-heterocycles found in FDA-approved drugs.[14]

Earlier studies from our laboratory on the enantioselective iridium-catalyzed C–C coupling of primary alcohols were conducted with excess allyl acetate using the alcohol as the limiting reagent.[15] To adapt this method for the catalytic conversion of ethanol to higher chiral non-racemic alcohols (Scheme 1), the more valuable and structurally complex

allylic acetates were chosen as limiting reagents. This posed a major challenge as competing transfer hydrogenolysis, which occurs via protonation of the intervening π-allyliridium nucleophile, represents a major side reaction. Indeed, protonolytic cleavage of the π-allyliridium precatalyst is required for entry into the catalytic cycle, and prior work from our laboratory suggests carbonyl addition is the turn-over limiting event in the catalytic cycle.[15b] Upon evaluation of different axially chiral chelating phosphine ligands in the reaction of ethanol with allylic acetate **1a**, it was found that optimal isolated yields of **2a** were obtained using the π-allyliridium-*C*,*O*-benzoate modified by (*S*)-Cl,MeO-BIPHEP, (*S*)-**Ir-V**.

Table 1: Diastereo- and enantioselective π-allyliridium-*C*,*O*-benzoate-catalyzed coupling of ethanol with allylic acetates **1a**–**1y** to form homoallylic alcohols **2a**–**2y**.[a]

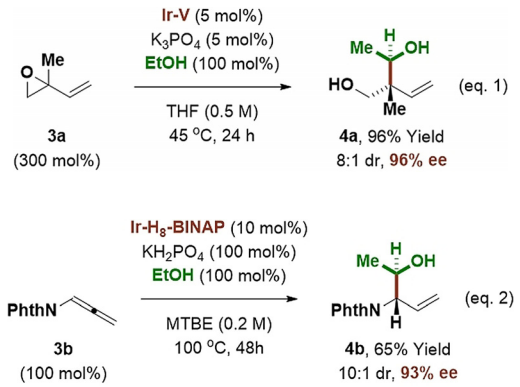




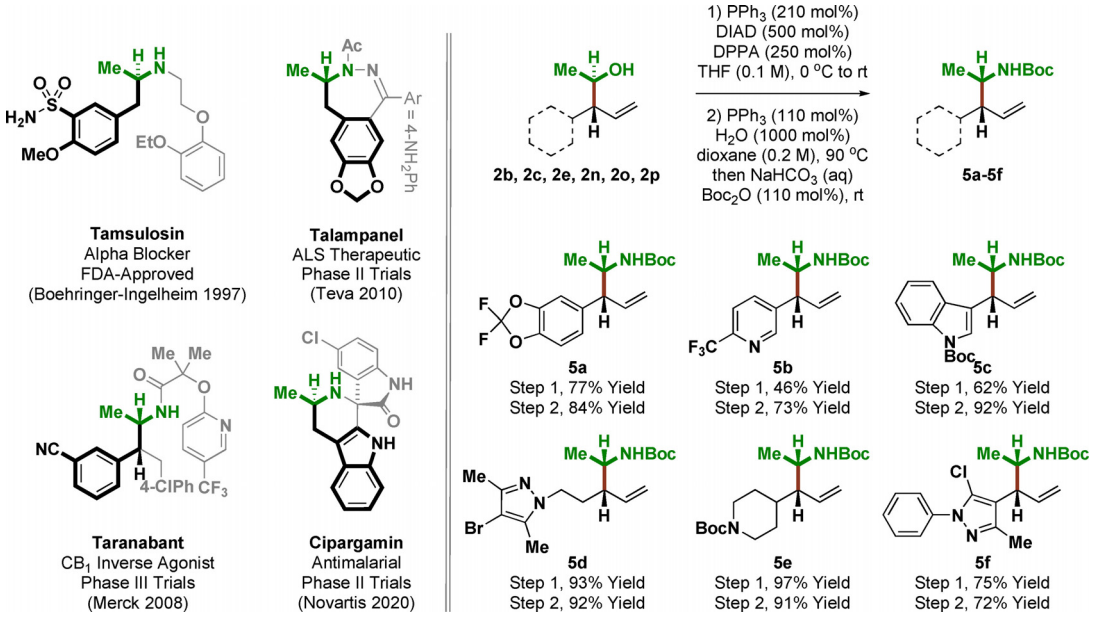
[a] Yields are of material isolated by silica gel chromatography. Enantioselectivities were determined by chiral stationary phase HPLC analysis. See Supporting Information for further experimental details. [b] Acetone (1.0 M), [c] (*S*)-Ir-IV, [d] EtOH (300 mol%), [e] K_2CO_3 (50 mol%), [f] K_2CO_3 (200 mol%).

This more electron-deficient ligand may retard the rate of π-allyl protonation, enabling higher conversion to **2a**. Reactions catalyzed by (*S*)-**Ir-V** also displayed significantly higher enantioselectivity, which we attribute to enhanced Lewis acidity at iridium, which, in turn, may shorten Ir–O and Ir–C bonds in the transition structure for carbonyl addition to enhance asymmetric induction. Finally, it was reasoned that a less Lewis basic solvent, MTBE, would further facilitate carbonyl addition by promoting association of transient acetaldehyde with the allyliridium intermediate. A substantial increase in the isolated yield of adduct **2a** was observed, which was further elevated by increasing reaction concentration.

These optimized conditions were applied to the enantioselective π-allyliridium-*C*,*O*-benzoate-catalyzed coupling of ethanol with a structurally diverse array of allylic acetates (Table 1). As determined in a recent structural survey of U.S. FDA approved drugs, 59% of small molecule drugs incorporate N-heterocycles.[14] Hence, to highlight the potential utility of this method vis-à-vis drug discovery, allylic acetates **1a**–**1y** that incorporate the 10 most frequently encountered N-heterocycles in FDA-approved drugs (beyond β-lactams) were specifically chosen for evaluation as coupling partners. To our delight, the products of ethanol-mediated C–C coupling **2a**–**2y** were formed in good yield with excellent levels of *anti*-diastereoselectivity and enantioselectivity. This includes allylic acetates substituted by aryl groups (**2a**, **2b**, **2f**–**2k**), heteroaryl groups (**2c**, **2d**, **2l**–**2o**), including *ortho*-,*ortho*-disubstituted heteroarene (**2o**), as well as alkyl (**2s**–**2y**) and cycloalkyl groups (**2p**–**2r**). Of particular significance, due to the high functional group tolerance of the catalyst, direct asymmetric (1-hydroxy)ethylation of allylic acetates derived from the FDA-approved drugs indomethacin (**2w**), losartan (**2x**), and seroquel (**2y**) can be achieved efficiently, establishing the utility of this method for late-stage functionalization of complex nitrogen-rich clinical candidates.[16] As illustrated by the conversion of chiral allylic acetate **1v** to adducts **2v** and *iso*-**2v**, which are derived from (+)-α-pinene, ethanol-mediated (1-hydroxy)ethylation proceeds with good levels of catalyst-directed diastereoselectivity. The absolute and relative stereochemical assignments of products **2a**–**2y** were made in analogy to that observed for compound **2p**, which was determined via single-crystal X-ray diffraction. Finally, beyond allylic acetates, the vinyl epoxide **3a**[17] and allenamide **3b**[18] are competent pronucleophiles, as illustrated by the diastereo- and enantioselective formation of adducts **4a** [Eq. (1)] and **4b** [Eq. (2)], respectively.



To illustrate the utility of the present method vis-á-vis drug discovery, selected products of (1-hydroxy)ethylation **2b**, **2c**, **2e**, **2n**, **2o**, and **2p** were converted to the *N*-Boc α-methylamines **5a**–**5f**, respectively (Scheme 2). α-Methylphenethylamines, such as the parent "amphetamine," are bioactive, often psychoactive,[19] substances that appear



Scheme 2. Representative phenethylamines and conversion of ethanol adducts to phenethylamines **5a**–**5f**. 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.

ubiquitously as substructures in clinical candidates. For example, the FDA-approved drug tamulosin[20a] and the clinical candidates talampanel,[20b] taranabant,[20c] and cipargamin[20d] all incorporate α-methylphenethylamine substructures, yet act against diverse disease. Exposure of adducts **2b**, **2c**, **2e**, **2n**, **2o**, and **2p** to diphenylphosphoryl azide under Mitsunobu conditions delivers the corresponding azides with inversion of stereochemistry.[21] Staudinger reduction[22] followed by treatment with di-*tert*-butyl dicarbonate in situ provided the *N*-Boc α-methylamines **5a**–**5f** in good yield with no erosion of diastereomeric enrichment.

In conclusion, we report the first catalytic enantioselective C–C couplings of ethanol, the world's most abundant renewable small molecule carbon feedstock. Specifically, in a hydrogen auto-transfer process catalyzed by a cyclometallated π-allyliridium-*C*,*O*-benzoate complex modified by (*S*)-Cl,MeO-BIPHEP, ethanol dehydrogenation drives reductive C–O bond cleavage of allylic acetates to form allyliridium nucleophiles and acetaldehyde, which combine to deliver products of (1-hydroxy)ethylation. The broad scope of this method is demonstrated by couplings with structurally complex, nitrogen-rich allylic acetates that incorporate the top 10 N-heterocycles found in FDA-approved drugs. Conversion of selected adducts to α-methylphenethylamines is described, further highlighting applicability of this method to drug discovery. The present method requires no premetalated reagents and generates acetic acid as the sole stoichiometric byproduct. Given the increasing importance of iridium-catalyzed dehydrogenation in process R&D,[23] it is the authors' hope this work will inspire other "green" catalytic methods for the atom-efficient conversion of renewable feedstocks to value-added products.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: enantioselectivity · ethanol · hydrogen transfer · iridium · renewable sources

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