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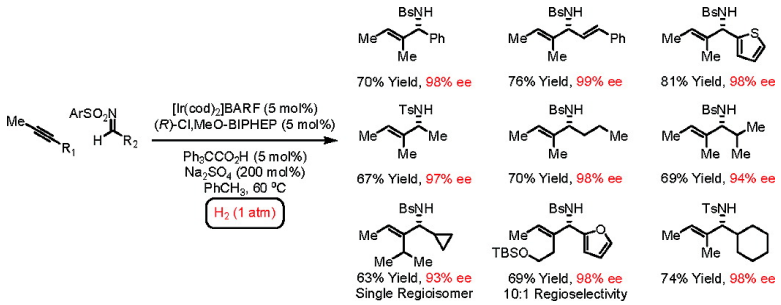

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Enantioselective Iridium-Catalyzed Imine Vinylation: Optically Enriched Allylic Amines via Alkyne−Imine Reductive Coupling Mediated by Hydrogen

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α-Chiral allylic amines are valuable synthetic intermediates en route to therapeutic agents and bioactive natural products.[1] Highly effective protocols for their preparation based on metal-catalyzed asymmetric allylic substitution have been devised.[2−4] An alternate approach to α-chiral allylic amines, though far less advanced, resides in catalytic asymmetric imine vinylation.[5−10] The catalyzed addition of vinylzirconocenes to imines is described by Taguchi and Wipf,[5,6] yet enantioselective variants remain undeveloped. Following alkyne−carbonyl reductive couplings developed by Montgomery,[7] enantioselective (51−89% ee) nickel-catalyzed three-component couplings of alkynes, imines, and triethylborane were reported by Jamison.[8] Finally, asymmetric alkyne−imine reductive couplings promoted by stoichiometric quantities of low-valent zirconocene complexes modified by Brintzinger's ligand are described by Buchwald.[10]

We have demonstrated that organometallics arising transiently in the course of catalytic hydrogenation may be diverted to products of C−C coupling, thus providing a byproduct-free alternative to the use of preformed organometallic reagents in diverse C═X (X = O, NR) addition processes.[11,12] In the case of hydrogenative alkyne−imine coupling, conjugated enynes and diynes were found to combine with ethyl (*N*-sulfinyl)iminoacetates[12a] to furnish α-amino esters, and gaseous acetylene was found to combine with *N*-arylsulfonyl aldimines[12b] to furnish (*Z*)-butadienyl allylic amines. These asymmetric imine additions employ rhodium catalysts and provide access to dienyl allylic amines. Attempted vinylation employing 1,2-dialkylsubstituted alkynes using rhodium catalysts led to conventional alkyne hydrogenation.

Recently, we found that unactivated 1,2-dialkylsubstituted alkynes couple to α-ketoesters[12c] and *N*-arylsulfonyl imines[12d] under the conditions of iridium-catalyzed hydrogenation.[13] The ability of iridium-based catalysts to activate nonconjugated alkynes may be due to the fact that iridium appears to be a stronger π-donor than rhodium,[14,15] which may facilitate alkyne−C═X (X = O, NR) oxidative coupling. In this account, we demonstrate that hydrogenation of simple nonconjugated alkynes in the presence of *N*-arylsulfonyl aldimines using chirally modified iridium catalysts enables formation of trisubstituted allylic amines with complete levels of *E*:*Z* selectivity (≥99:1) and exceptional levels of enantioselection (92−99% ee).

Initial studies focused on the coupling of 2-butyne to aldimine **8a** using chirally modified iridium catalysts prepared in situ from [Ir(cod)$_2$]BARF. Gratifyingly, using (*R*)-Cl,MeO-BIPHEP as ligand, excellent levels of asymmetric induction were observed. As indicated in Table 1, 2-butyne couples to aromatic imines (**1b**−**6b**), α,β-unsaturated imines (**7b**), heteroaromatic imines (**8b**, **9b**), and aliphatic imines (**10b**−**16b**) with consistently outstanding levels of asymmetric induction (92−99% ee). Nonsymmetric alkynes participate in highly regio- and enantioselective coupling. 2-Hexyne couples to imines **8a** and **12a** to furnish adducts **17b** and **18b**. Coupling proximal to the more highly substituted alkyne terminus is observed with a 10:1 regioisomeric ratio in each case. For

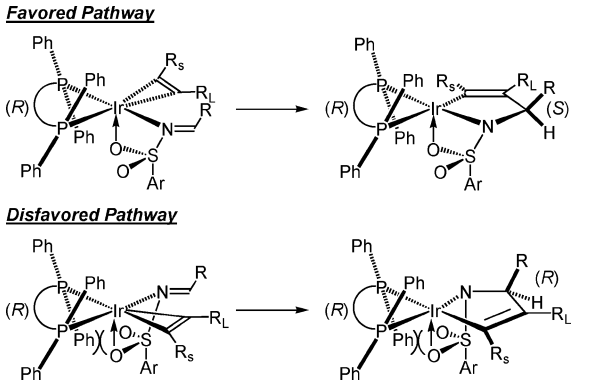

Figure 1. Stereochemical models accounting for the observed sense of absolute stereoinduction.

4-methyl-2-pentyne, wherein steric differentiation of the propargylic positions is more pronounced, adducts **19b** and **20b** are produced as single regioisomers, again in highly optically enriched form. Finally, 1-(*tert*-butyldimethylsilyloxy)-3-pentyne couples to imine **8a** to furnish adduct **21b** as a 10:1 ratio of regioisomers. As exemplified by the coupling of 4-methyl-2-pentyne to aldimine **8a**, uniformly high levels of asymmetric induction are observed across a range of commercially available chiral atropisomeric chelating phosphines: (*R*)-Cl,MeO-BIPHEP, 80% yield, 97% ee; (*R*)-BIPHEMP, 80% yield, 97% ee; (*R*)-SOLPHOS, 67% yield, 97% ee; (*R*)-SYNPHOS, 76% yield, 97% ee; (*R*)-cyclohexyl-SONIPHOS, 77% yield, 97% ee.

The absolute stereochemical assignment of allylic amines **1b**−**21b** is based upon single-crystal X-ray diffraction analysis of **22b**, the *p*-bromophenylsulfonyl analogue of adduct **1b**, using the anomalous dispersion method. A plausible stereochemical model accounting for the observed sense of absolute stereoinduction and regioselectivity is indicated in Figure 1. The alkyne and imine are complexed at adjacent coordination sites by iridium(I), which possesses a square planar geometry. As explained by the Dewar−Chatt−Duncanson model,[16] and as borne out by single-crystal X-ray diffraction analysis of iridium(I) alkyne complexes,[15] coordination of the alkyne should confer iridacyclopropene character. Complexation of the *N*-arylsulfonyl imine is anticipated to occur in a bidentate fashion, wherein one of the sulfoxide oxygens is bound at the apical coordination site of iridium.[17] Enantiodetermining insertion of the imine into the iridium−carbon bond of the iridacyclopropene delivers the indicated aza-iridacyclopentene, which is converted to the allylic amine as previously described.[12d] Whereas nonbonded interactions of the arylsulfonyl moiety with the phenyl groups of (*R*)-Cl,MeO-BIPHEP disfavor insertion onto the *pro*-(*R*) imine π-face, such interactions are absent in the alternate mode of approach involving insertion into the *pro*-(*S*) imine π-face. Regioselective coupling requires the larger propargylic position of the alkyne to reside distal to the metal center at the stage of the alkyne complex and incipient metallacycle.

To conclude, we report the first asymmetric iridium-catalyzed C−C bond forming hydrogenations, which, in turn, have enabled

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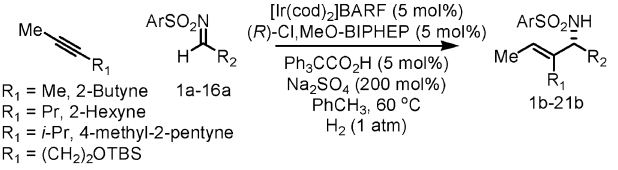
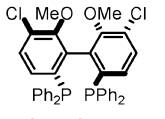
Table 1. Enantioselective Hydrogenative Coupling of Alkynes to Aromatic and Aliphatic *N*-Arylsulfonyl Aldimines[a]

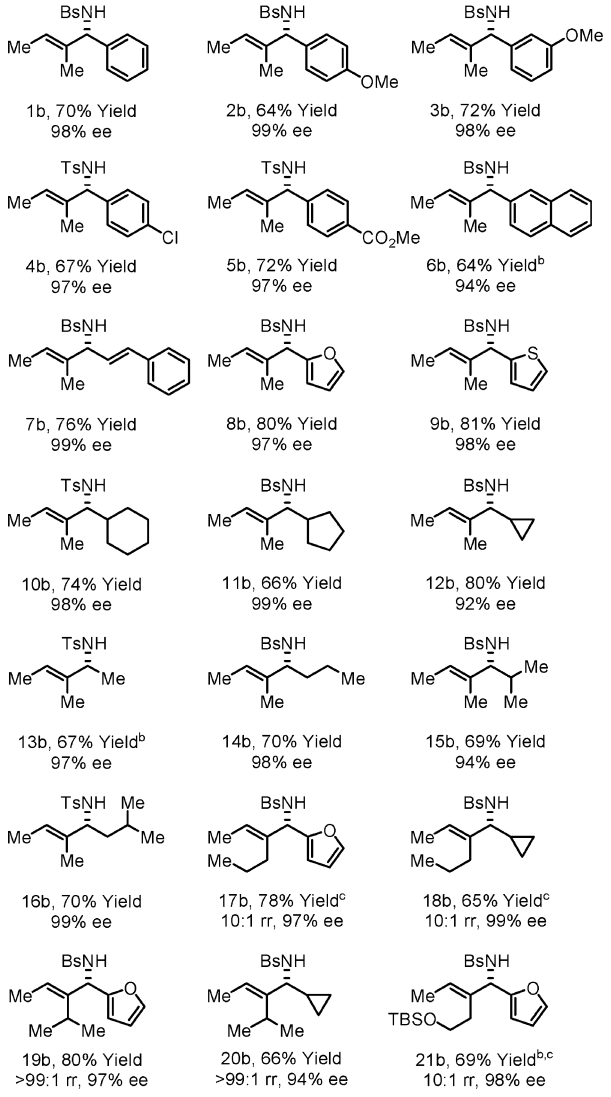


R_1 = Me, 2-Butyne
R_1 = Pr, 2-Hexyne
R_1 = *i*-Pr, 4-methyl-2-pentyne
R_1 = $(CH_2)_2OTBS$

1a, R = Ph, Ar = Bs
2a, R = *p*-MeOPh, Ar = Bs
3a, R = *m*-MeOPh, Ar = Bs
4a, R = *p*-ClPh, Ar = Ts
5a, R = *p*-CO_2MePh, Ar = Ts
6a, R = 2-Naphthyl, Ar = Bs
7a, R =HC=CHPh, Ar = Bs
8a, R = 2-Furyl, Ar = Bs
9a, R = 2-Thienyl, Ar = Bs
10a, R = *c*-Hexyl, Ar = Ts
11a, R = *c*-Pentyl, Ar = Bs
12a, R = *c*-Pr, Ar = Bs
13a, R = Me, Ar = Ts
14a, R = *n*-Bu, Ar = Bs
15a, R = *i*-Pr, Ar = Bs
16a, R = *i*-Bu, Ar = Ts



(*R*)-Cl,MeO-BIPHEP



[a] Cited yields are of isolated material (Bs = benzenesulfonyl, Ts = *p*-toluenesulfonyl). Enantiomeric excess was determined by chiral stationary phase HPLC analysis. See Supporting Information for detailed experimental procedures. [b] Benzene was used as solvent. [c] Reaction was conducted at 80 °C.

the first catalytic enantioselective alkyne−imine reductive couplings. By simply hydrogenating alkynes in the presence of *N*-arylsulfonyl imines using a chirally modified iridium catalyst, one obtains the corresponding allylic amines in highly optically enriched form without stoichiometric generation of byproducts. Future studies will focus on the development of related hydrogenative C−C coupling reactions, in particular those applicable to basic chemical feedstocks.

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Supporting Information Available: Experimental procedures and characterization data (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For reviews encompassing the synthesis of allylic amines, see: (a) Cheik, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, 685. (b) Laurent, A.; Mison, P.; Nafti, A.; Cheik, R. B.; Chaabouni, R. *J. Chem. Res. (S)* **1984**, 354. (c) Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689.

(2) For reviews encompassing enantioselective iridium-catalyzed allylic amination, see: (a) Miyabe, H.; Takemoto, Y. *Synlett* **2005**, 1641. (b) Takeuchi, R.; Kezuka, S. *Synthesis* **2006**, 3349. (c) For a seminal contribution, see: Hartwig, J. F.; Ohmura, T. *J. Am. Chem. Soc.* **2002**, *124*, 15164.

(3) For reviews encompassing enantioselective palladium-catalyzed allylation of N-nucleophiles, see: (a) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (b) Trost, B. M. *J. Org. Chem.* **2004**, *69*, 5813 and references cited therein.

(4) For chiral allylic amines via allylic trihaloacetimidate rearrangement, see: Overman, L. E.; Carpenter, N. E. *Org. React.* **2005**, *66*, 1.

(5) (a) Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **2003**, *44*, 923. (b) Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761.

(6) For reviews encompassing catalytic enantioselective aldehyde vinylation using organozinc reagents, see: (a) Wipf, P.; Kendall, C. *Chem.—Eur. J.* **2002**, *8*, 1778. (b) Wipf, P.; Nunes, R. L. *Tetrahedron* **2004**, *60*, 1269.

(7) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065.

(8) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2004**, *432*, 3941.

(9) For recent reviews encompassing catalytic enantioselective addition of nonstabilized carbanions to imines, see: (a) Vilaivan, T.; Bhanthumnavin, W.; Sritana-Anant, Y. *Curr. Org. Chem.* **2005**, *9*, 1315. (b) Friestad, G. K.; Mathies, A. K. *Tetrahedron* **2007**, *63*, 2541.

(10) Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 2321.

(11) For recent reviews encompassing hydrogen-mediated C−C coupling, see: (a) Ngai, M.-Y.; Krische, M. J. *J. Org. Chem.* **2007**, *72*, 1063. (b) Iida, H.; Krische, M. J. *Top. Curr. Chem.* **2007**, *279*, 77.

(12) (a) Kong, J.-R.; Cho, C.-W.; Krische, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 11269. (b) Skucas, E.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242. (c) Ngai, M.-Y.; Barchuk, A.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 280. (d) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8432.

(13) For reviews encompassing iridium-catalyzed hydrogenation, see: (a) Pfaltz, A.; Blankenstein, J.; Hilgraf, R.; Hörmann, E.; McIntynre, S.; Menges, F.; Schönleber, M.; Smidt, S. P.; Wustenberg, B.; Zimmerman, N. *Adv. Synth. Catal.* **2003**, *345*, 33. (b) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272. (c) Kaellstroem, K.; Munslow, I.; Andresson, P. G. *Chem.—Eur. J.* **2006**, *12*, 3194.

(14) π-Backbonding in the metal−alkyne complex, as described by the Dewar−Chatt−Duncanson model, may facilitate alkyne−C=X (X = O, NR) oxidative coupling by conferring nucleophilic character to the bound alkyne. Due to relativistic effects, iridium is a stronger π-donor than rhodium: $(Ph_3P)_2M(Cl)(CO)$, M = Ir, ν_{co} = 1965 cm^{-1}; M = Rh, ν_{co} = 1980 cm^{-1} (Vaska, L.; Peone, J. *Chem. Commun.* **1971**, 419). This may account for the ability of iridium-based catalysts to activate nonconjugated alkynes, which embody higher lying LUMOs. See also: Haynes, A.; McNish, J.; Pearson, J. M. *J. Organomet. Chem.* **1998**, *551*, 339. Grotjohn, D. B.; Collins, L. S. B.; Wolpert, M.; Bikzhanova, G. A.; Lo, H. C.; Combs, D.; Hubbard, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 8260.

(15) Alkyne complexation by iridium(I) results in substantial deviation from linearity, as revealed by single-crystal X-ray diffraction analysis: (a) Kirchner, R. M.; Ibers, J. A.; Saran, M. S.; King, R. B. *J. Am. Chem. Soc.* **1973**, *95*, 1095. (b) Calabrese, J. C.; Roe, D. C.; Thorn, D. L.; Tulip, T. H. *Organometallics* **1984**, *3*, 1223. (c) Rappoli, B. J.; Churchill, M. R.; Janik, T. S.; Rees, W. M.; Atwood, J. D. *J. Am. Chem. Soc.* **1987**, *109*, 5145. (d) Rees, W. M.; Churchill, M. R.; Fettinger, J. C.; Atwood, J. D. *J. Organomet. Chem.* **1987**, *319*, 411. (e) Marinelli, G.; Streib, W. E.; Huffman, J. C.; Caulton, K. G.; Gagne, M. R.; Takats, J.; Dartiguenave, M.; Chardon, C.; Jackson, S. A.; Eisenstein, O. *Polyhedron* **1990**, *9*, 1867.

(16) (a) Dewar, M. J. S. *Bull. Soc. Chim. Fr.* **1951**, *18*, C71. (b) Chatt, J.; Duncanson, L. A. *J. Chem. Soc.* **1953**, 2939. (c) Dewar, M. J. S.; Ford, G. P. *J. Am. Chem. Soc.* **1979**, *101*, 783.

(17) The bidentate κ^2-mode of binding has been observed by single-crystal X-ray diffraction analysis for a related palladium *N*-arylsulfonamidate complex: Fujita, K.-I.; Yamashita, M.; Puschmann, F.; Martinez Alvarez-Flacon, M.; Incarvito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9044.

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