Enantiomerically Enriched Allylic Alcohols and Allylic Amines via C–C Bond-Forming Hydrogenation: Asymmetric Carbonyl and Imine Vinylation

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ABSTRACT

Hydrogenation of alkynes in the presence of carbonyl compounds and imines using cationic rhodium(I) and iridium(I) precatalysts enables the formation of allylic alcohols and allylic amines, respectively. Through the use of hydrogenation catalysts modified by chiral ligands, allylic alcohols and allylic amines may be generated in highly optically enriched forms. Hydrogenative fragment couplings of this type circumvent the use of preformed organometallic reagents and avoid the generation of stoichiometric byproducts.

Introduction to Carbonyl and Imine Vinylation

The synthetic utility of allylic alcohols and allylic amines has driven efforts toward the development of catalytic enantioselective protocols for the vinylation of carbonyl compounds and imines. The majority of work in this area stems from the seminal studies of Oguni[1a] and Noyori[1b] on the enantioselective addition of dialkylzinc reagents to aldehydes.[2] The first asymmetric aldehyde vinylations of this type were reported by Oppolzer[3a,4] and involve the generation of vinylzinc reagents via alkyne hydroboration, followed by transmetalation of the resulting vinyl boron reagent to zinc using $ZnMe_2$. A related strategy for asymmetric aldehyde vinylation is reported by Wipf and involves alkyne hydrozirconation–transmetalation en route to vinylzinc reagents.[3d] Finally, after catalytic enantioselective additions of alkylzinc and arylzinc reagents to ketones[2b–d] described by Yus[5a,b] and Fu,[5c] respectively, catalytic asymmetric ketone vinylations were devised by Walsh.[6]

Parallel efforts toward the development of enantioselective imine additions using preformed metallic reagents reveal an additional set of challenges.[7] Pursuant to Soai's seminal report,[8a] several organocatalysts for the enantioselective addition of organozinc reagents to imines emerged.[8] Because conventional imines are generally less reactive than aldehydes with respect to organocatalyzed organozinc addition, these studies employ *N*-acyl and *N*-(diphenylphosphinoyl) imines. To address the issue of reactivity, enantioselective metal-catalyzed organozinc additions to imines were developed,[9] as first described by Tomioka in the case of copper.[9a] Early transition-metal catalysts (Ti, Zr, and Hf)[10] and late transition-metal catalysts (Rh)[11] also have been found to promote highly enantioselective organozinc additions to imines.

Beyond organozinc reagents, the enantioselective addition of organolithium reagents to imines catalyzed by chiral Lewis basic chelating agents has been described.[12] Additionally, under the conditions of rhodium catalysis, organotin,[13a,b] organotitanium,[13c] and organoboron[13d–h] reagents have served in catalytic asymmetric imine additions. Despite considerable effort, highly enantioselective vinyl transfer to imines employing preformed organometallic reagents has not been achieved.[14,15]

The aforementioned approaches to enantioselective carbonyl and imine vinylation are highly effective in terms of directing enantioselection. However, these strategies uniformly exploit preformed organometallic reagents, which are generally prepared via transmetalation from a "primary organometallic reagent", which itself may require preparation through metalation of a precursor. For example, organoboron reagents are generally prepared from the corresponding organolithium reagents, which in turn

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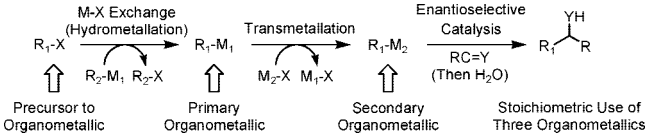
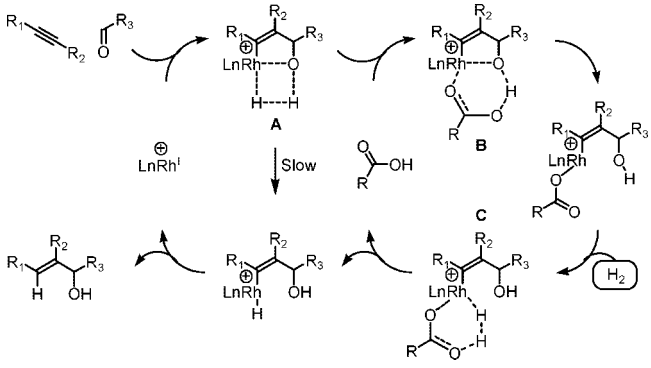
are prepared by metal halogen exchange using butyl lithium. Here, three preformed organometallic reagents are used stoichiometrically in advance of C–C coupling. Such protocols mandate the generation of multiple stoichiometric byproducts and require the handling of multiple air- and moisture-sensitive materials (Scheme 1).



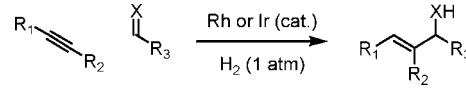
Direct metal-catalyzed reductive coupling circumvents the successive use of stoichiometrically preformed organometallic reagents.[16] Of direct relevance to this Account are catalysts enabling direct alkyne–aldehyde reductive coupling.[17] The first catalytic process of this type was reported by Ojima and involves the rhodium-catalyzed reductive cyclization of acetylenic aldehydes mediated by silane.[18] Corresponding titanocene-catalyzed cyclizations were disclosed by Crowe,[19] and nickel-catalyzed cyclizations were reported by Montgomery.[20a–c,e] Finally, intermolecular reductive alkyne–aldehyde coupling was achieved using nickel-based catalysts, as described by Jamison,[21] Takai,[22] and Montgomery.[20d] Reductive couplings of this type involve the capture of organometallics that arise transiently under catalytic conditions, signaling a departure from the stoichiometric preformation of organometallic reagents. However, the aforementioned methods employ terminal reductants, such as hydrosilanes, hydrostannanes, organozinc reagents, organoboron reagents, or chromium(II) chloride, which ultimately produce molar equivalents of chemical byproducts.

Completely atom economical and, hence, byproduct-free reductive C–C couplings are potentially achieved under the conditions of catalytic hydrogenation. Despite the fact that catalytic hydrogenation of organic compounds has been known for over a century,[23] use of elemental hydrogen as a terminal reductant in metal-catalyzed C–C coupling has only been explored in connection with processes involving carbon monoxide insertion, as exemplified by the Fischer–Tropsch[24] reaction and alkene hydroformylation.[25] Despite the impact of these prototypical hydrogen-mediated C–C bond formations, systematic efforts toward hydrogenative C–C couplings that apply to conventional electrophilic partners in the form of carbonyl compounds and imines were absent from the literature prior to our work.[26–29]

Scheme 1. General Catalytic Mechanism for Hydrogenative Alkyne–Carbonyl Coupling



In this Account, we present a summary of our work on the hydrogenative coupling of alkynes to carbonyl compounds and imines to furnish allylic alcohols and allylic amines. Related hydrogenative couplings of alkenes to carbonyl compounds and imines, as exemplified by the hydrogen-mediated reductive aldol and Mannich reaction, and the hydrogen-mediated coupling of olefins to anhydrides are the subject of recent reviews.[26,30] The collective hydrogenative fragment couplings that we report constitute a broad new class of catalytic C–C bond formations that circumvent byproduct generation and the requirement of stoichiometrically preformed organometallic reagents in certain C=X (X = O, NR) addition processes.

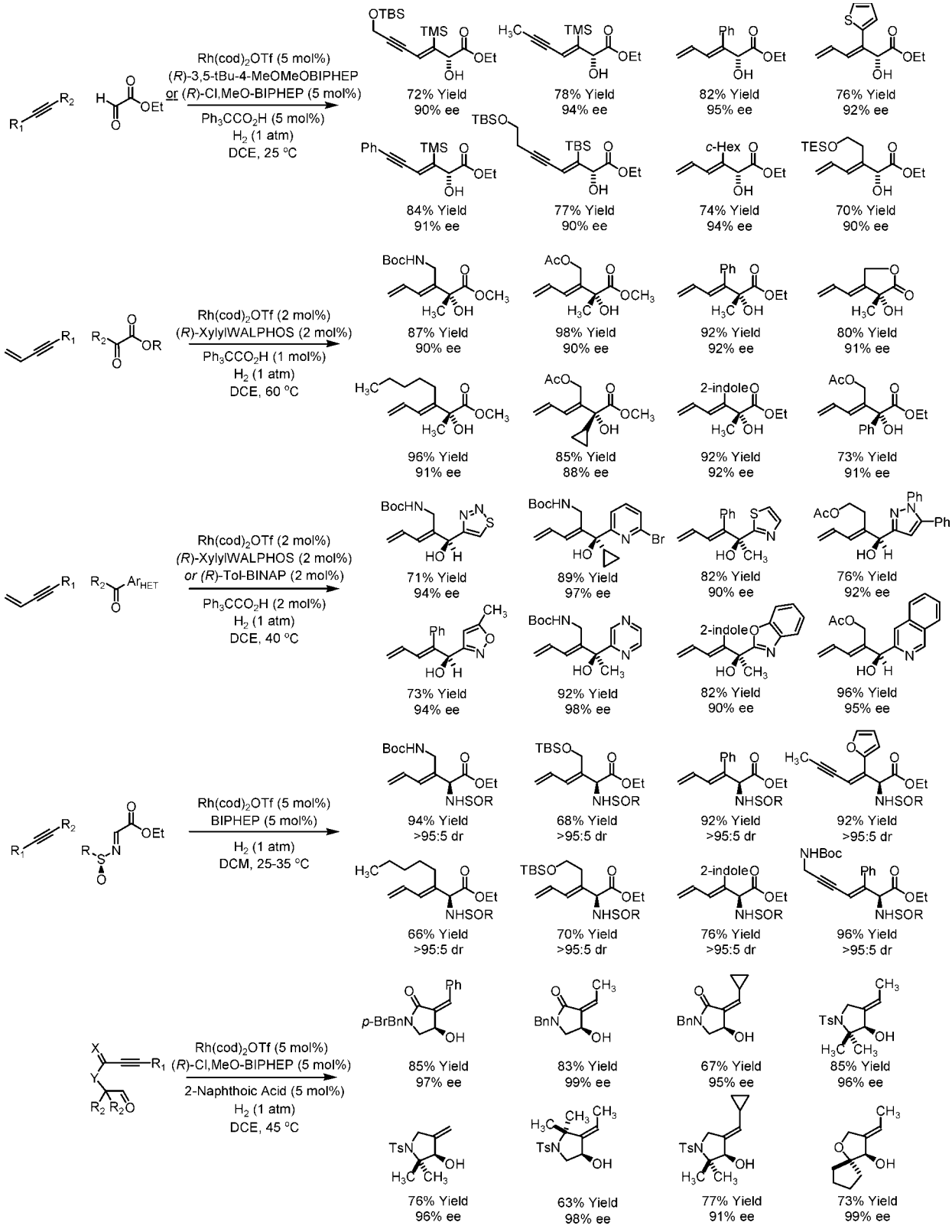


Hydrogenative Coupling of Alkynes to Carbonyl Compounds and Imines

Proof of concept studies toward the development of first-generation catalysts for hydrogenative C–C coupling, along with preliminary mechanistic studies corroborating their proposed mode of action, are described in prior accounts.[26] Salient features are summarized below. The collective data are consistent with a general mechanism involving alkyne–C=X (X = O, NR) oxidative coupling followed by direct or Brønsted acid co-catalyzed hydrogenolysis of the resulting metallacyclic intermediate. To mitigate competitive conventional substrate hydrogenation, cationic complexes of rhodium and iridium are required. A plausible explanation is as follows. Unlike corresponding neutral complexes, hydrogen activation is generally slower for cationic rhodium precatalysts,[31,32] thus providing a greater kinetic window for entry into alkyne–C=X (X = O, NR) oxidative coupling manifolds. Oxidative coupling pathways are promoted further by the increased coordinative unsaturation of cationic complexes. As supported by theoretical studies,[33] Brønsted acid co-catalysts are postulated to circumvent highly energetic four-centered transition structures "A" for σ-bond metathesis, as required for direct hydrogenolysis of metallacyclic intermediates, with six-centered transition structures "C" for hydrogenolysis of rhodium carboxylates derived upon metallacycle protonolysis, which itself may occur through six-centered transition structure "B". The collective data suggest that the oxarhodacyclopentene is the catalyst resting state and that hydrogenolysis of the oxarhodacyclopentene is the turnover limiting step in the catalytic mechanism (Scheme 1).

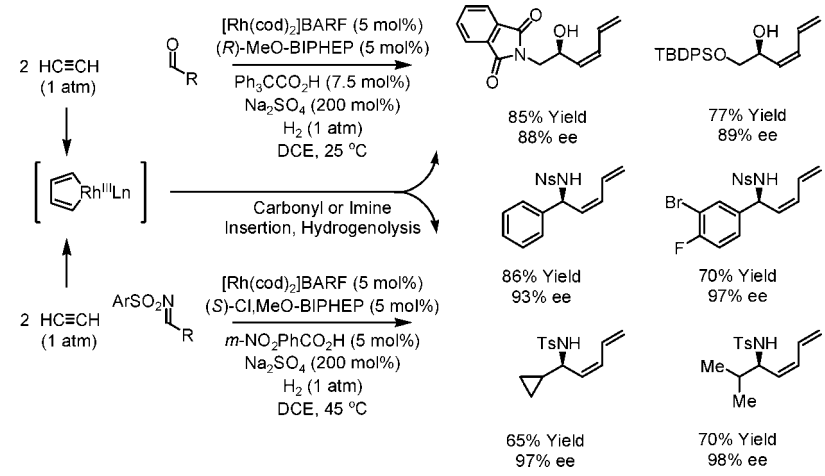
When conjugated alkynes are simply hydrogenated in the presence of vicinal dicarbonyl compounds, glyoxalates, and pyruvates, at ambient pressure using chirally modified cationic rhodium catalysts, reductive C–C coupling occurs to furnish α-hydroxy esters in highly optically enriched form.[34a,b] Under nearly identical conditions, conjugated

Scheme 2. Rhodium-Catalyzed Hydrogenative C–C Coupling of Alkynes to Carbonyl Compounds and Imines

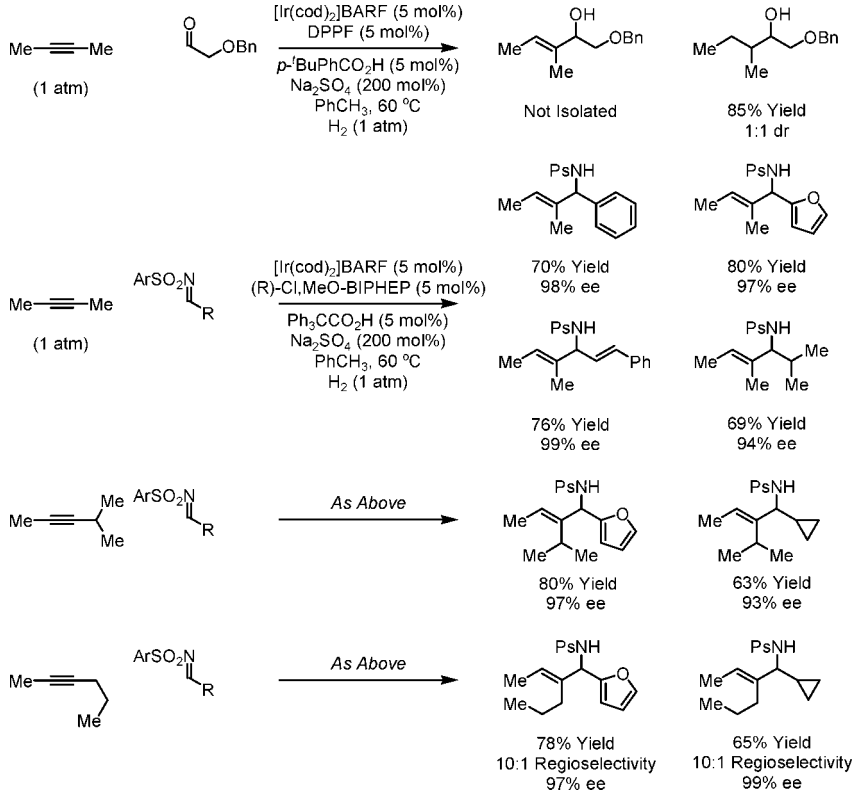


alkynes hydrogenatively couple to heterocyclic aromatic aldehydes and ketones that are isoelectronic with respect to the vicinal dicarbonyl motif, thereby providing access to highly optically enriched heteroaryl-substituted secondary and tertiary alcohols. [34c] Hydrogenation of 1,3-enynes in the presence of optically enriched ethyl (*N*-sulfinyl)iminoacetates delivers novel nonproteogenic amino acid esters.[34d] Finally, catalytic hydrogenation of acetylenic aldehydes using chirally modified rhodium catalysts provides products of reductive carbocyclization, again with excellent levels of asymmetric induction. [34e] Brønsted acid co-catalysts were found to enhance the rate and con-

Scheme 3. Enantioselective (*Z*)-Butadienylation via Hydrogenative Coupling of Acetylene to Aldehydes and Imines



Scheme 4. Enantioselective Iridium-Catalyzed Hydrogenative Coupling of 2-Butyne to Aldehydes and Imines



version in all couplings examined. Couplings to ethyl (*N*-sulfinyl)iminoacetates were studied prior to the discovery of the Brønsted acid co-catalyst effect (Scheme 2).

Intermolecular hydrogenative couplings of alkynes to carbonyl compounds under the conditions of rhodium catalysis require highly activated electrophilic partners, such as vicinal dicarbonyl compounds and their structural relatives. It was found that gaseous acetylene couples to conventional aldehydes under hydrogenation conditions to furnish products of *Z*-butadienylation.[35a] Isotopic labeling and electrospray ionization mass spectrometry (ESI–MS) analysis are consistent with a catalytic mechanism involving oxidative dimerization of acetylene to form a cationic rhodacyclopentadiene[36] followed by carbonyl insertion and Brønsted-acid-assisted hydrogenolysis of the resulting oxarhodacycloheptadiene to provide the carbonyl addition product and cationic rhodium(I) to close the cycle. More recently, corresponding couplings to aldimines have been achieved.[35b] For both aldehyde and imine couplings, chirally modified rhodium catalysts deliver highly optically enriched allylic alcohols and allylic amines, respectively (Scheme 3).

Attempted imine vinylation under the conditions of rhodium catalysis using 1,2-dialkylsubsituted alkynes is not an efficient process. Our rationale for addressing this limitation is as follows. In hydrogenative alkyne–carbonyl coupling, our collective studies suggest that a key feature of the catalytic mechanism involves oxidative coupling of the π-unsaturated reactants to furnish oxametallacyclic intermediates. Hydrogenolytic cleavage of this species via

σ-bond metathesis furnishes the coupling product with concomitant regeneration of the catalyst. It is plausible that π-backbonding in the metal–alkyne complex, as described by the Dewar–Chatt–Duncanson model,[37] facilitates the oxidative coupling event by conferring nucleophilic character to the bound alkyne. For rhodium, a comparatively weak π donor, conjugated alkynes are required, possibly because of the fact that they embody lower lying unoccupied molecular orbitals (LUMOs). Iridium is a stronger π donor than rhodium because of relativistic effects.[38,39] These data suggest that iridium complexes may catalyze the hydrogenative coupling of nonconjugated alkynes that embody higher lying LUMOs.

The veracity of this analysis was challenged through experiment. Gratifyingly, it was found that using $[Ir(cod)_2]$-BARF as a precatalyst, hydrogenation of 2-butyne in the presence of α-benzyloxy acetaldehyde provides an 81% isolated yield of the fully saturated reductive coupling product as an equimolar mixture of diastereomers. Here, the initially formed allylic alcohol is subject to further hydrogenation to deliver the saturated alcohol. In contrast, iridium-catalyzed hydrogenation of 2-butyne in the presence of various *N*-arylsulfonyl imines provides the corresponding trisubstituted allylic amines with complete levels of *E*/*Z* selectivity (≥95:5) and, using catalysts modified by (*R*)-Cl,MeO-BIPHEP, exceptional levels of asymmetric induction.[40] Notably, over-reduction of the unsaturated allylic amines are not observed. These results are consistent with the role of hydroxyl and sulfonamide moieties as active and inactive volumes, respectively, in iridium-catalyzed hydrogenation.[41] The nonsymmetric alkynes 4-methyl-2-pentyne and 2-hexyne couple to *N*-arylsulfonyl imines with excellent regioselectivity proximal to the more highly substituted alkyne terminus to provide the corresponding allylic amines with uniformly high levels of enantiomeric excess (Scheme 4).

Future Directions

The prototypical C–C bond-forming hydrogenations, the Fischer–Tropsch reaction and alkene hydroformylation, were reported over half a century ago and are practiced on an enormous scale.[24,25] While these processes are restricted to the use of carbon monoxide as a coupling partner, studies from our laboratory extend hydrogenative C–C coupling to the use of conventional electrophiles in the form of carbonyl compounds and imines. The generation and capture of nonstabilized carbanion equivalents under the essentially neutral conditions of hydrogenation dispenses with the requirement of stoichiometrically preformed organometallic reagents in certain C=X (X = O, NR) addition processes, enabling C–C bond formation in the absence of any stoichiometric byproducts. These studies open a new chapter in the area of catalytic hydrogenation and raise numerous possibilities *vis-à-vis* development of related byproduct-free C–C couplings.

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