Literature Report

Asymmetric Synthesis of *α*-Amino Boronate Esters *via* Pinacolboryl Addition to Imines

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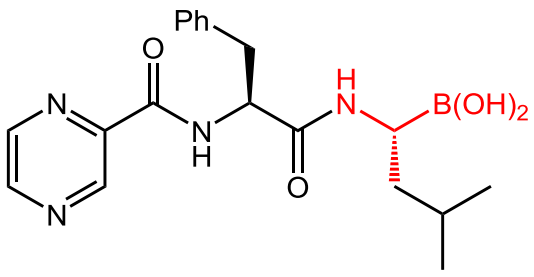
Checker: Xiang Gao
Date: 2015-12-22

Contents

Introduction

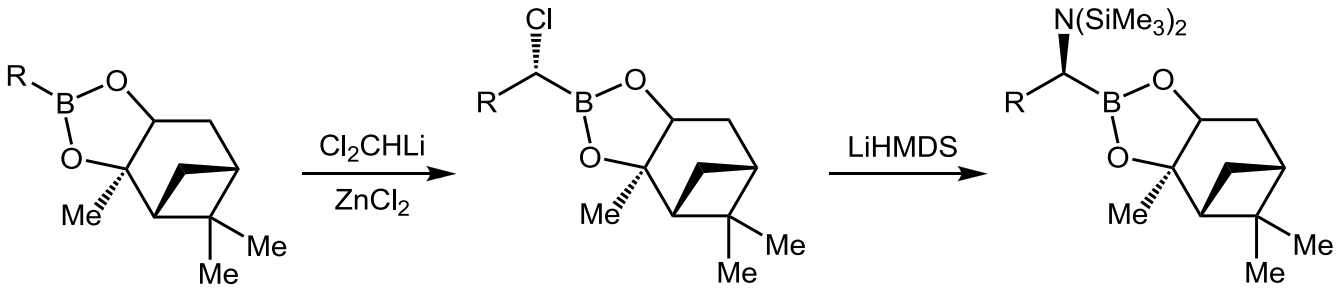


Velcade

- The first successful proteasome inhibitor；
- The first therapeutic agent containing boron；
- Treatment of relapsed and refractory multiple myeloma.

Introduction

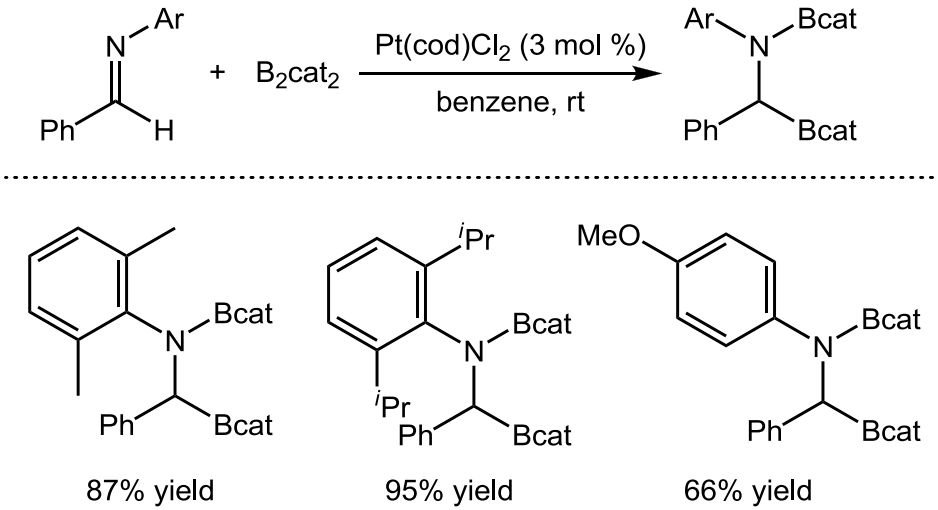
Classic synthetic method:



Matteson, D. S. *et al*. *J. Am. Chem. Soc*. **1981**, *103*, 5241.

Pt-catalyzed pinacolboryl addition to imines

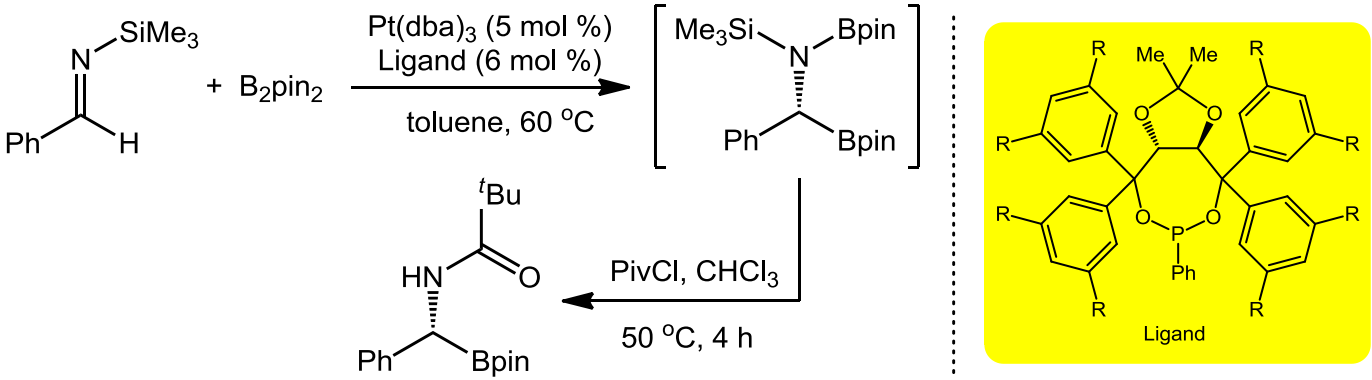
Baker's work:



Baker, R. T. *et al*. *Org. Lett.* **2000**, *2*, 2105.

Pt-catalyzed pinacolboryl addition to imines

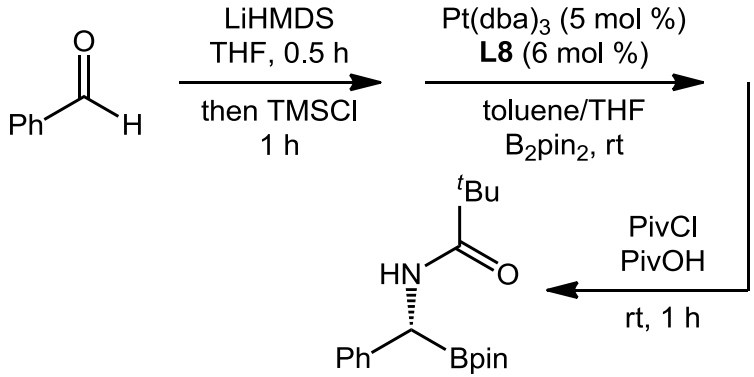
Morken's work:

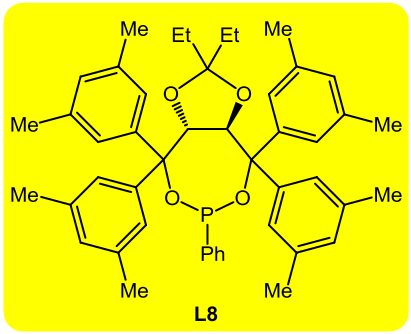


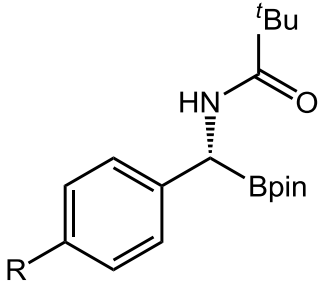
Entry	Ligand	R	Yield (%)	Er
1	**L1**	H	76	84:16
2	**L2**	Me	80	89:11
3	**L3**	F	64	83:17
4	**L4**	Et	79	90:10
5	**L5**	^{i}Pr	70	89:11
6	**L6**	Ph	71	73:27
7	**L7**	^{t}Bu	72	81:19

Morken, J. P. *et al. J. Am. Chem. Soc.* **2013**, *135*, 9252.

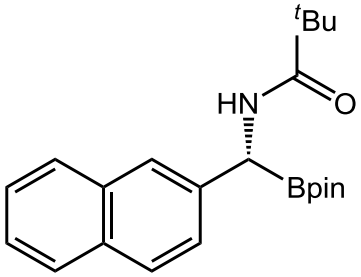
Pt-catalyzed pinacolboryl addition to imines



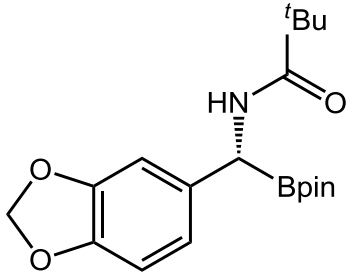




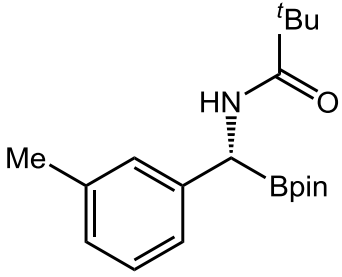
R = H, 81% yield, 90% ee
R = F, 86% yield, 88% ee
R = CF_3, 74% yield, 88% ee
R = Cl, 87% yield, 88% ee
R = OMe, 84% yield, 90% ee



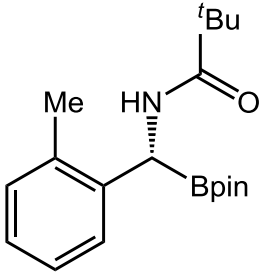
87% yield, 94% ee



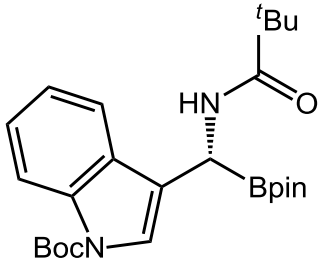
79% yield, 86% ee



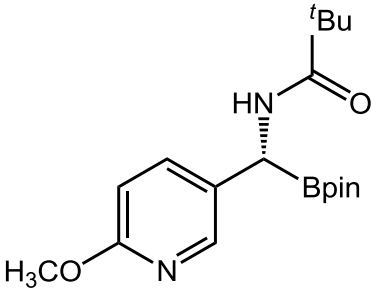
88% yield, 94% ee



82% yield, 14% ee



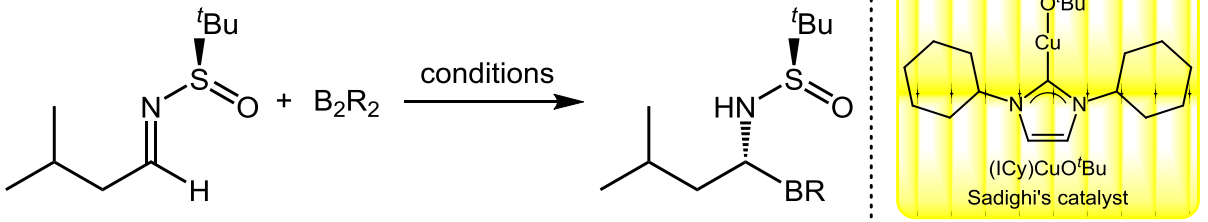
83% yield, 90% ee



65% yield, 78% ee

Cu-catalyzed pinacolboryl addition to imines

Ellman's work:

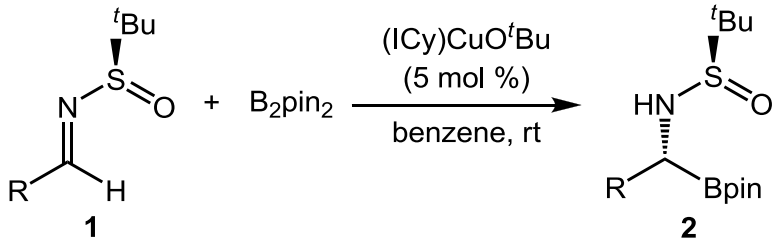


Entry	B_2R_2	Cat.[a]	T(°C)	Solvent	Yield (%)[b]	Dr[c]
1	B_2cat_2	$Pt(cod)Cl_2$	rt	C_6H_6	NR	NA
2	B_2pin_2	(ICy)CuO^{t}Bu	rt	C_6H_6	78	>98:2
3	B_2pin_2	none	rt	C_6H_6	NR	NA
4	B_2pin_2	(ICy)CuO^{t}Bu	10	C_6H_6	71	>98:2
5	B_2pin_2	(ICy)CuO^{t}Bu	50	C_6H_6	54	97:3
6	B_2pin_2	(ICy)CuO^{t}Bu	rt	toluene	69	>98:2
7	B_2pin_2	(ICy)CuO^{t}Bu	rt	dioxane	62	98:2
8	B_2pin_2	(ICy)CuO^{t}Bu	rt	THF	50	99:1

[a] With 5 mol % of catalyst used. [b] Yields were determined by ^{1}H NMR of the crude material relative to 1,3,5-trimethoxybenzene as an internal standard. [c] Diastereomeric ratio was determined by ^{19}F NMR of the corresponding (*R*)- and (*S*)-MTPA amides.

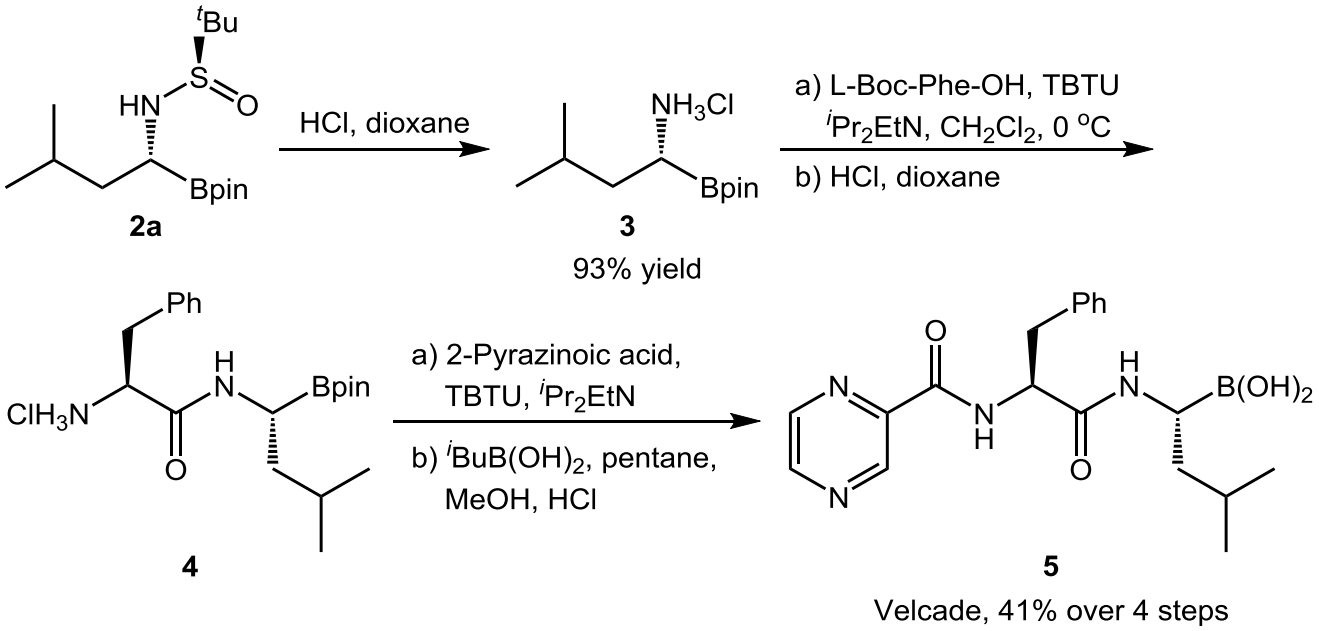
Ellman, J. A. *et al*. *J. Am. Chem. Soc*. **2008**, *130*, 6910.

Cu-catalyzed pinacolboryl addition to imines



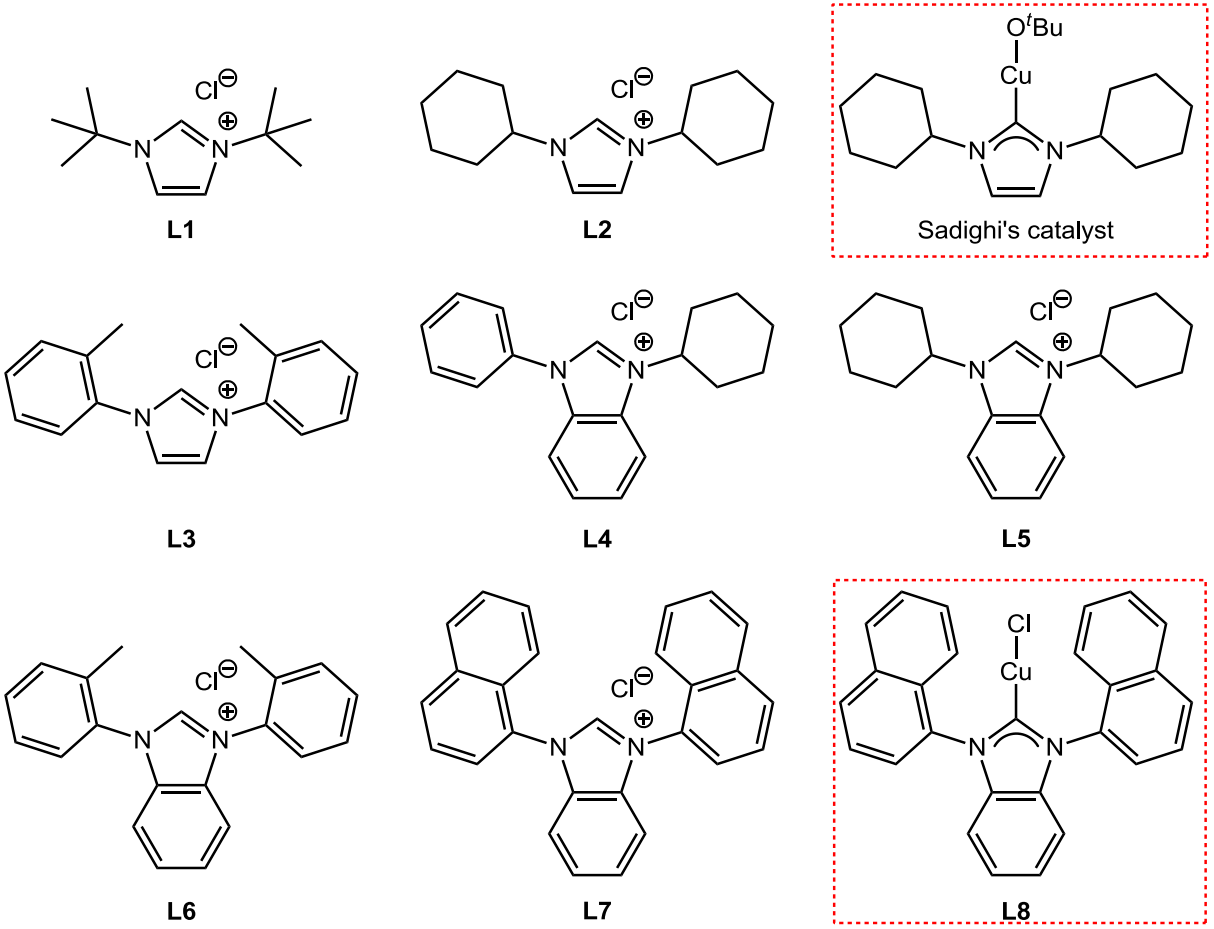
Entry	R	Product	Yield (%)	Dr
1	$(CH_3)_2CHCH_2$–	**2a**	74	>98:2
2	$(CH_3)_3C$–	**2b**	75	96:4
3	Cyclohexyl–	**2c**	81	97:3
4	$PhCH_2$–	**2d**	59	>98:2
5	Ph–	**2e**	54	99:1
6	4-MeO-Ph–	**2f**	57	>98:2
7	4-Cl-Ph–	**2g**	61	99:1
8	4-CF_3-Ph–	**2h**	66	>95:5

Cu-catalyzed pinacolboryl addition to imines



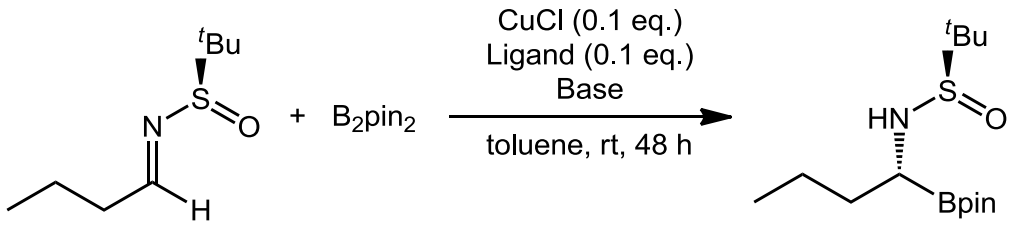
Cu-catalyzed pinacolboryl addition to imines

Sun's work:



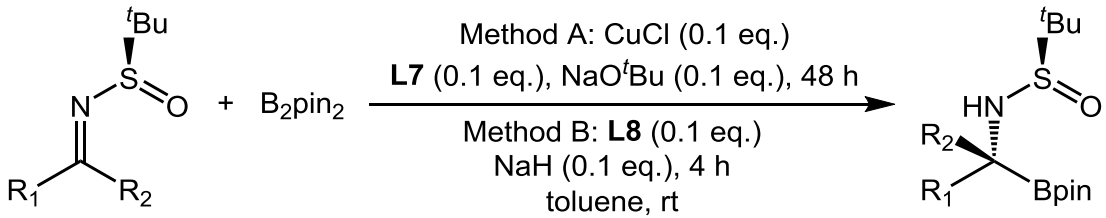
Sun, Z. *et al*. *J. Org. Chem*. **2013**, *78*, 3405.

Cu-catalyzed pinacolboryl addition to imines



Entry	Ligand	Base	Yield (%)
1	**L1**	0.1 eq. of NaO^{t}Bu	none
2	**L2**	0.1 eq. of NaO^{t}Bu	none
3	**L2**	0.2 eq. of NaO^{t}Bu	18
4	**L3**	0.1 eq. of NaO^{t}Bu	23
5	**L3**	0.2 eq. of NaO^{t}Bu	45
6	**L4**	0.1 eq. of NaO^{t}Bu	65
7	**L5**	0.1 eq. of NaO^{t}Bu	none
8	**L6**	0.1 eq. of NaO^{t}Bu	52
9	**L7**	0.1 eq. of NaO^{t}Bu	88

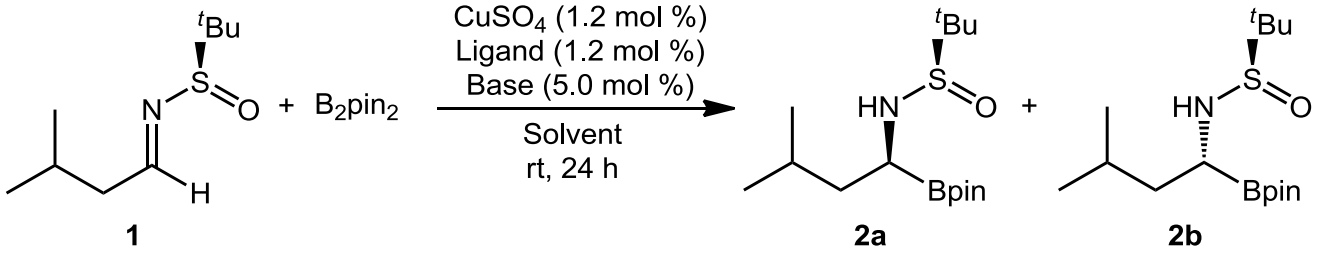
Cu-catalyzed pinacolboryl addition to imines



Entry	R_1	R_2	Yield (method)	Dr
1	$(CH_3)_3C$–	H	86% (A) 89% (B)	>99:1
2	$PhCH_2$–	H	85% (A) 88% (B)	98:2
3	4-Me-Ph–	H	82% (A) 84% (B)	>99:1
4	4-Cl-Ph–	H	79% (A) 86% (B)	>99:1
5	Ph–	CH_3	48% (A) 56% (B)	71:29
6	CH_3CH_2–	CH_3	66% (A) 75% (B)	74:26

Cu-catalyzed pinacolboryl addition to imines

Ellman's work:

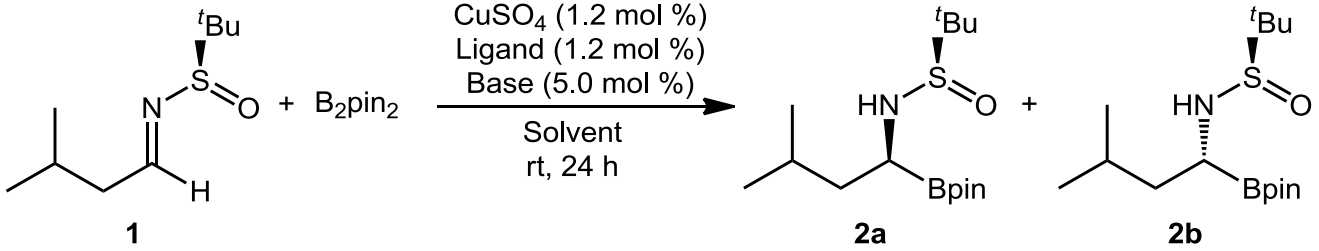


1 **2a** **2b**

Entry	Solvent	Base	Ligand	Yield (%)	Dr (**2a:2b**)
1	H_2O	4-Picoline	none	41	1:1
2	toluene/H_2O (1:5)	4-Picoline	none	34	5:1
3	toluene/H_2O (5:1)	4-Picoline	none	29	>9:1
4	toluene/H_2O (5:1)	Et_3N	none	35	>9:1
5	toluene/H_2O (5:1)	Piperidine	none	27	>9:1
6	toluene/H_2O (5:1)	$CyNH_2$	none	38	>9:1
7	toluene/H_2O (5:1)	$BnNH_2$	none	51	>9:1

Ellman, J. A. *et al*. *J. Org. Chem.* **2014**, *79*, 3671.

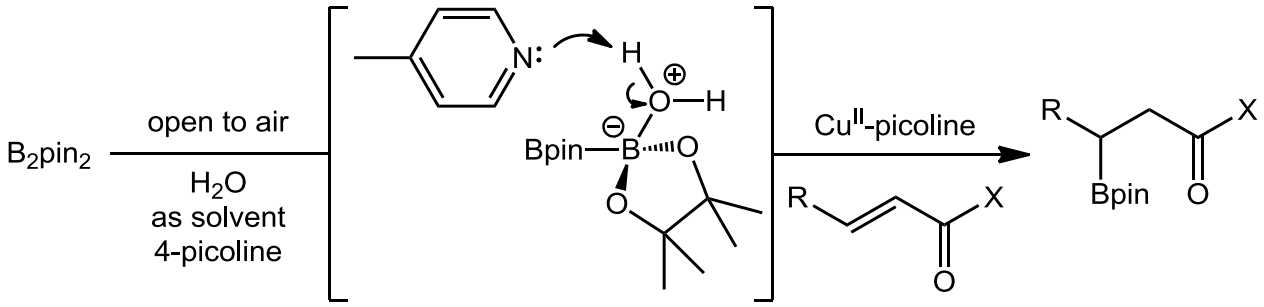
Cu-catalyzed pinacolboryl addition to imines



1 **2a** **2b**

Entry	Solvent	Base	Ligand	Yield (%)	Dr (**2a:2b**)
8	toluene/H_2O (5:1)	$BnNH_2$	ICy·HBF_4	46	4:1
9	toluene/H_2O (5:1)	$BnNH_2$	$P(OPh)_3$	85	95:5
10	toluene/H_2O (5:1)	$BnNH_2$	PCy_3	94	10:90
11	toluene/H_2O (5:1)	$BnNH_2$	$POCy_3$	31	92:8
12	toluene/H_2O (5:1)	$BnNH_2$	PCy_3·HBF_4	89	6:94

Cu-catalyzed pinacolboryl addition to α,β-unsaturated ketone



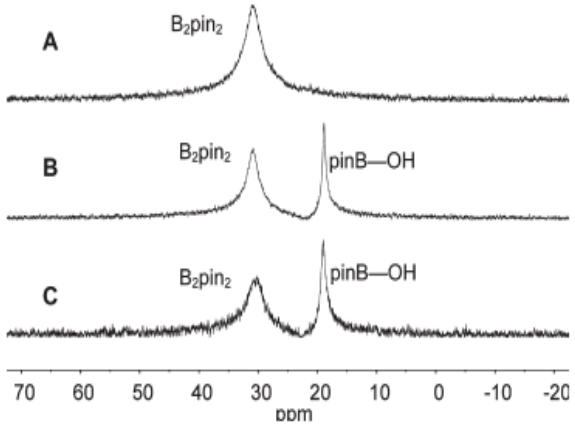
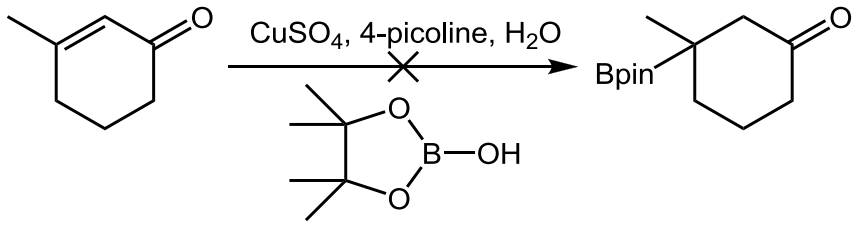
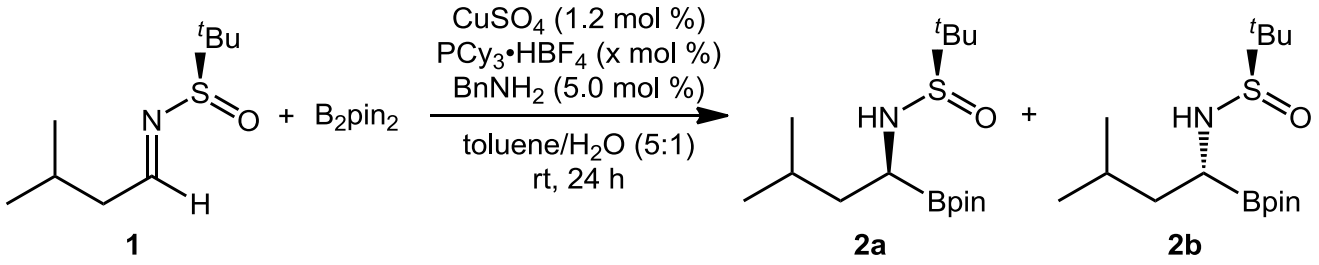


Figure 1. ^{11}B NMR spectra of B_2pin_2 in (A) 4-picoline, (B) water, and (C) water with 4-picoline (1.0 equiv) at 4 °C.



Santos, W. L. *et al*. *Org. Lett.* **2012**, *14*, 1918.

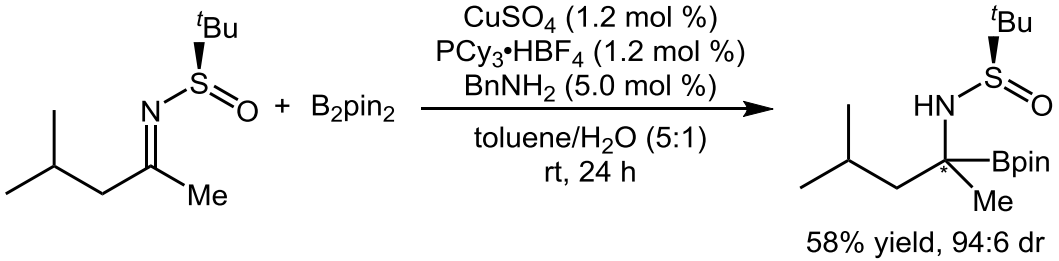
Cu-catalyzed pinacolboryl addition to imines

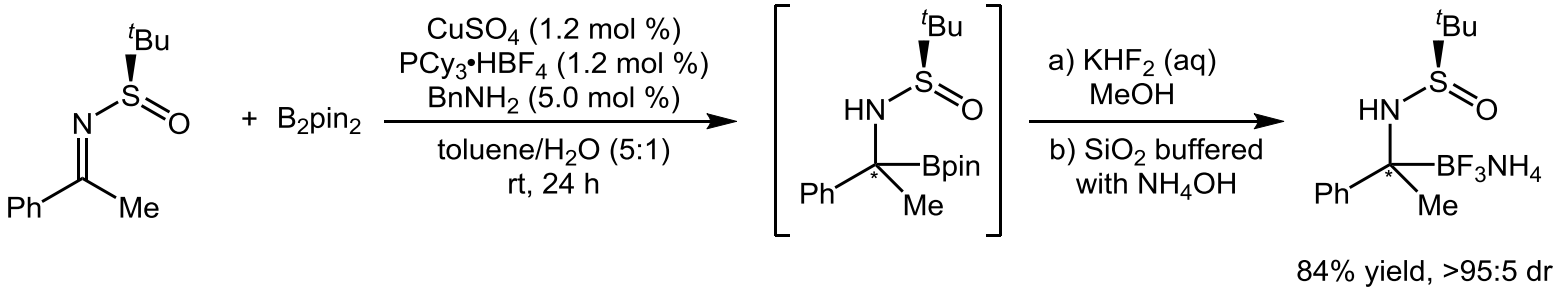


1 **2a** **2b**

Entry	$CuSO_4/PCy_3$	Yield (%)	Dr (**2a:2b**)
1	2:1	89	25:75
2	1:1	88	6:94
3	1:2	89	7:93
4	1:4	91	5:95

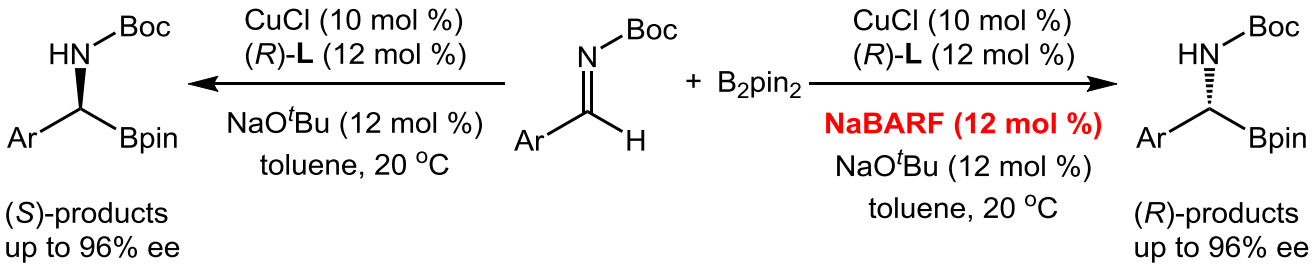
Cu-catalyzed pinacolboryl addition to imines

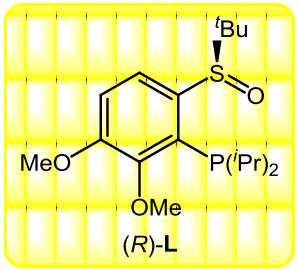




Cu-catalyzed pinacolboryl addition to imines

Liao's work:

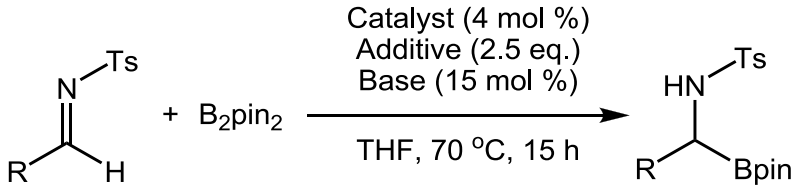




Liao, J. *et al*. *Org. Lett.* **2015**, *17*, 2420.

Organocatalytic pinacolboryl addition to imines

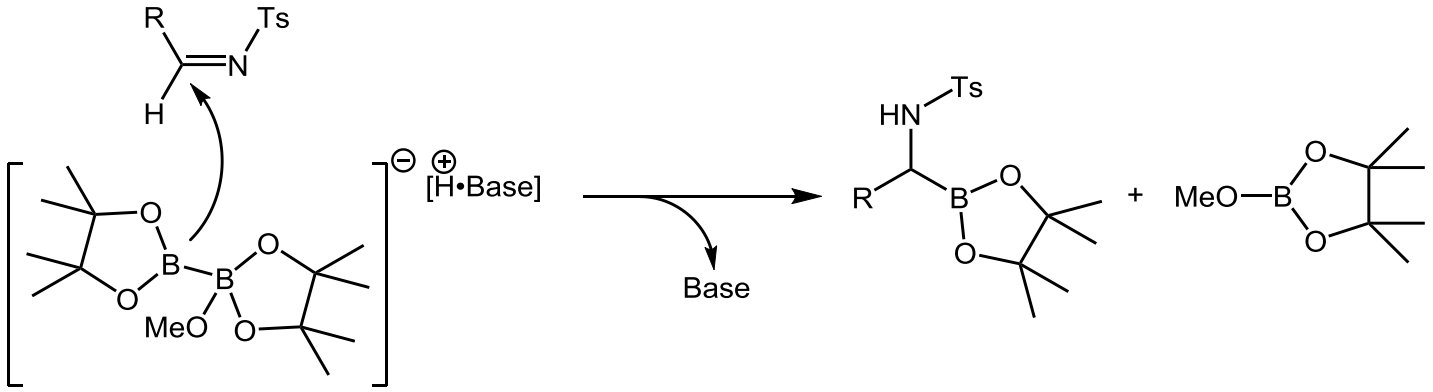
Fernández's work:



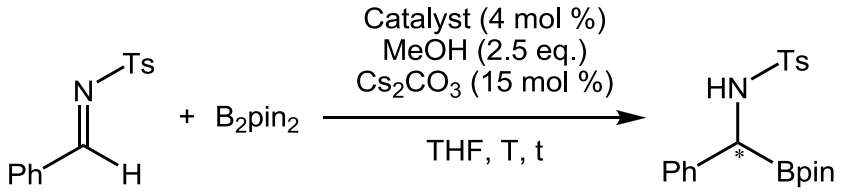
Entry	Base	Catalyst	Additive	Conv. (%)
1	Cs_2CO_3	none	MeOH	70
2	Cs_2CO_3	PPh_3	MeOH	91
3	Cs_2CO_3	PPh_3	none	NR
4	none	PPh_3	MeOH	NR
5	K_2CO_3	PPh_3	MeOH	83
6	KOH	PPh_3	MeOH	58
7	NaOMe	PPh_3	MeOH	88
8	NaO^{t}Bu	PPh_3	MeOH	85
9	Cs_2CO_3	PPh_3	PhOH	89
10	Cs_2CO_3	PPh_3	^{i}PrOH	83
11	Cs_2CO_3	PPh_3	BuOH	78

Fernández. E. *et al*. *Chem. Commun.* **2012**, *48*, 3769.

Organocatalytic pinacolboryl addition to imines

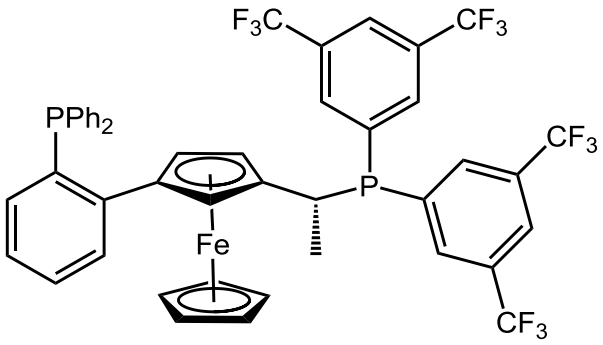


Organocatalytic pinacolboryl addition to imines

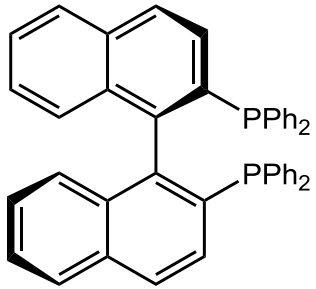


Entry	T (°C)	Catalyst	t (h)	Conv. (%)	Ee (%)
1	45	**a**	15	87	90
2	45	**b**	15	88	67
3	45	**c**	15	99	41
4	45	**d**	15	33	86
5	45	**e**	15	40	90
6	45	**f**	15	55	79
7	25	**a**	24	56	99
8	25	**c**	24	45	99

Organocatalytic pinacolboryl addition to imines



a



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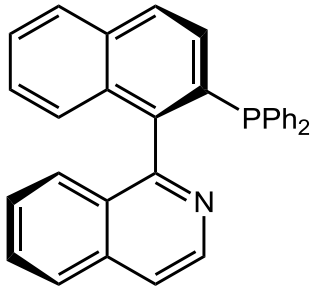

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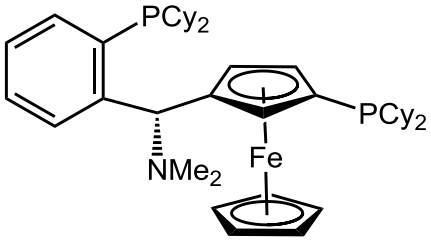
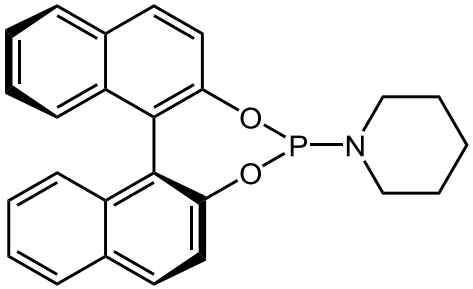


d



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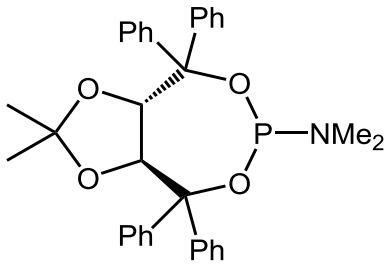
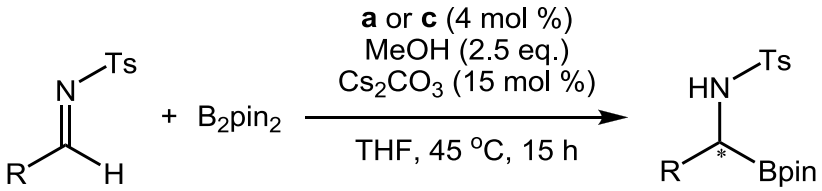


f

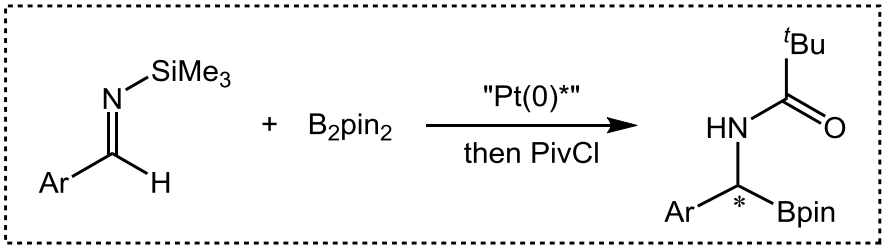
Organocatalytic pinacolboryl addition to imines



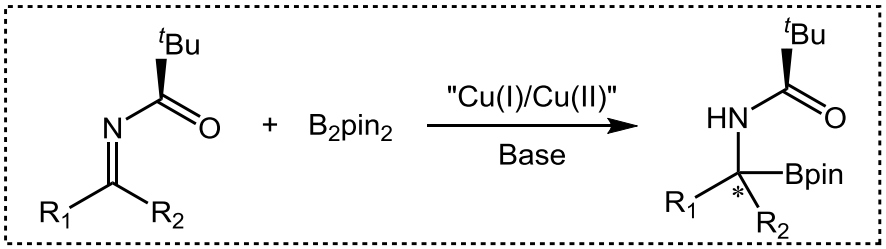
Entry	R	Catalyst	Yield (%)	Ee (%)
1	4-MeO-Ph–	**a**	83	75
2	4-MeO-Ph–	**c**	74	55
3	4-CF_3-Ph–	**a**	95	71
4	4-CF_3-Ph–	**c**	90	52
5	C_6H_{13}–	**a**	97	24
6	C_6H_{13}–	**c**	99	14

Summary

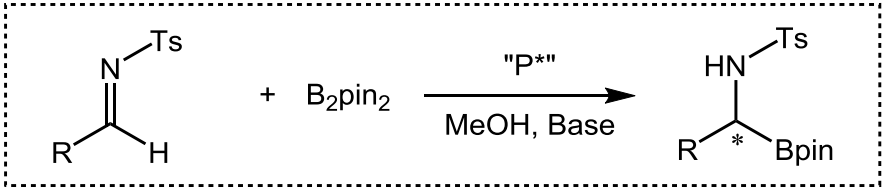
Pt-catalyzed strategy



Cu-catalyzed strategy

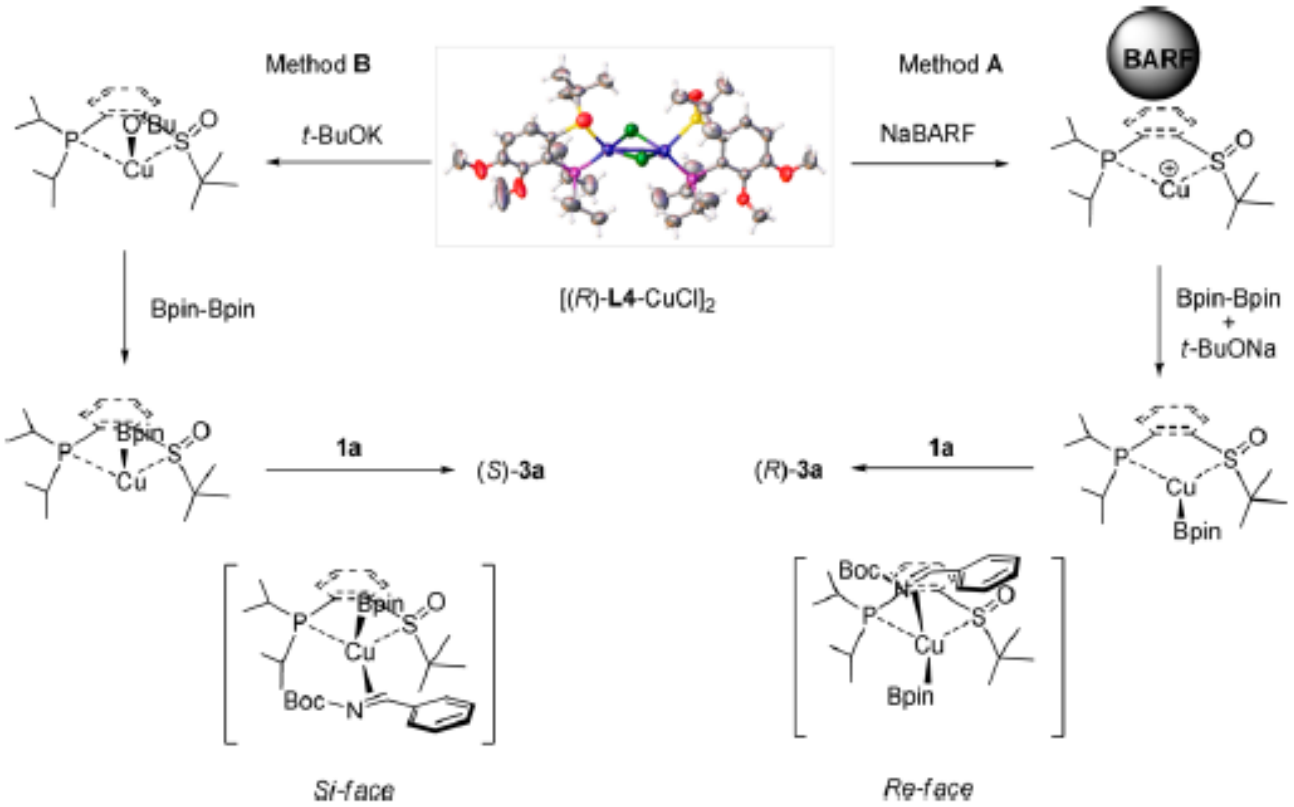


Organocatalytic strategy



Enantiopure *α*-amino boronic acids and esters, owing to their substantial selectivity in the formation of reversible covalent bonds with the targeted enzyme, have emerged as a unique class of enzyme inhibitors and been used as potential therapeutic agents. In contrast to classic synthetic methods, transition-metal-catalyzed addition of bis(pinacolato)diboron to imines can be the most efficient and straightforward approach to prepare *α*-amino boronate derivatives. In 2008, Ellman pioneered a (ICy)Cu(I)-catalyzed borylation of chiral *N*-(*tert*-butanesulfinyl) aldimines and furnished a highly diastereoselective *α*-amino boronate ester. Very recently, Morken reported an asymmetric platinum(0) phosphonite catalyzed strategy which converted aldehydes into applicable *N*-acyl-*α*-amino boronates.

As important as *N*-acyl-*α*-amino boronic acids are, their preparation through enantioselective borylative addition of *N*-acylimine still remains a challenge. *N*-Boc-imine is a versatile and readily available starting material widely used in organic synthesis, whereas the *N*-Boc-protected group can be easily removed for synthetic purposes. However, catalytic asymmetric pinacolboryl addition of *N*-Boc-imines, even in a nonasymmetric fashion, has not been reported. Since literature's strategy has been proved unsuitable for enantioselective diboration of *N*-acylimine, a new and efficient catalytic approach is desirable to realize *N*-Boc-imine borylative addition. In this paper, we report a copper(I)-catalyzed pinacolboryl addition of *N*-Boc-imines, and high enantioselectivities were achieved by using a chiral sulfoxide phosphine ligand.


Method B
t-BuOK
Method A
NaBARF
BARF
[(R)-L4-CuCl]2
Bpin-Bpin
Bpin-Bpin
+
t-BuONa
1a
(S)-3a
1a
(R)-3a
Si-face
Re-face