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Enantioselective Reductive Coupling of Acetylene to *N*-Arylsulfonyl Imines via Rhodium Catalyzed C−C Bond-Forming Hydrogenation: (*Z*)-Dienyl Allylic Amines

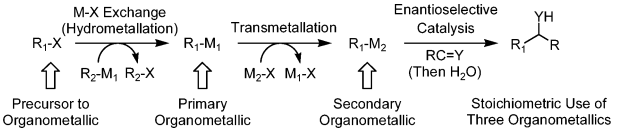
Eduardas Skucas, Jong Rock Kong, and Michael J. Krische*

University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, Texas 78712

Received March 6, 2007; E-mail: mkrische@mail.utexas.edu

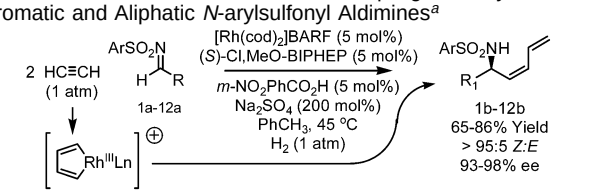
Following seminal studies by Oguni (1984)[1a] and Noyori (1986),[1b] myriad catalysts promoting highly enantioselective addition of organozinc reagents to aldehydes have been developed.[2] Subsequently, catalytic enantioselective aldehyde vinylations employing organozinc reagents were reported by Oppolzer (1992),[3a,4] enantioselective catalytic additions to ketones[2b−d] were described by Yus (1998, alkylation)[5a,b] and Fu (1998, arylation),[5c] and catalytic asymmetric ketone vinylations were devised by Walsh (2004).[6] Corresponding imine additions reveal additional challenges.[7] After Soai's initial report (1992),[8a] a number of nonmetallic catalysts for enantioselective organozinc addition to imines emerged.[8] Because conventional imines are less reactive to aminoalcohol catalyzed organozinc addition, such reactions employ *N*-acyl and *N*-(diphenylphosphinoyl) imines. As first shown by Tomioka (2000), issues of reactivity in additions to conventional imines are overcome via enantioselective copper-catalyzed organozinc addition.[9a] Other metallic catalysts (Zr, Ti) followed.[10] Finally, organolithium,[11] organotin,[12a] organotitanium, and organoboron[12c,d] reagents have served in catalytic asymmetric imine additions.[12] Catalytic reductive alkyne−carbonyl couplings are reported by Montgomery (1997)[13a] and Jamison (2000),[13b] and promising results on asymmetric alkyne−imine coupling are described by the latter author (2004).[13c] To date, highly enantioselective imine vinylation remains an elusive goal.[13c,14,16a]

Though effective, most methods for catalytic enantioselective coupling of nonstabilized carbanion equivalents to imines rely upon preformed organometallics. Further, many organometallics used in such transformations are prepared via transmetallation. Here, preparation of the "primary organometallic" may itself require preexisting functionality to direct regiocontrolled metalation. For example, in metal-catalyzed imine arylations employing organoboron reagents,[12c,d] aryllithiums that are prepared via metal−halogen exchange using *n*-BuLi are then transmetalated to boron, meaning three metallic reagents are used stoichiometrically prior to C−C coupling.

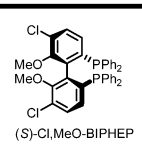


Direct methods for the catalytic asymmetric coupling of nonstabilized organic fragments to carbonyl compounds and imines circumvent use of preformed organometallics. Accordingly, we have developed a family of catalytic C−C couplings wherein two or more unsaturated compounds are hydrogenated together to furnish a single, more complex product.[15] Whereas conventional hydrogenations involve H_2 addition across a single functional group, "C−C bond forming hydrogenations" involve H_2 addition across two or more functional groups. This method enables reductive addition of acetylene to carbonyl compounds to provide (*Z*)-dienyl allylic alcohols.[16b] Here, we report that *N*-arylsulfonyl imines couple to acetylene to provide (*Z*)-dienyl allylic amines. Further, using chirally modified catalysts, adducts are formed with uniformly high levels of enantioselection (93−98% ee).

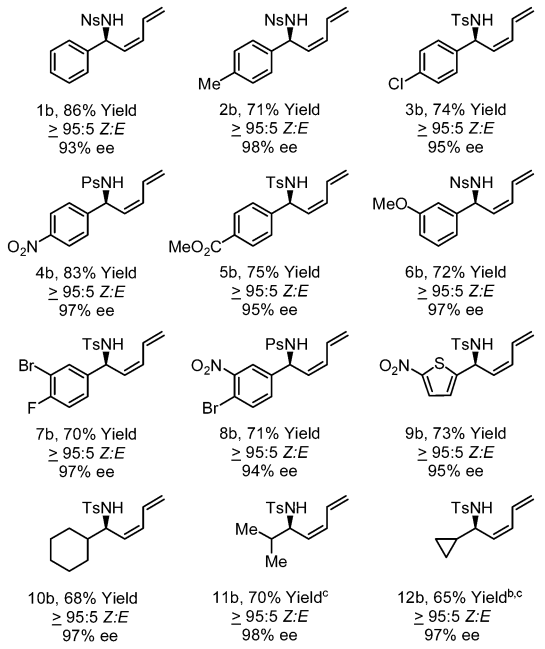
Table 1. Enantioselective Reductive Coupling of Acetylene to Aromatic and Aliphatic *N*-arylsulfonyl Aldimines[a]



1a, R = Ph, Ar = Ns
2a, R = *p*-MePh, Ar = Ns
3a, R = *p*-ClPh, Ar = Ts
4a, R = *p*-NO_2Ph, Ar = Ps
5a, R = *p*-CO_2MePh, Ar = Ts
6a, R = *m*-MeOPh, Ar = Ns
7a, R = *m*-Br, *p*-FPh, Ar = Ts
8a, R = *m*-NO_2, *p*-BrPh, Ar = Ps
9a, R = 5-NO_2Thienyl, Ar = Ts
10a, R = C_6H_{12}, Ar = Ts
11a, R = *i*-Pr, Ar = Ts
12a, R = C_3H_5, Ar = Ts



(*S*)-Cl,MeO-BIPHEP



[a] Cited yields are of isolated material (Ps = benzenesulfonyl, Ts = *p*-toluenesulfonyl, Ns = *p*-nitrophenylsulfonyl). The indicated data represent the average of two runs on 0.2 mmol scale. Best results are obtained using an apparatus in which mixtures of hydrogen and acetylene are delivered from a gas bag via cannula. See Supporting Information for detailed experimental procedures. [b] Reaction was performed at ambient temperature. [c] Reaction was performed using 600 mol % of Na_2SO_4.

Initial studies involved exposure of *N*-(*p*-nitrophenylsulfonyl) aldimine **1a** to ambient pressures of acetylene and hydrogen gas at 45 °C using conditions developed for the related aldehyde couplings as the starting point for optimization.[16b] Employing BIHPEP as a ligand, various cationic rhodium precatalysts, $[Rh(cod)_2]X$, where X = OTf, BF_4, SbF_6, and "BARF" (BARF = $B(3,5\text{-}(CF_3)_2C_6H_3)_4$) were screened. This assay reveals that the SbF_6 and BARF salts are equally effective for reactions conducted in 1,2-dichloroethane solvent. However, since $[Rh(cod)_2]$BARF exhibits greater solubility in toluene, which was later identified as the optimal reaction solvent, it was chosen as the standard precatalyst.

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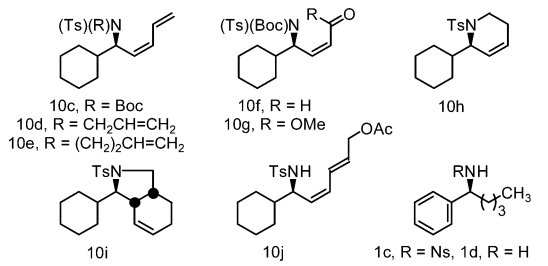
Table 2. Elaboration of Coupling Products **1b** and **10b**[a]



[a] Cited yields are of isolated material **10c**: **10b**, Boc_2O, DMAP, MeCN, 25 °C, 95%. **10d**: **10b**, $BrCH_2CH{=}CH_2$, K_2CO_3, DMF, 25 °C, 99%. **10e**: **10b**, $Br(CH_2)_2CH{=}CH_2$, Cs_2CO_3, DMF, 70 °C, 84%. **10f**: **10c**, OsO_4, $NaIO_4$, THF−H_2O, 25 °C, 83%. **10g**: **10f**, MnO_2, NaCN, MeOH, 25 °C, 77%. **10h**: Grubbs-II, **10e**, DCM, 40 °C, 94%. **10i**: $Rh(COD)SbF_6$, PPh_3, **10d**, $PhCH_3$, 80 °C, 87%, 9:1 dr. **10j**: $(IMes)(Cy_3P)(Cl)_2Ru{=}CHPh$, *cis*-1,4-diacetoxybutene, DCM, 25 °C, 72% (6:1, *E*/*Z*). **1c**: H_2 (1 atm), $[Ir(Cy_3P)(cod)(pyr)]PF_6$, **1b**, DCM, 25 °C, 99%. **1d**: PhSH, K_2CO_3, **1c**, MeCN, 45 °C, 66%. See Supporting Information for experimental procedures.

Through a systematic assay of Brønsted acids, *m*-nitrobenzoic acid was identified as the optimal cocatalyst. A potential role for the Brønsted acid additive has been outlined for analogous couplings of acetylene to carbonyl compounds.[16b] The collective data suggest that Brønsted acids facilitate coupling by circumventing highly energetic 4-centered transition structures for σ-bond metathesis, as required for direct hydrogenolysis of metallacyclic intermediates, with 6-centered transition structures for hydrogenolysis of rhodium carboxylates derived upon protonolysis of the metallacycle.[15] Gratifyingly, the first chiral ligands screened, (*S*)-MeO-BIPHEP and (*S*)-Cl,MeO-BIPHEP, were both found to promote equally favorable levels of asymmetric induction. Selection of the latter was arbitrary.

Under these optimized conditions aromatic and aliphatic *N*-arylsulfonyl aldimines **1a**−**12a** were found to engage in highly enantioselective couplings to gaseous acetylene to furnish (*Z*)-dienyl allylic amines **1b**−**12b** as single geometrical isomers (Table 1). Benzaldimines possessing ortho substitution do not react efficiently. The choice of arylsulfonyl protecting group was made in response to issues of solubility and reactivity. If the *p*-toluenesulfonyl derivative was not sufficiently reactive, the *p*-nitrophenylsulfonyl was used. If the *p*-toluenesulfonyl derivative was not sufficiently soluble, the benzenesulfonyl derivative was used. Increased yields are observed upon introduction of Na_2SO_4, which presumably mitigates imine hydrolysis and the production of catalytically inactive hydroxy-bridged dimers of rhodium. To illustrate the unique features of the (*Z*)-dienyl side chain, adducts **1b** and **10b** were selectively transformed to **1c**, **1d**, and **10c**−**j**, which embody a variety of useful functional group arrays (Table 2). The absolute stereochemical assignment of coupling products **1b**−**12b** is based upon correlation of **1d** to an authentic sample of optically enriched material, as described in the Supporting Information.

In summary, we report the first highly enantioselective catalytic vinylation of aldimines.[13c,14,16a] The present protocol does not employ preformed organometallic reagents nor does it generate stoichiometric byproducts. Reductions employing hydrogen as terminal reductant, termed "hydrogenations," are used extensively in academia and industry. As further demonstrated by the results herein, C−C bond formations employing hydrogen as terminal reductant, termed "C−C bond forming hydrogenations," evoke boundless possibilities in terms of innovative methodologies and applications to arise in the future.

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Supporting Information Available: Experimental procedures, spectral data for all new compounds, and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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