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Branch-Selective Reductive Coupling of 2-Vinyl Pyridines and Imines *via* Rhodium Catalyzed C-C Bond Forming Hydrogenation

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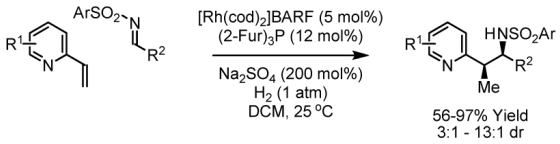
Nitrogen-bearing heterocycles are among the most prevalent substructures found in approved therapeutic agents.1 Among all heterocycles, pyridines most often appear in pharmaceutically active compounds.[2] Modular methods for the catalytic coupling of pyridines and higher azines are largely limited to metal catalyzed cross-coupling processes (Suzuki, Stille, Kumada-Corriu, Negishi and Hiyama coupling reactions) and *ortho*-C-H activation initiated biaryl couplings[3] and insertions of olefins or alkynes.[4] A notable exception involves the rhodium catalyzed coupling of 2-vinyl azines[5a] and 2-alkynyl azines5b,c to organoboron reagents, which result in C-C coupling at the β-position of the vinyl or alkynyl moiety, respectively. Vinylpyridines also participate in rhodium catalyzed couplings to olefins, typically initiated *via* C-H insertion, again resulting in functionalization at the β-position of the vinyl moiety.[6] Despite the significance of azine substructures, there are remarkably few methods available for catalytic C-C coupling of azine-containing building blocks.[7,8,9]

We have found that diverse π-unsaturated reactants engage in C-C coupling under the conditions of catalytic hydrogenation.[10] For example, rhodium catalyzed hydrogenation of vinyl arenes in the presence of anhydrides was found to deliver formal products of acyl substitution with complete branched regioselectivity.[11] Additionally, activated olefins in the form of conjugated enones engage in highly diastereo- and enantioselective reductive aldol and Mannich couplings when hydrogenated in the presence of aldehydes and imines.[12,13] Here, we report the first catalytic reductive C-C couplings of vinyl azines. Specifically, we find that catalytic hydrogenation of 2-vinyl azines in the presence of *N*-arylsulfonyl imines results in regio- and diastereoselective reductive coupling to furnish branched products of imine addition.



Initial studies focused on the hydrogenative coupling of 6-bromo-2-vinylpyridine **1a** and *N*-*ortho*-toluenesulfonyl aldimine **2a**. After extensive optimization, it was found that hydrogenation of 6-bromo-2-vinylpyridine **1a** and imine **2a** at ambient temperature and pressure employing a cationic rhodium catalyst ligated by $(2\text{-Fur})_3P$[14] leads to formation of the reductive coupling product **3a** in 97% isolated yield with complete branched regioselectivity and modest *syn*-diastereoselectivity (3:1 dr). Added Na_2SO_4 was found to suppress imine hydrolysis. To evaluate scope, these conditions were applied to aromatic imines **2a-2d**, heteroaromatic imines **2e** and **2f**, α,β-unsaturated imine **2g**, and aliphatic imines

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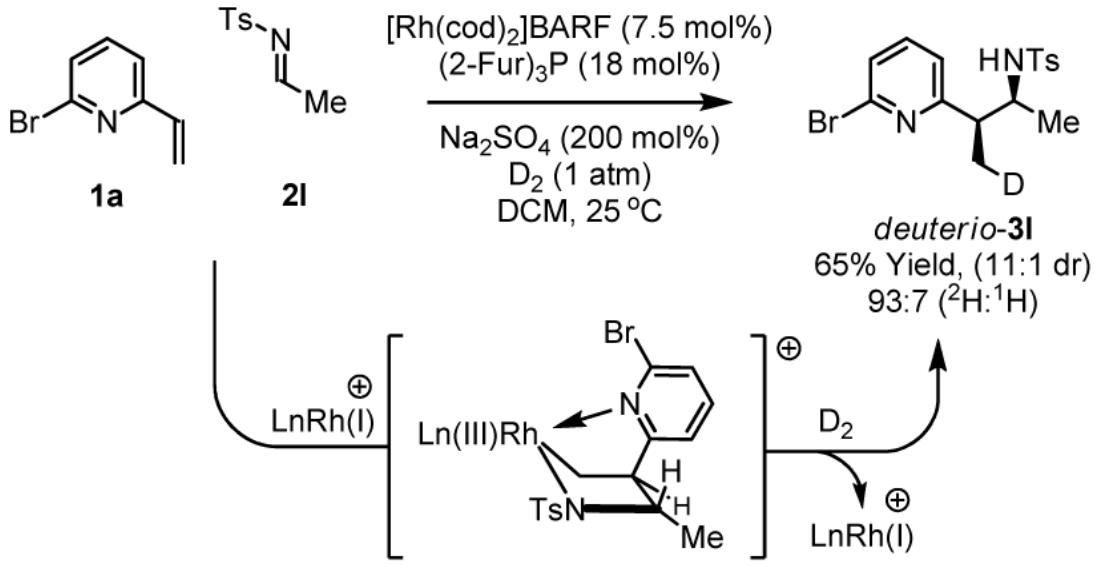
Supporting information available: Experimental procedures and spectral data for new compounds. Single crystal X-ray diffraction data for compounds **3a** and **3f**. This material is available free of charge *via* the internet at http://pubs.acs.org.

2h-2l, which were all found to couple efficiently to provide adducts **3a-3l**, respectively, in good to excellent yield with complete branched regioselectivity and modest to good levels of *syn*-diastereoselectivity (3:1 – 13:1 dr).[15] The stereochemical assignment of adducts **3a** and **3f** were confirmed by single crystal X-ray diffraction analysis of diastereomerically pure samples. The stereochemical assignment of the remaining adducts are made in analogy to **3a** and **3f** (Table 1).

The scope of the vinyl azine partner was evaluated next. Whereas the parent 2-vinylpyridine does not participate in the coupling, presumably due to strong coordination at nitrogen, 6-substituted-2-vinyl pyridines **1b-1d** couple efficiently to (hetero)aromatic and aliphatic imines **2f**, **2i** and **2k** (Table 2). Higher azines, for example 2,3-diphenyl-5-vinylpyrazine couple in diminished yield under standard conditions.[16] However, as exemplified by the coupling of 8-benzyloxy-2-vinylquinoline **1e** to imines **2e**, **2f**, **2i** and **2k**, fused vinyl azines are effective coupling partners.

To gain insight into the catalytic mechanism, the reductive coupling of 6-bromo-2-vinylpyridine **1a** to imine **2l** was performed under an atmosphere of elemental deuterium (99.6% purity). As corroborated by ^{1}H and ^{2}H NMR spectroscopy, the branched adduct *deuterio*-**3l** incorporates deuterium exclusively at the former β-position of the vinyl moiety (93:7, ^{2}H:^{1}H). Deuterium incorporated at nitrogen is lost through exchange during chromatographic isolation. The results of isotopic labeling are consistent with a mechanism in which oxidative coupling of vinyl azine **1a** and imine **2l** delivers the indicated cationic aza-rhodacyclopentane, which upon deuteriolytic cleavage of the metallacycle[17] releases *deuterio*-**3l** and regenerates cationic rhodium(I) to close the catalytic cycle. Mechanisms involving vinyl azine hydrometallation to form nucleophilic benzylrhodium intermediates cannot be excluded on the basis of this experiment.



In summary, we report the first metal catalyzed reductive C-C coupling of vinyl azines. By simply hydrogenating vinyl azines **1a-1e** in the presence of *N*-arylsulfonyl aldimines **2a-2l**, one gains access to the branched products of reductive coupling **3a-3v**, which appear as single regioisomers. Using a rhodium catalyst ligated by tri-2-furylphosphine, modest to high levels of *syn*-diastereoselectivity may be achieved. Future studies will focus on the development of enantioselective variants of this process and related vinyl azine-carbonyl reductive couplings.

Ultimately, through hydrogenative C-C coupling, byproduct-free protocols for the coupling of diverse unsaturated feedstocks will be achieved.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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(15). In the rhodium catalyzed hydrogenative coupling of vinyl ketones to aldehydes and imines (references 12e-h, 13), Fur_3P enforces high levels of *syn*-diastereoselectivity. Given the structural homology of vinyl ketones and 2-vinyl azines, it is not surprising that analogous ligand effects are observed.

(16). Coupling of 2,3-diphenyl-5-vinylpyrazine to imine **2f** under standard conditions provides the branched adduct in 35% yield and 5:1 dr.

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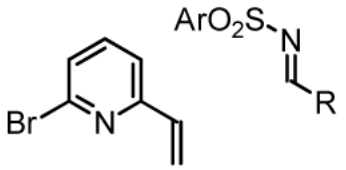
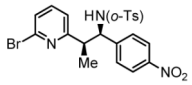
Table 1

Hydrogenative coupling of 6-bromo-2-vinylpyridine **1a** to *N*-arylsulfonyl aldimines **2a-2l**.

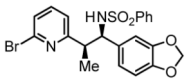


1a **2a-2l**

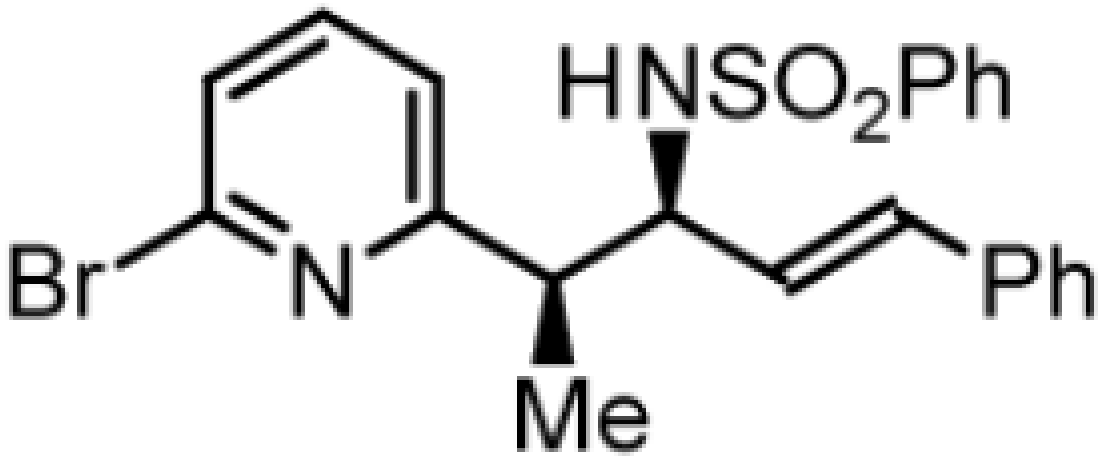
2a, R = *p*-NO_2Ph
2d, R = Piperonyl
2g, R = Cinnamyl
2j, R = CH_2OBn



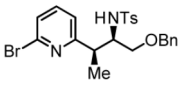
97% Yield
3:1 dr, **3a**



91% Yield
5:1 dr, **3d**



67% Yield
4:1 dr, **3g**



69% Yield
5:1 dr, **3j**

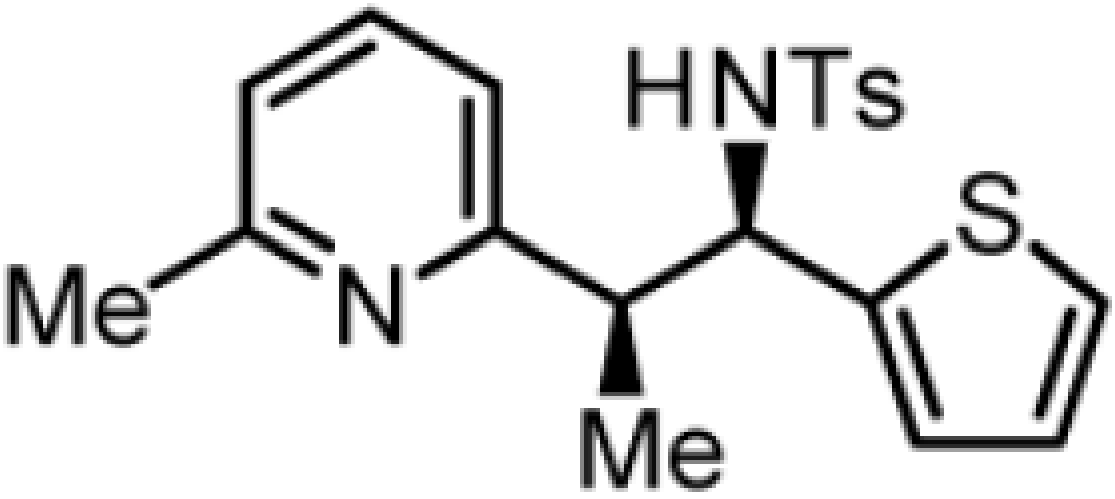
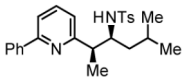
[a] Cited yields are of isolated diastereomeric mixtures. Standard conditions employ 3 equiv. of **1a** and 1 equiv. of imines **2a-2l**. See Supporting Information for details.

[b] Reaction was performed at 35 °C.

[c] Reaction was performed using 7.5 mol% $[Rh(cod)_2]BARF$ and 18 mol% $(2\text{-}Fur)_3P$.

Table 2

Hydrogenative coupling of vinyl azines **1b-1d** to *N*-toluenesulfonyl aldimines **2f, 2i** and **2k**.

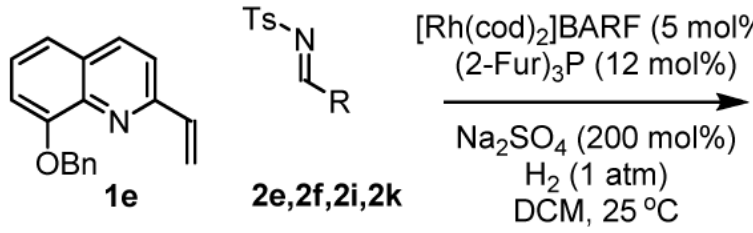
1b, R = Me
   70% Yield[b] 5:1 dr, **3m**
   80% Yield 4:1 dr, **3p**

[a] Cited yields are of isolated diastereomeric mixtures. Standard conditions employ 3 equiv. of **1b-1d** and 1 equiv. of imines **2f, 2i** and **2k**. See Supporting Information for further details.

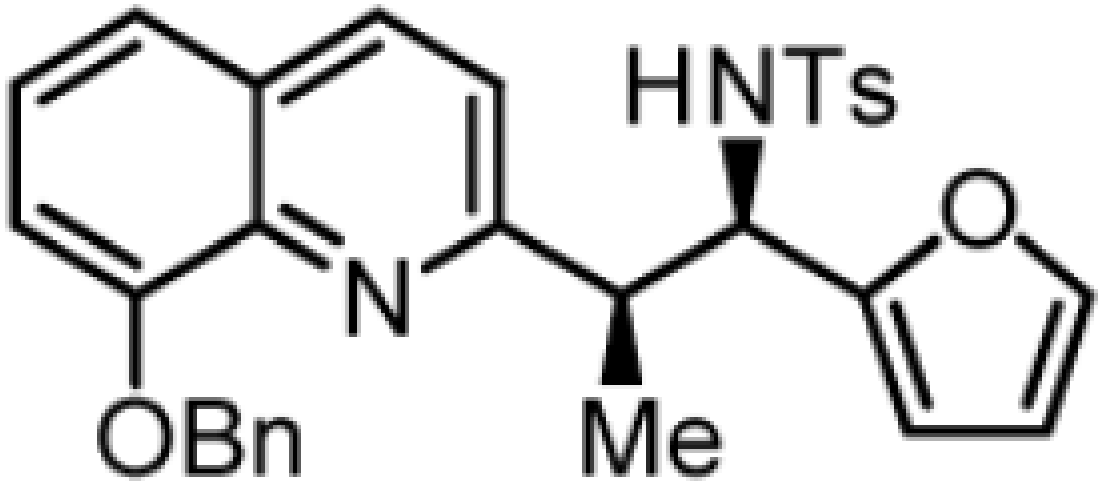
[b] Reaction was performed using 7.5 mol% $[Rh(cod)_2]BARF$ and 18 mol% (2-Fur)3P.

Table 3

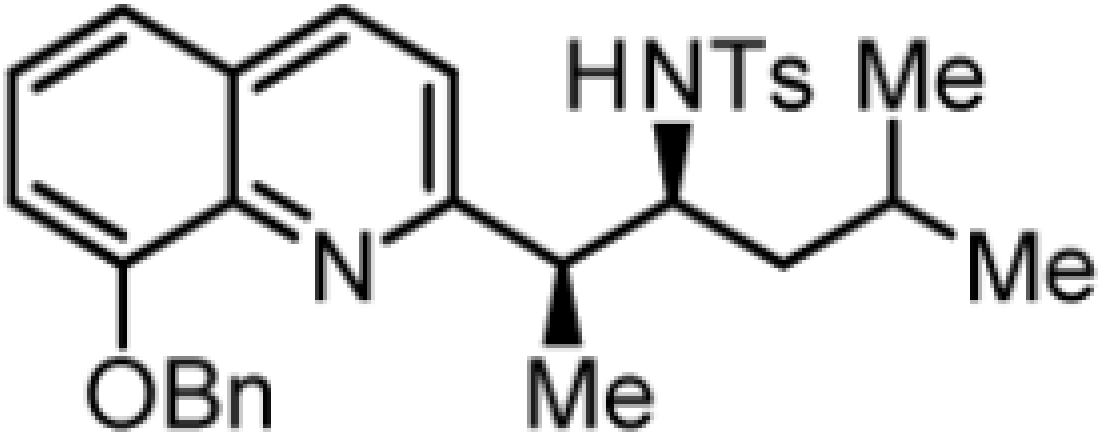
Hydrogenative coupling of vinyl azine **1e** to *N*-toluenesulfonyl aldimines **2e, 2f, 2i** and **2k**.[a]



1e **2e,2f,2i,2k**



94% Yield
3:1 dr, **3s**



68% Yield
8:1 dr, **3u**

[a] Cited yields are of isolated material. Standard conditions employ 3 equivalents of 6-bromo-2-vinylpyridine and 1 equivalent of imine. See Supporting Information for further details.