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Asymmetric Synthesis of α-Branched Allylic Amines by the Rh(I)-Catalyzed Addition of Alkenyltrifluoroborates to *N-tert*-Butanesulfinyl Aldimines

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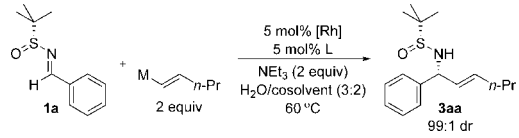
Chiral α-branched amines are prevalent in therapeutic agents and natural products necessitating the availability of practical and general methods for their asymmetric synthesis. The Rh(I)-catalyzed addition of arylboron reagents to activated imines has attracted considerable attention as a promising method for the asymmetric synthesis of α-aryl branched amines.[1] In contrast, despite the clear synthetic importance of allylic amines,[2,3] the corresponding Rh(I)-catalyzed addition of alkenylboron reagents to imines has yet to be reported.[4,5] Herein, we describe the practical and highly stereoselective Rh(I)-catalyzed addition of alkenyltrifluoroborates to both aromatic and aliphatic *N-tert*-butanesulfinyl imines.[6]

Trifluoroborates have emerged as promising alternatives to the corresponding boronic acids because of their greater stability to air and water, ease of synthesis and isolation, and generally higher reactivity in many processes.[7] Consequently, we began by evaluating the reaction between sulfinyl imine **1a** and pentenyltrifluoroborate **2a**. A small amount of the desired product was first observed with a cationic Rh(I) complex in the presence of water and base (Table 1, entry 1). A subsequent ligand screen revealed that 1,2-bis-(diphenylphosphinoyl)benzene (dppbenz) provided a significant increase in yield (entry 2). Upon screening rhodium catalysts, we found that commercially available and air stable $[Rh(Cl)(cod)]_2$ and $[Rh(OH)(cod)]_2$ proved to be competent as well (entries 4−5). Consistent with the reaction proceeding via a Rh−OH species,[8] $[Rh(OH)(cod)]_2$ was the most active precatalyst and loadings as low as 1 mol% could be employed without reductions in yield (entry 6).

Table 1. Reaction Optimization

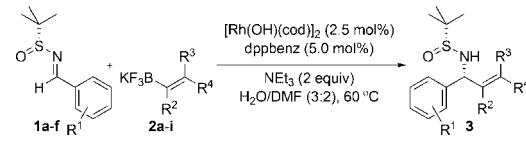


entry	catalyst	base	cosolvent	M	yield (%)[a]
1	$[Rh(cod)(CH_3CN)_2]BF_4$	NEt_3	dioxane	BF_3K	5
2	$[Rh(cod)(CH_3CN)_2]BF_4$, dppbenz	NEt_3	dioxane	BF_3K	61
3	$[Rh(cod)(CH_3CN)_2]BF_4$, dppbenz	NEt_3	DMF	BF_3K	73
4	$[Rh(cod)(Cl)]_2$, dppbenz	NEt_3	DMF	BF_3K	70
5	$[Rh(cod)(OH)]_2$, dppbenz	NEt_3	DMF	BF_3K	82
6[b]	$[Rh(cod)(OH)]_2$, dppbenz	NEt_3	DMF	BF_3K	81
7[c]	$[Rh(cod)(OH)]_2$, dppbenz	NEt_3	DMF	BF_3K	49
8[d]	$[Rh(cod)(OH)]_2$, dppbenz	K_3PO_4	DMF	BF_3K	84
9	$[Rh(cod)(OH)]_2$, dppbenz	Cs_2CO_3	DMF	BF_3K	68
10	$[Rh(cod)(OH)]_2$, dppbenz	NEt_3	DMF	$B(OH)_2$	40

[a] Yields were determined by ^1H NMR relative to an external standard. [b] Reaction was run with 1 mol% $[Rh(cod)(OH)]_2$ and 2 mol% dppbenz. [c] Reaction was run with 1:9 H_2O/DMF. [d] For aliphatic imines the yields were ∼20% lower with K_3PO_4.

A solvent screen established that polar solvents that solubilize the trifluoroborate provided the highest yields, with DMF as the optimal cosolvent (entry 3). The best results were obtained with a 3:2 H_2O/DMF solvent system. Lowering the amount of water resulted in reduced yields of **3aa** (entry 7). An extensive base screen confirmed that NEt_3 is optimal with other bases commonly employed in Suzuki−Miyaura reactions such as K_3PO_4 and Cs_2CO_3 also resulting in high conversions (entries 8−9).[9] We also confirmed that trifluoroborate salts are much more effective than boronic acids in the Rh-catalyzed alkenylation (entry 10). Notably, in all cases the diastereoselectivity was excellent (99:1).

Table 2. Alkenylation of Aryl *N-tert*-Butanesulfinyl Imines



entry	R^1	trifluoroborate **2**		**3**	yield (%)[a]	dr[b]
1[c]	4-H	BF_3K	**2a**	**3aa**	82	99:1
2	2-Me		**2a**	**3ba**	83	>99:1
3	4-Cl		**2a**	**3ca**	94	99:1
4	4-CF_3		**2a**	**3da**	96	98:2
5	3-Ac		**2a**	**3ea**	96	99:1
6	4-OMe		**2a**	**3fa**	52	99:1
7	4-Cl	Cy, BF_3K	**2b**	**3cb**	91	99:1
8	4-Cl	Ph, BF_3K	**2c**	**3cc**	66	99:1
9	4-Cl	4-CF_3-Ph, BF_3K	**2d**	**3cd**	22	99:1
10	4-Cl	4-OMe-Ph, BF_3K	**2e**	**3ce**	91	99:1
11[d]	4-Cl	BF_3K	**2f**	**3cf**	91	98:2
12	4-Cl	BF_3K	**2g**	**3cg**	70	98:2
13	4-Cl	BF_3K	**2h**	**3ch**	97	96:4
14	4-Cl	BF_3K	**2i**	**3ci**[e]	75	99:1

[a] Isolated yield. [b] Determined by HPLC comparison to authentic diastereomers. [c] Identical results were obtained whether set up in the glovebox or using Schlenk techniques. [d] Reaction was run for 1 h to avoid isomerization (*Z*/*E* 99:1). [e] The absolute stereochemistry was determined by X-ray crystallography.

The optimal reaction conditions were next evaluated with a range of different *N*-sulfinyl aromatic imines (Table 2). Electron-neutral (entries 1−2) and -deficient (entries 3−5) *N*-sulfinyl imines provided the corresponding allylic amines in excellent yields with high diastereoselectivity. Addition to the ortho-methyl substituted *N*-sulfinyl imine is significant as the steric interaction did not affect reaction yield (entry 2). Furthermore, the successful addition to 3-acetylphenyl *N*-sulfinyl imine highlights the functional group compatibility of the method (entry 5).[10] The addition to electron-rich 4-methoxyphenyl *N*-sulfinyl imine also proceeded with very

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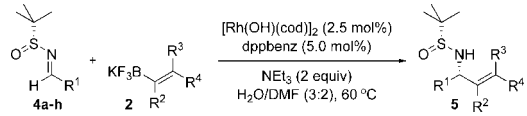
high selectivity although with a moderate reduction in yield (entry 6). Note that due to the air stability of the Rh(I) precatalyst and dppbenz, identical results were obtained whether the reaction was set up in the glovebox or using standard Schlenk techniques (entry 1).

The scope of the organotrifluoroborate coupling partner was next examined (Table 2). Trifluoroborates with branched aliphatic β-substituents added in good yields with excellent selectivity (entry 7). The alkenylation was, however, influenced by electronic effects on the trifluoroborate with additions of electron-deficient trifluoroborates proceeding in lower yield (entries 8−9) than the additions of electron-rich trifluoroborates (entry 10). Cis-substituted alkenyl trifluoroborates are also competent coupling partners and proceed without olefin isomerization at short reaction times (entry 11).

We were interested in evaluating the alkene substitution pattern beyond disubstituted alkenyltrifluoroborates. The addition of trisubstituted alkenyltrifluoroborates proceeded with high yields and selectivities (entry 12−13). Remarkably, a tetrasubstituted alkenyltrifluoroborate also added in good yield and with high stereoselectivity (entry 14).

Significantly, the scope of the alkenylation reaction could be extended to aliphatic imines (Table 3). Good yields and high selectivities were obtained for unbranched (entries 1−3) and δ-branched (entries 4−5) sulfinyl imines. Additions to both β- (entry 6) and α-branched (entry 7) sulfinyl imines were successful albeit in somewhat reduced yield due to competitive imine hydrolysis. A moderate yield was obtained for the sulfinyl imine derived from phenylacetaldehyde, which is typically a challenging substrate due to imine tautomerization (entry 8).

Table 3. Alkenylation of Aliphatic *N-tert*-Butanesulfinyl Imines

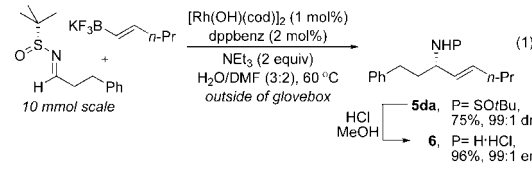


entry	imine	trifluoroborate 2	5	yield (%)[a]	dr[b]
1		**2a**	**5aa**	72	98:2
2		**2a**	**5ba**	62	98:2
3		**2a**	**5ca**	52	98:2
4	Ph	**2a**	**5da**	78	99:1
5		**2a**	**5ea**	76	98:2
6	Cy	**2a**	**5fa**	64	98:2
7	Cy	**2a**	**5ga**	45	98:2
8	Ph	**2a**	**5ha**	44	97:3
9	Ph	**2b**	**5db**	69	99:1
10[c]	Ph	**2f**	**5df**	70	98:2
11	Ph	**2h**	**5dh**	90	95:5

[a] Isolated yields after chromatography. [b] Determined by HPLC comparison to authentic diastereomers. [c] Reaction was run for 1 h to minimize isomerization (*Z*/*E* 95:5).

The scope in trifluoroborate was also explored with aliphatic sulfinyl imines. Trifluoroborates with branched β-substituents (entry 9) and cis-substitution (entry 10) added in good yields with high selectivity. Similar to the aryl imines, the α-substituted trifluoroborate added in excellent yield with a slight decrease in selectivity (entry 11).

The robustness of the method was demonstrated by the addition of pentenyl trifluoroborate **2a** to aliphatic N-sulfinyl imine **4d** on a 10 mmol scale with 1 mol% of the Rh catalyst using standard Schlenk techniques (eq 1). Analytically pure material was obtained in good yield and high selectivity. Furthermore, cleavage of the



tert-butanesulfinyl group provided allylic amine **6** in high yield with no loss in stereochemical purity.

In conclusion, the catalytic asymmetric addition of alkenyltrifluoroborates to aryl and aliphatic sulfinyl imines proceeds with very high selectivity and with good substrate scope for both the imine and the trifluoroborate. This method enables the practical asymmetric synthesis of allylic amines from readily accessible *N*-sulfinyl imine and trifluoroborate starting materials.

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

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