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

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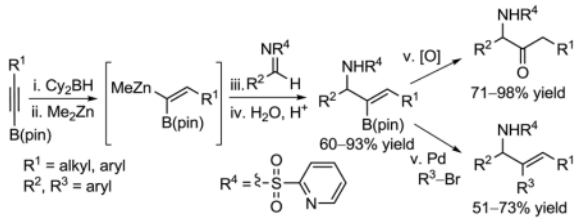
Abstract



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 transmetallation with dimethylzinc and addition to aldimines provides B(pin)-substituted allylic amines in 60–93% 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.[2,3,4,6] 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.

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 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 transmetallation 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,b,c] α-hydroxy ketones,[7a] trisubstituted (*E*)-allylic alcohols,[7a] B(pin)-substituted cyclopropyl alcohols[7b] and B(pin)-substituted allylic acetates.[7d]

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

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 coworkers reported the addition of vinylzinc reagents to aldimines activated with a diphenylphosphonoyl moiety (Scheme 3).[13] Carretero[14a,b] 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.

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 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 °C to −10 °C led to 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 electron withdrawing groups were good substrates, providing the B(pin) substituted allylic amines in 60–93% 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 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). The addition/oxidation reaction can also be executed in a tandem fashion. Thus, after the 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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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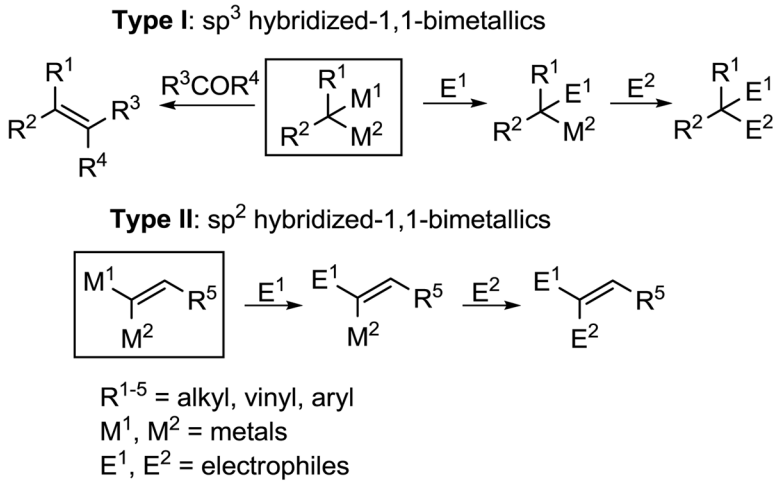
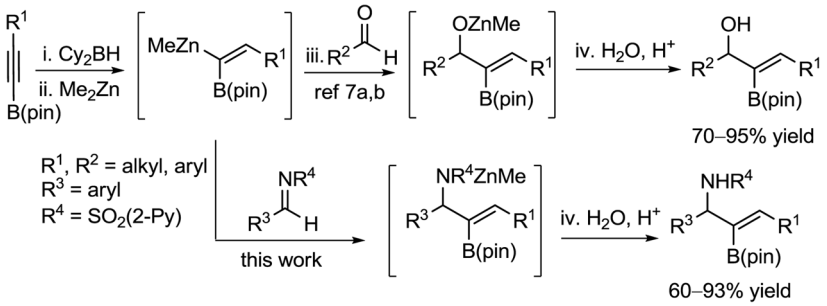
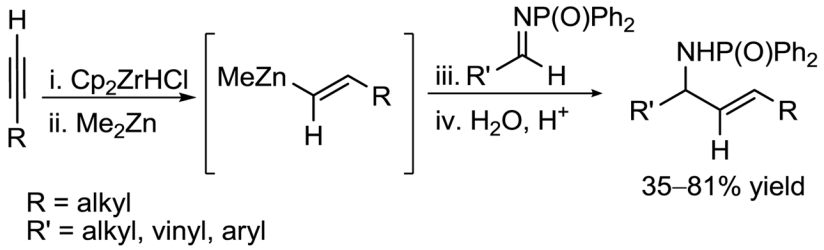


Scheme 1.
1,1-Heterobimetallics in Organic Synthesis

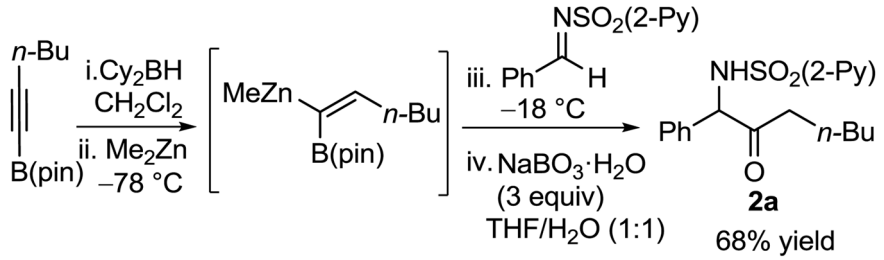


Scheme 2.

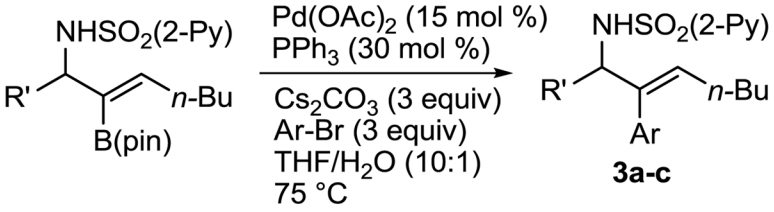
Generation of 1-Alkenyl-1,1-heterobimetallics of Boron/Zinc and Additions to Electrophiles



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

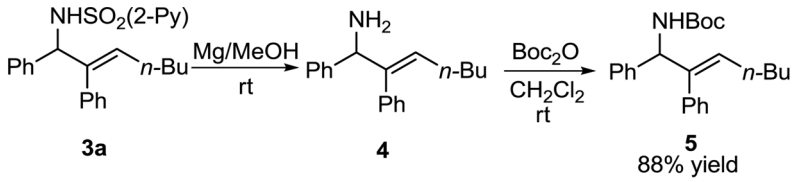


Scheme 4.
Tandem Addition/B–C Bond Oxidation to Yield α-Amino Ketone **2a**



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 5.
Suzuki Cross-Coupling of Allylic Amines

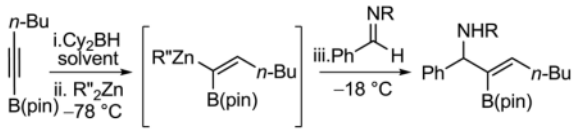


Scheme 6.

Removal of the 2-Pyridyl Sulfonyl Group followed by Boc-protection

Table 1

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



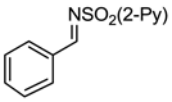
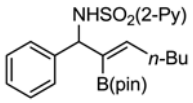
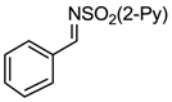
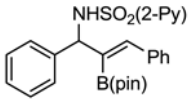
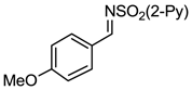
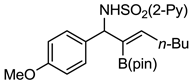
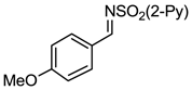
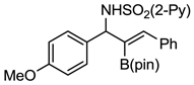
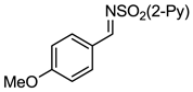
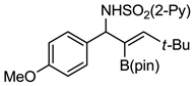
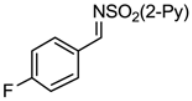
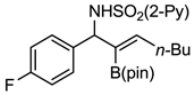
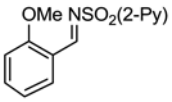
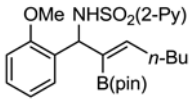
entry	R''_2Zn	solvent	R	yield (%)[a]
1	Me_2Zn	toluene	SO_2Tol	trace
2	Me_2Zn	toluene	Boc	trace
3	Me_2Zn	toluene	$P(O)Ph_2$	<30
4	Me_2Zn	toluene	SO_2(2-Py)	73
5	Me_2Zn	THF	SO_2(2-Py)	trace
6	Me_2Zn	CH_2Cl_2	SO_2(2-Py)	68[b]
7	Me_2Zn	CH_2Cl_2	SO_2(2-Py)	80
8	Et_2Zn	toluene	SO_2(2-Py)	64
9	Et_2Zn	CH_2Cl_2	SO_2(2-Py)	65

[a] Isolated yields,

[b] Reaction performed at −10°C

Table 2

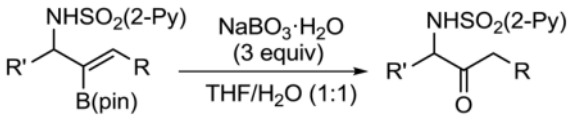
Addition of Alkenyl-1,1-hetrobimetallics to *N*-Pyridyl Sulfonyl Imines

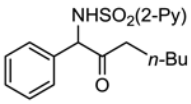
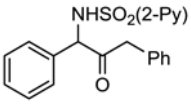
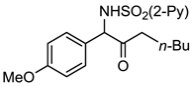
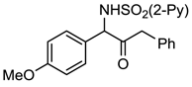
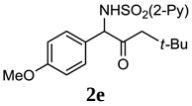
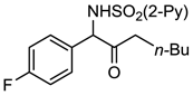
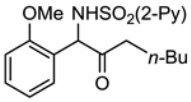
entry	borane	imine	allylic amines	yield (%)[a]
1			 **1a**	80
2			 **1b**	68
3			 **1c**	87
4			 **1d**	93
5			 **1e**	60
6			 **1f**	70
7			 **1g**	53

[a] Isolated yields

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