ORGANIC LETTERS

2011
Vol. 13, No. 24
6464–6467

# Stereoselective Vinylation of Aryl *N*-(2-Pyridylsulfonyl) Aldimines with 1-Alkenyl-1,1-heterobimetallic Reagents

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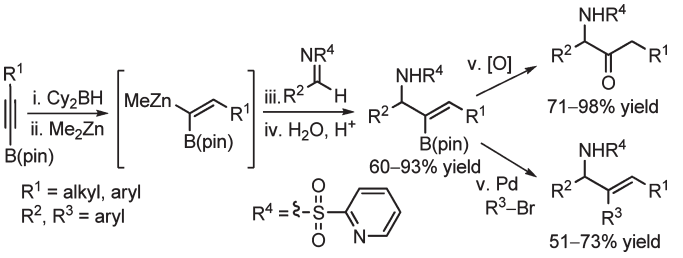
**Received October 14, 2011**

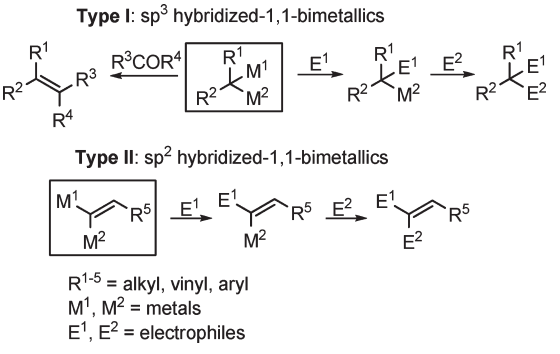
## ABSTRACT




**Vinylation of aryl *N*-(2-pyridylsulfonyl) aldimines with versatile 1-alkenyl-1,1-borozinc heterobimetallic reagents is disclosed. In situ hydroboration of air-stable B(pin)-alkynes followed by chemoselective transmetalation with dimethylzinc and addition to aldimines provides B(pin)-substituted allylic amines in 53−93% yield in a one-pot procedure. The addition step can be followed by either B−C bond oxidation to provide α-amino ketones (71−98% yield) or Suzuki cross-coupling to furnish trisubstituted 2-arylated (*E*)-allylic amines (51−73% yield).**

Highly stereoselective construction of C−C double bonds remains a challenge in organic synthesis.[1] In this regard, $sp^3$ and $sp^2$ hybridized heterobimetallic reagents of type I and II (Scheme 1) are potentially useful intermediates, because each metal−carbon bond can be chemoselectively exploited in C−C bond forming reactions.[2−4,6] Furthermore, these versatile heterobimetallic reagents can be employed in tandem reactions, minimizing isolation and purification of intermediates.[5] These attributes allow for rapid development of molecular complexity from simple building blocks.

**Scheme 1.** 1,1-Heterobimetallics in Organic Synthesis




As part of our program in developing stereoselective C−C bond forming reactions,[6] we have reported the generation of 1-alkenyl-1,1-heterobimetallic reagents

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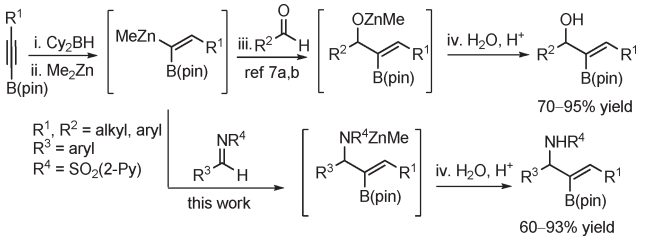
10.1021/ol202766g 
**Published on Web 11/15/2011**

based on boron and zinc from readily available, air-stable B(pin)-substituted alkynes (Scheme 2).[7a] Thus, regioselective hydroboration of B(pin)-alkynes generates the 1,1-bis (boro) intermediates.[7a,8] Chemoselective transmetalation of the more reactive vinyl-$BCy_2$ bond generates 1-alkenyl-1,1- heterobimetallic reagents. The difference in reactivity between Zn−C vs B−C bonds allows for selective reaction at the Zn−C bond with aldehydes to yield B(pin)-substituted allylic zinc alkoxide intermediates. The alkoxide intermediates were then employed in various tandem reactions to form an array of compounds such as B(pin)-substituted allylic alcohols,[7a−c] α-hydroxy ketones,[7a] trisubstituted (*E*)-allylic alcohols,[7a] B(pin)-substituted cyclopropyl alcohols,[7b] and B(pin)-substituted allylic acetates.[7d]

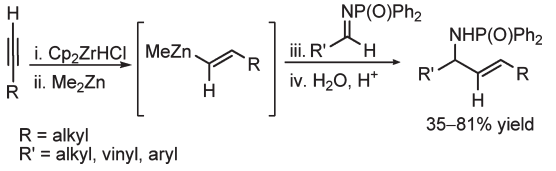
**Scheme 2.** Generation of 1-Alkenyl-1,1-heterobimetallics of Boron/Zinc and Additions to Electrophiles




Herein, we report the addition of alkenyl-1,1- heterobimetallic reagents to *N*-(2-pyridylsulfonyl) aldimines to furnish B(pin)-substituted allylic amines (Scheme 2, lower part). The addition can be followed by oxidation of the B−C bond to provide α-aminoketones or by Suzuki cross-coupling to provide densely functionalized trisubstituted (*E*)-allylic amines.

Allylic amines[9] are important pharmacophores that can exhibit significant biological properties. Examples include Acrivastine (Semprex),[10] Flunarizine,[11] and several GABA uptake inhibitors.[12] As a result, additions to imines have attracted considerable attention. For example, Wipf and co-workers reported the addition of vinylzinc reagents to aldimines activated with a diphenylphosphinoyl moiety (Scheme 3).[13] Carretero[14] and co-workers demonstrated that the reactivity of *N*-sulfonyl imines could be increased in the presence of an appropriately positioned heteroaryl group. Using this strategy, they developed the alkylation of aryl *N*-(2-pyridylsulfonyl) aldimines with organozinc halides.[14b] The Carretero and Toru groups both have utilized the *N*-pyridylsulfonyl as a novel stereocontrol element in enantioselective Mannich-type reactions with silyl enol ethers in the presence of chiral copper catalysts.[15] Various related nucleophilic reagents, such as dialkyl zinc,[5,16,17] alkynylzinc,[5,18] diethylaluminium cyanide,[19] and Danishefsky's diene,[20] have also been investigated in imine addition reactions to yield the desired amines.

**Scheme 3.** Wipf's Vinylation of Aryl Diphenylphosphinoyl Imines via Vinylzinc Reagents




Our first task in the addition of bimetallics to imines was to find a suitable imine activating group. The bimetallic reagent was generated and allowed to react with activated imines at −18 °C (Table 1). *N*-Tosylimines gave a trace addition product with our alkenyl heterobimetallic reagents (entry 1). Rather, a significant amount of reduction product was isolated. The *N*-Boc imine behaved similarly, failing to furnish the desired amine (entry 2). When the activating group was changed to diphenylphosphinoyl, less than 30% of the allylic amine was isolated. Gratifyingly, the bimetallic addition to *N*-pyridyl sulfonyl imine occurred smoothly in 73% yield in toluene at −18 °C to furnish the desired product (entry 4). The addition was then optimized with the *N*-pyridyl sulfonyl imines. Switching the solvent from toluene to dicholoromethane improved the yields slightly (entry 4 vs 7), while, in THF, almost no product was formed (entry 5). Dimethylzinc performed better than diethylzinc (entry 7 vs 9). Increasing the reaction temperature from −18 to −10 °C led to a diminished yield (entry 6 vs 7). With the optimized conditions in entry 7, the scope of the reaction was examined.

Aryl aldimines with electron-donating or -withdrawing groups were good substrates, providing the B(pin)

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(19) Nakamaru, S.; Sato, N.; Sugimoto, M.; Toru, T. *Tetrahedron: Asymmetry* **2004**, *15*, 1513.

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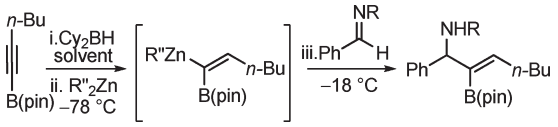
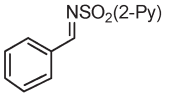
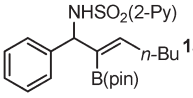
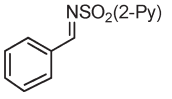
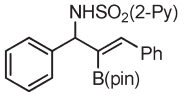
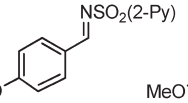
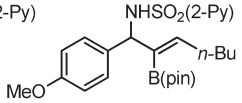
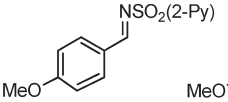
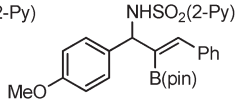
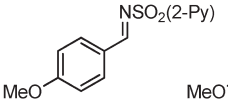
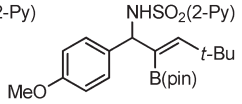
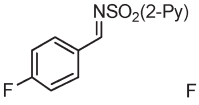
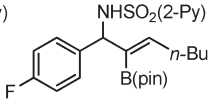
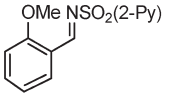
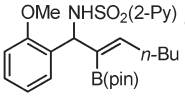
**Table 1.** Optimization of the Addition of Alkenyl-1, 1-heterobimetallics to *N*-Pyridyl Sulfonyl Imines




| entry | $R_2''Zn$ | solvent | R | yield (%)[a] |
|---|---|---|---|---|
| 1 | $Me_2Zn$ | toluene | $SO_2Tol$ | trace |
| 2 | $Me_2Zn$ | toluene | Boc | trace |
| 3 | $Me_2Zn$ | toluene | $P(O)Ph_2$ | <30 |
| 4 | $Me_2Zn$ | toluene | $SO_2$(2-Py) | 73 |
| 5 | $Me_2Zn$ | THF | $SO_2$(2-Py) | trace |
| 6 | $Me_2Zn$ | $CH_2Cl_2$ | $SO_2$(2-Py) | 68[b] |
| 7 | $Me_2Zn$ | $CH_2Cl_2$ | $SO_2$(2-Py) | 80 |
| 8 | $Et_2Zn$ | toluene | $SO_2$(2-Py) | 64 |
| 9 | $Et_2Zn$ | $CH_2Cl_2$ | $SO_2$(2-Py) | 65 |

[a] Isolated yields. [b] Reaction performed at −10 °C.

**Table 2.** Addition of Alkenyl-1,1-hetrobimetallics to *N*-Pyridyl Sulfonyl Imines

| entry | borane | imine | allylic amines | | yield (%)[a] |
|---|---|---|---|---|---|
| 1 |  |  |  | **1a** | 80 |
| 2 |  |  |  | **1b** | 68 |
| 3 |  |  |  | **1c** | 87 |
| 4 |  |  |  | **1d** | 93 |
| 5 |  |  |  | **1e** | 60 |
| 6 |  |  |  | **1f** | 70 |
| 7 |  |  |  | **1g** | 53 |

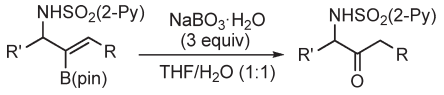
[a] Isolated yields.

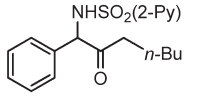
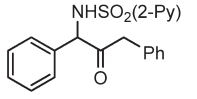
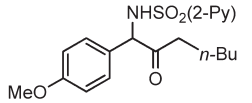
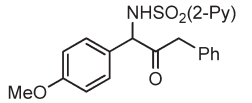
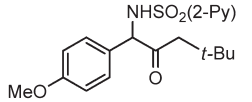
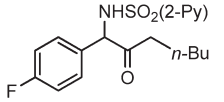
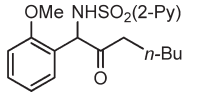
substituted allylic amines in 53−93% yield (Table 2). The air-stable B(pin)-substituted alkynes can contain aromatic or aliphatic substituents (R = aryl, alkyl). Even the bulky *tert*-butyl-substituted B(pin) alkyne underwent addition to generate the corresponding allylic amine in 60% yield (entry 5). Substitution at the ortho position of the aldimine resulted in a slightly lower yield (entry 7 vs 3−5).

Having established vinylation of aldimines with our heterobimetallics, we sought to examine tandem reactions involving the B−C bond. Two such reactions are B−C bond oxidation and Suzuki cross-coupling.

We envisioned that oxidation of the 2-B(pin)-substituted allylic amines would provide access to valuable α-amino ketones, which have important biological activity.[21] In the presence of $NaBO_3 \cdot H_2O$[22] in THF/$H_2O$ (1:1) at rt, B(pin)-substituted allylic amines were smoothly oxidized to the corresponding α-amino ketones in 71−98% yield (Table 3).

**Table 3.** Oxidation of Allylic Amines to α-Amino Ketones




| entry | allylic amines | amino ketones | | yield (%)[a] |
|---|---|---|---|---|
| 1 | **1a** |  | **2a** | 80 |
| 2 | **1b** |  | **2b** | 75 |
| 3 | **1c** |  | **2c** | 96 |
| 4 | **1d** |  | **2d** | 98 |
| 5 | **1e** |  | **2e** | 87 |
| 6 | **1f** |  | **2f** | 71 |
| 7 | **1g** |  | **2g** | 87 |

[a] Isolated yields.

(21) (a) Hanada, M.; Sugawara, K.; Koko, K.; Toda, S.; Nishiyama, Y.; Tomita, K.; Yamamoto, H.; Konishi, M.; Oki, T. *J. Antibiot.* **1992**, *45*, 1746. (b) Soaresa, C. O.; Alvesa, M. J. M.; Becharaa, E. J. H. *Free Radic. Med.* **2011**, *50*, 1760.

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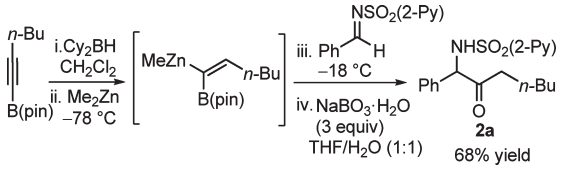
**Scheme 4.** Tandem Addition/B−C Bond Oxidation To Yield α-Amino Ketone **2a**




The addition/oxidation reaction can also be executed in a tandem fashion. Thus, after completion of the bimetallic addition to the aldimine, the reaction mixture was subjected to $NaBO_3 \cdot H_2O$ to provide the α-amino ketone in 68% yield in one pot (Scheme 4).

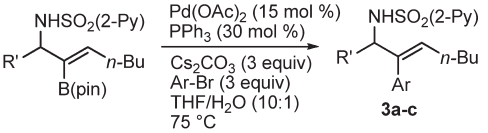
We next utilized the B−C bond in Suzuki cross-coupling reactions. In the presence of $Pd(OAc)_2$ (15 mol %), $PPh_3$ (30 mol %), $Cs_2CO_3$ (3 equiv), and aryl bromide (3 equiv) in $THF/H_2O$ (10:1) at 75 °C, the B(pin)-substituted allylic amines smoothly underwent cross-coupling to furnish the 2-arylated trisubstituted (*E*)-allylic amines in 51−73% yield (Scheme 5). No (*Z*)-double bond isomers were observed in these reactions.

Although the 2-pyridyl sulfonyl group is essential for the addition step, its removal is important for applications of the products. The 2-pyridyl sulfonyl group was readily cleaved on treatment of **1a** with magnesium in MeOH to liberate the free amine **4** (Scheme 6).[23,24] The free amine **4** was then transformed into its Boc-derivative **5** on treatment with $Boc_2O$ at rt in 88% overall yield (Scheme 6).

In summary, the nucleophilic addition of 1-alkenyl-1,1-borozinc heterobimetallic reagents to aryl *N*-(2-pyridylsulfonyl) aldimines has been developed. This protocol provides a variety of B(pin)-substituted allylic amines in good yields. The addition step can be followed by a tandem oxidative cleavage of the B−C bond to furnish valuable α-amino ketones or by Suzuki cross-coupling to form

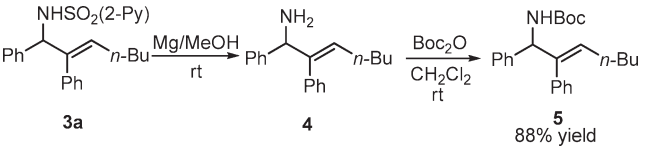
(23) Pak, C. S.; Lim, D. S. *Synth. Commun.* **2001**, *31*, 2209.
(24) Arrayás, R. G.; Cabrera, S.; Carretero, J. C. *Org. Lett.* **2005**, *7*, 219.

**Scheme 5.** Suzuki Cross-Coupling of Allylic Amines




R' = Ph, Ar = Ph (**3a**), 73% yield
R' = 4-$C_6H_4$-OMe, Ar = 4-$C_6H_4$-OMe (**3b**), 70% yield
R' = 4-$C_6H_4$-F, Ar = Ph (**3c**), 51% yield

**Scheme 6.** Removal of the 2-Pyridyl Sulfonyl Group followed by Boc-Protection




2-arylated trisubstituted (*E*)-allylic amines. It is noteworthy that 2-arylated trisubstituted (*E*)-allylic amines are not currently accessible via the Tsuji−Trost reaction, because 2-arylated allylic acetates are not good substrates for the allylic substitution reaction.[7d] Given that amino ketones and allylic amines are important pharmacophores,[10−12,21] we anticipate that the methods described herein will be useful to the synthetic community.

**Acknowledgment.** We acknowledge the NIH (NIGMS GM58101) and the NSF (CHE-0848467). Funds for instrumentation were provided by the NIH for an MS (1S10RR023444). M.M.H. thanks the University of Pennsylvania SAS for a Dissertation Completion Fellowship.

**Supporting Information Available.** Procedures and full characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.