Communication

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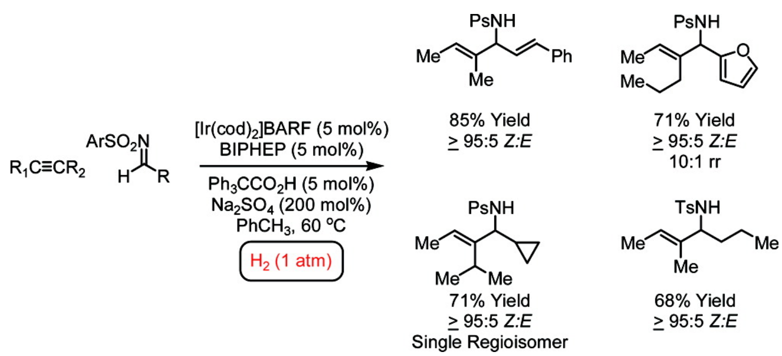

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Allylic Amines via Iridium-Catalyzed C−C Bond Forming Hydrogenation: Imine Vinylation in the Absence of Stoichiometric Byproducts or Metallic Reagents

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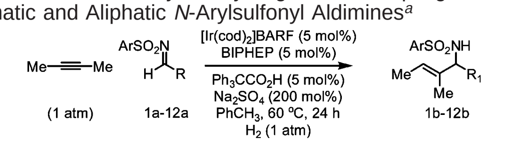
Elemental hydrogen is the cleanest, most cost-effective reductant available. Accordingly, reductions mediated by hydrogen, termed "hydrogenations", are practiced industrially on vast scale.[1,2] Conventional hydrogenation involves delivery of hydrogen to a single functional group. The addition of hydrogen across multiple functional groups accompanied by C−C bond formation is observed in hydroformylation, the largest volume application of homogeneous metal catalysis,[3] and the parent Fischer−Tropsch reaction, a process enabling production of petroleum from hydrogen and carbon monoxide.[4] These prototypical hydrogen-mediated C−C bond formations require carbon monoxide as a coupling partner. Given the impact of these processes, systematic efforts toward hydrogen-mediated C−C bond formations beyond carbon monoxide coupling are warranted.[5,6]

We have developed a novel class of hydrogenations wherein two or more unsaturated molecules combine to furnish a single, more complex molecule upon exposure to gaseous hydrogen in the presence of a metal catalyst.[5,6] Such "*C−C bond forming hydrogenations*" enable direct coupling of diverse π-unsaturated compounds to conventional electrophiles, such as carbonyl compounds and imines, providing an alternative to stoichiometrically preformed organometallic reagents in certain C=X (X = O, NR) addition processes. In the specific case of imine addition, the asymmetric coupling of 1,3-enynes and 1,3-diynes to ethyl (*N*-sulfinyl)-iminoacetates[7a] and the enantioselective coupling of acetylene to *N*-arylsulfonyl aldimines[7b] were devised. These transformations, which employ rhodium-based catalysts, furnish *dienyl allylic amines*. Attempted imine vinylation under the conditions of rhodium catalysis using 1,2-dialkyl-substituted alkynes led to conventional alkyne hydrogenation.

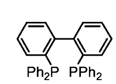
Recently, under the conditions of iridium-catalyzed hydrogenation,[8] we found that simple 1,2-dialkyl-substituted alkynes undergo reductive coupling to α-ketoesters to furnish β,γ-unsaturated α-hydroxy esters.[7c,9] Here, we report that iridium-catalyzed hydrogenation of simple nonconjugated alkynes in the presence of *N*-arylsulfonyl aldimines provides the corresponding trisubstituted allylic amines with complete levels of *E*:*Z* selectivity (≥95:5). Remarkably, the unsaturated products are not subject to over-reduction under the conditions of hydrogen-mediated coupling. Further, nonsymmetric alkynes are found to couple with excellent levels of regiocontrol. This protocol enables direct imine vinylation in the absence of preformed organometallic reagents and represents the first iridium-catalyzed alkyne−imine reductive coupling.[10−16]

Initial studies involved hydrogenation of 2-butyne in the presence of furfural-derived aldimines employing $[Ir(cod)_2]$BARF and BIPHEP as catalyst precursors. The selection of the *N*-substituent proved critical. For example, attempted hydrogenative coupling of 2-butyne to the "PMP"-protected imine derived from *p*-anisidine and furfural under conditions cited in Table 1 provides the product of conventional imine reduction in 65% isolated yield. In contrast, the corresponding *p*-toluenesulfonyl imine **7a** smoothly couples to

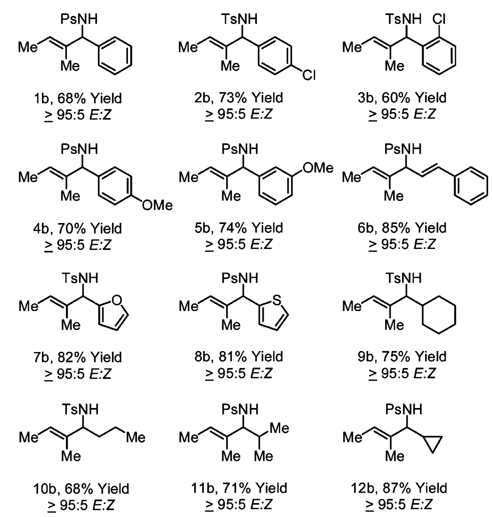
Table 1. Iridium Catalyzed Hydrogenative Coupling of 2-Butyne to Aromatic and Aliphatic *N*-Arylsulfonyl Aldimines[a]



1a, R = Ph, Ar = Ps	7a, R = 2-Furyl, Ar = Ts
2a, R = *p*-ClPh, Ar = Ts	8a, R = 2-Thienyl, Ar = Ps
3a, R = *o*-ClPh, Ar = Ts	9a, R = *c*-Hex, Ar = Ts
4a, R = *p*-MeOPh, Ar = Ps	10a, R = *n*-Pr, Ar = Ts
5a, R = *o*-MeOPh, Ar = Ps	11a, R = *i*-Pr, Ar = Ps
6a, R = CH=CHPh, Ar = Ps	12a, R = *c*-Pr, Ar = Ps



BIPHEP



[a] Cited yields are of isolated material (Ps = benzenesulfonyl, Ts = *p*-toluenesulfonyl). 2-Butyne is delivered as a vapor via cannula transfer with the assistance of a hydrogen balloon to a 60 °C toluene solution of imine. See Supporting Information for detailed experimental procedures.

2-butyne under these conditions to deliver allylic amine **7b** in 82% isolated yield. A range of aromatic, heteroaromatic, and aliphatic *N*-arylsulfonyl imines **1a**−**12a** couple under these conditions, enabling access to trisubstituted allylic amines **1b**−**12b**, which appear as single geometrical isomers (Table 1). As previously observed,[7c] carboxylic acid cocatalysts enhance rate and conversion, presumably by circumventing highly energetic four-centered transition structures for σ-bond metathesis, as required for direct hydrogenolysis of azametallacyclic intermediates **I**, with six-centered transition structures for hydrogenolysis of iridium carboxylates **II** derived upon protonolytic cleavage of the nitrogen−iridium bond (Scheme 1).[17]

To probe regioselectivity, nonsymmetric alkynes 4-methyl-2-pentyne and 2-hexyne were used as nucleophilic partners in hydrogenative couplings to imines **6a**, **12a**, and **13a** under standard conditions cited in Table 1. Using 4-methyl-2-pentyne, the isopropyl-substituted allylic amines **13b**, **14b**, and **15b** are formed as single regioisomers. Hydrogenative couplings employing 2-hexyne

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Scheme 1. Reductive Coupling under an Atmosphere of Deuterium

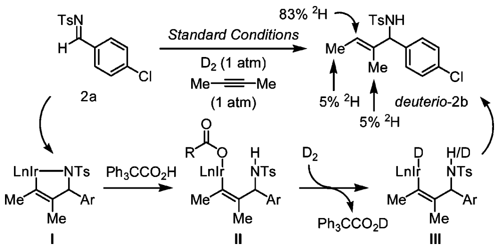
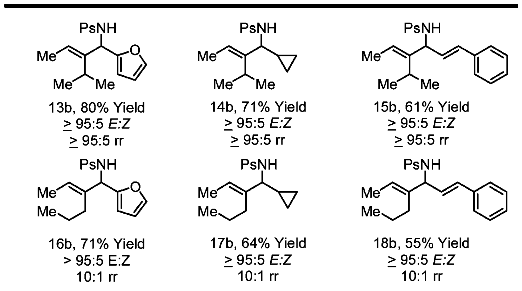
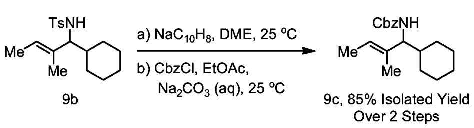


Table 2. Regioselective Hydrogenative Coupling of Nonsymmetric Alkynes to Imines **6a**, **12a**, and **13a**[a]



[a] Standard conditions described in Table 1. Couplings to form **16b**, **17b**, and **18b** were conducted at 80 °C. Cited yields are of isolated material.

furnish adducts **16b**, **17b**, and **18b** in 10:1 regiochemical ratios for each case. Interestingly, coupling proximal to the more highly substituted alkyne terminus is observed, and regioselectivity was found to improve with increasing reaction temperature. Regioisomeric ratios (rr) were determined by ^{1}H NMR analysis of the crude reaction product (Table 2). For certain examples cited in Tables 1 and 2, unreacted starting material and competitive imine reduction are observed. Aryl-substituted alkynes, such as 1-phenylpropyne, do not couple efficiently under standard conditions due to competitive imine reduction. Deprotection of the sulfonamide moiety occurs readily under standard conditions, as demonstrated by the conversion of **9b** to the corresponding Cbz-protected allylic amine **9c** (eq 1).



(1)

To corroborate the proposed catalytic mechanism, the reductive coupling of 2-butyne to imine **2a** was conducted under an atmosphere of deuterium. As revealed by ^{2}H NMR analysis, *deuterio*-**2b** incorporates deuterium at the vinylic position (83% ^{2}H). Small quantities of deuterium also are incorporated at the allylic methyl groups (5% ^{2}H). The equal distribution of deuterium at the allylic methyl groups suggests H−D exchange at the propargylic positions of 2-butyne in advance of C−C coupling. As previously observed in iridium-catalyzed couplings of 2-butyne to α-ketoesters,[7c] excess Brønsted acid cocatalyst does not influence the extent of deuterium incorporation (Scheme 1).

In summary, allylic amines are formed upon hydrogenation of 1,2-dialkyl-substituted alkynes in the presence of *N*-arylsulfonyl aldimines. Our collective studies reveal that organometallics arising transiently under hydrogenation conditions may be coupled to conventional electrophiles, thus circumventing use of preformed organometallic reagents as nonstabilized carbanion equivalents in certain carbonyl and imine addition processes.

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Supporting Information Available: Experimental procedures and spectral data (^{1}H NMR, ^{13}C NMR, IR, HRMS) for all new compounds, including ^{2}H NMR spectra of *deuterio*-**2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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